Amended Safety Assessment of *Mentha piperita* (Peppermint)-derived Ingredients as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: November 10, 2017
Panel Date: December 4-5, 2017

The 2017 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, 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 report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Ivan Boyer, Ph.D., former Senior Toxicologist.

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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Date: November 10, 2017

Subject: Draft Final Amended Report on *Mentha piperita* (Peppermint)-Derived Ingredients

At the September 11-12, 2017 Panel meeting, the Panel issued a tentative amended report for public comment with a conclusion stating that the available data are insufficient to make a determination of safety for 9 out of the 10 *Mentha piperita* (peppermint)-derived ingredients. These 9 ingredients, and the data that are needed to complete this safety assessment, are stated below.

Mentha Piperita (Peppermint) Leaf Extract
Mentha Piperita (Peppermint) Leaf
Mentha Piperita (Peppermint) Leaf Water
Mentha Piperita (Peppermint) Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Water
Mentha Piperita (Peppermint) Leaf Cell Extract
Mentha Piperita (Peppermint) Leaf Juice
Mentha Piperita (Peppermint) Meristem Cell Culture

However, it was determined that Mentha Piperita (Peppermint) Oil is safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing.

The Panel's prior 1% pulegone limitation is not included in the current conclusion because the Panel determined that the cerebellar lesions previously observed in the rat brain are not believed to have been induced by pulegone. Furthermore, after reviewing results from the 2011 National Toxicology Program (NTP) oral carcinogenicity study on pulegone, the Panel did not express concern over these findings relative to pulegone as a component of Mentha Piperita (Peppermint) Oil in cosmetic products, based on the understanding that the cytotoxic dose-response relationship (renal and liver toxicity) that was associated with cancer development would not be relevant to pulegone exposure from a cosmetic product containing Mentha piperita (Peppermint) Oil at current use concentrations.

The Panel determined that the following data are needed to complete this safety assessment:

- Composition data on all ingredients except for Mentha Piperita (Peppermint) Oil.
    - Depending on the composition data that are received, other toxicological endpoints may be needed.

- Skin irritation and sensitization data on all ingredients except Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, and Mentha Piperita (Peppermint) Leaf Water.

The following data were received in response to the insufficient data conclusion on 9 *Mentha piperita* (peppermint)-derived ingredients that was issued at the September 2017 Panel Meeting, and are attached for the Panel's review: (1) Human 48-h occlusive patch test, evaluating skin irritation potential, on a lipstick product containing 0.2961% Mentha Piperita (Peppermint) Leaf Extract (*pepper122017data1)*; (2) Composition, method of manufacturing, and physical properties data on Mentha Piperita (Peppermint) Leaf Extract (*pepper122017data2)*, and (3) Updated use concentration data on *Mentha piperita* (peppermint)-derived ingredients (*pepper122017data3*). These data are enclosed within horizontal borders within the report text.

According to the updated use concentration data, use concentrations of Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract are no longer being reported and Mentha Piperita (Peppermint) Leaf Extract is being used at concentrations ranging from 0.3% to 0.5% in lipstick products. The Draft Final Amended Report has been revised to include these data (enclosed within horizontal borders in the report text). Comments that were received from the Council (*pepper122017pcpc1, pepper122017pcpc2, and pepper122017pcpc3)* have been addressed.

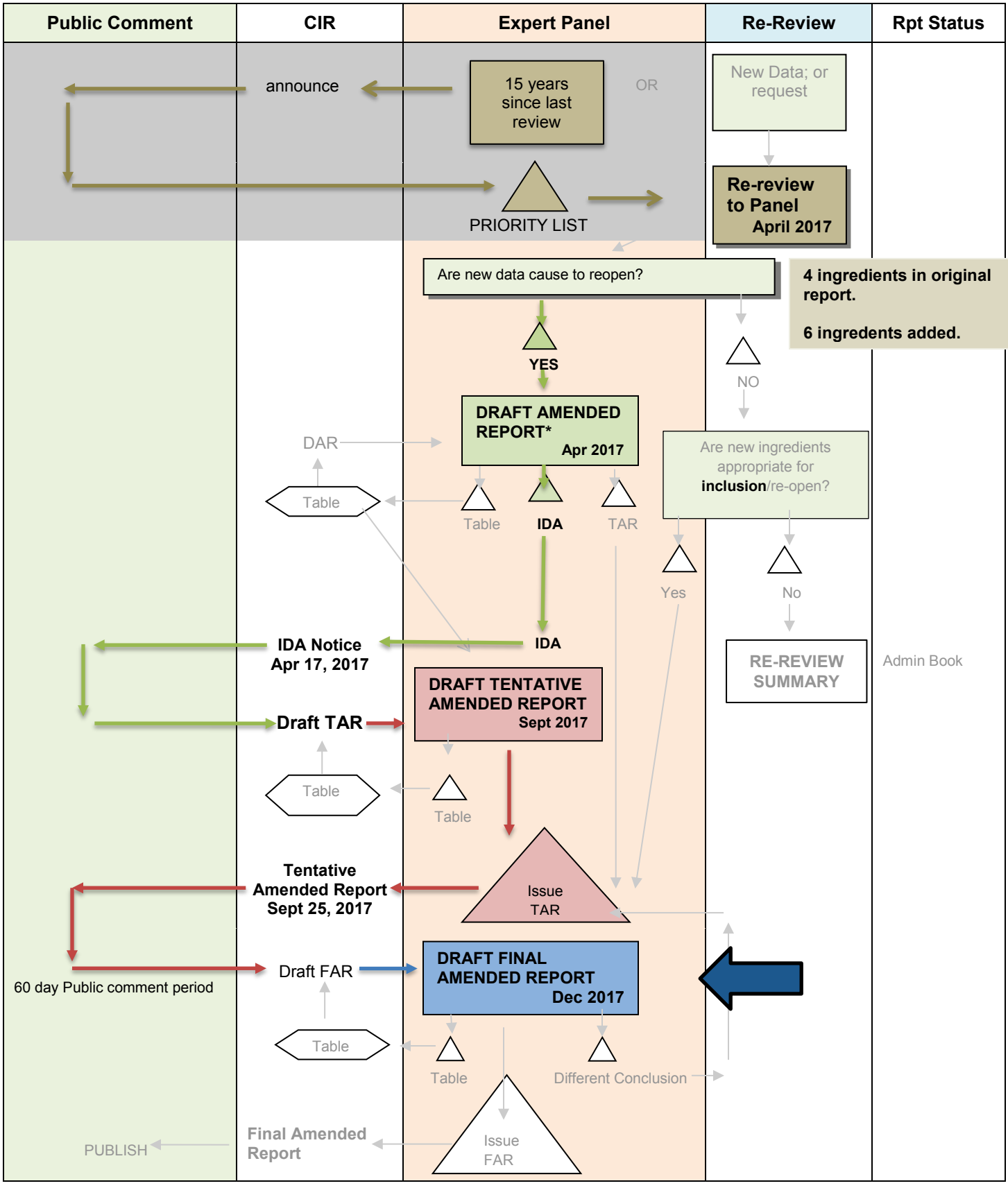
Also included in this package for your review are the Draft Final Amended Report (*pepper122017rep*), the CIR report history (*pepper122017hist.docx*), Flow chart (*pepper122017flow.docx*), Literature search strategy (*pepper122017strat.docx*), Ingredient data profile (*pepper122017prof.docx*), 2017 FDA VCRP data (*pepper122017FDA.docx*), and minutes from the September 11-12, 2017 Panel meeting and prior Panel meetings (*pepper122017min.docx)*. The original final report may be accessed at the CIR website (https://www.cir-safety.org/ingredients).

After reviewing these documents, the Panel will determine whether the data are now sufficient for arriving at a conclusion (safe as used or safe with qualifications) on the safety of the 9 *Mentha piperita* (Peppermint)-derived Ingredients, or, if not, whether a Final Report with the two conclusion that are stated above should be issued.

RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Mentha Piperita (Peppermint)-Derived Ingredients

MEETING Dec 2017



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

CIR History of:

Mentha Piperita-derived Ingredients

A Final Report with a conclusion stating that the following ingredients are safe as used in cosmetic formulations was issued at the September 10-11, 1998 CIR Expert Panel meeting and published in 2001: Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint) Leaf Water. The conclusion also contains a statement indicating that the concentration of pulegone in these ingredients should not exceed 1%.

Re-review document, Teams/Panel: April 10-11, 2017

Use concentration data on Mentha Piperita-derived ingredients and human skin irritation, sensitization, and ocular irritation data on Mentha Piperita (Peppermint) Leaf Water that were received from the Council have been added to the report text.

The Panel agreed that the 2001 final report (published in 2001) on Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint) Leaf Water should be reopened to add 6 Mentha piperita (peppermint)-derived ingredients:

Mentha Piperita (Peppermint) Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Water
Mentha Piperita (Peppermint) Leaf Cell Extract
Mentha Piperita (Peppermint) Leaf Juice
Mentha Piperita (Peppermint) Meristem Cell Culture

The Panel issued an Insufficient Data Announcement (IDA) with the following data requests for all ten ingredients:

- Skin irritation and sensitization data
- Composition, method of manufacture, and impurities data

Draft Tentative Amended Report, Teams/Panel: September 11-12, 2017

The following data were received in response to the Panel's IDA: (1) use concentration data on the 6 ingredients that are being added; (2) method of manufacture, composition, and impurities data on Peppermint Leaf Extract (butylene glycol/water), Peppermint Leaf Extract (water/ethanol), Peppermint Leaf Extract Powder, and Peppermint Leaf Water) [It should be noted that, according to the International Cosmetic Ingredient Dictionary and Handbook, Peppermint Leaf Extract Powder is not an ingredient name that is associated with any of the Mentha Piperita (Peppermint)-derived ingredients that are included in this safety assessment.]; and *in vitro* skin irritation data on Peppermint Leaf Extract (water/ethanol) (at concentrations of 10% and 100%) and an HRIPT on Peppermint Leaf Extract (water/ethanol) (at a concentration of 100%).

The Panel issued a tentative report for public comment with a conclusion stating that the available data are insufficient to make a determination of safety for 9 out of the 10 Mentha piperita (peppermint)-derived ingredients. These 9 ingredients, and the data that are needed to complete this safety assessment, are stated below.

Mentha Piperita (Peppermint) Leaf Extract
Mentha Piperita (Peppermint) Leaf
Mentha Piperita (Peppermint) Leaf Water
Mentha Piperita (Peppermint) Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Water*
Mentha Piperita (Peppermint) Leaf Cell Extract*
Mentha Piperita (Peppermint) Leaf Juice*
Mentha Piperita (Peppermint) Meristem Cell Culture*

*Not reported to be in use.

The data needed to formulate a conclusion of safety include:

☐Composition data on each of the above ingredients.

- o Depending on the composition data that are received, other toxicological endpoints may be needed.

☐Skin irritation and sensitization data on all of the above ingredients, except Mentha Piperita (Peppermint) Leaf Extract and Mentha Piperita (Peppermint) Leaf Water.

However, it was determined that Mentha Piperita (Peppermint) Oil is safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing.

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

This group of ingredients was established at the April 2017 Expert Panel meeting, whereby the Panel agreed that the original final report (published in 2001) on Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint) Leaf Water should be reopened to add 6 Mentha piperita (peppermint)-derived ingredients. Therein, the Panel also issued an IDA relating to all 10 ingredients, and composition, irritation, and sensitization data were requested.

Data were received in response to the IDA. The Panel agreed that the available composition data on Mentha Piperita (Peppermint) Oil are sufficient, but the data relating to composition of the other ingredients, are inadequate. After considering the available skin irritation and sensitization data, the Panel determined that skin sensitization data on all ingredients, except for the Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, and Mentha Piperita (Peppermint) Leaf Water, are still insufficient.

The Panel considered the positive effects that were observed in female rats, and in male and female mice, dosed with pulegone (component of Mentha Piperita (Peppermint) Oil) in the 2011 National Toxicology Program (NTP) oral carcinogenicity study. However, the Panel did not express concern over these findings relative to pulegone as a component of Mentha Piperita (Peppermint) Oil in cosmetic products, based on the understanding that the cytotoxic dose-response relationship (renal and liver toxicity) that was associated with cancer development would not be relevant to pulegone exposure from a cosmetic product. The Panel also reconsidered the 1% concentration limit on pulegone in the published final report on Mentha piperita (peppermint)- derived ingredients that appears to have been based on observations of brain lesions in rats. As the brain lesions were an artifact of the fixation method, the Panel determined that this study was not relevant to cosmetic safety. It was therefore agreed, that the 1% concentration limit and the carcinogenicity of pulegone should be addressed in the report discussion and not in the conclusion.

Draft Amended Final Report, Teams/Panel: December 4-5, 2017

The following data were received in response to the insufficient data conclusion on 9 *Mentha piperita* (peppermint)-derived ingredients (listed above) that was announced at the September 2017 Panel Meeting: (1) Human 48-h occlusive patch test, evaluating skin irritation potential, on a lipstick product containing 0.2961% Mentha Piperita (Peppermint) Leaf Extract; (2) Composition, method of manufacturing, and physical properties data on Mentha Piperita (Peppermint) Leaf Extract, and (3) Updated use concentration data on *Mentha piperita* (peppermint)-derived ingredients. According to the updated use concentration data, use concentrations of Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract are no longer being reported and Mentha Piperita (Peppermint) Leaf Extract is being used at concentrations ranging from 0.3% to 0.5% in lipstick products. The Draft Amended Final Report has been revised to include these data.

Mentha piperita-derived Ingredients Data Profile for December 4th-5th, 2017 Panel – Wilbur Johnson

	Used in Cosmetics?	Safety Data Available?	Dermal Penetration: In Vivo -Animal	Dermal Penetration: In Vitro-Human	Dermal Penetration: In Vivo-Human	Nail Penetration: In Vitro-Human	Penetration Enhancement: In Vitro-Animal	ADME: In Vitro-Human Dermal	ADME: Animal-Dermal	ADME: Animal-Oral	ADME: Animal-IV	ADME: Human-Oral	Acute Toxicity: Animal-Dermal	Acute Toxicity: Animal-Oral	Acute Toxicity: Animal-Inhalation	Short-Term Toxicity: Animal	Sub-Chronic Toxicity: Animal	Chronic Toxicity: Animal	DART: In Vitro	DART: In Vivo	Genotoxicity: In Vitro	Carcinogenicity: In Vivo	Other Relevant Studies: In Vitro	Other Relevant Studies: In Vivo-Animal	Dermal Irritation*: Animal/Human/in vitro	Dermal Sensitization*/ Phototoxicity*: Animal	Dermal Sensitization*/ Phototoxicity*: Human	Ocular Irritation *: In Vitro	Ocular Irritation *: Animal/Human	Clinical Studies: Human-Dermal/Oral	Case Reports: Human-Dermal	Case Reports: Human-Oral	Epidemiology Studies: Human
Mentha Piperita (Peppermint) Oil	**X**	**X**	**X**				**X**					**X**		**X**		**X**	**X**			**X**	**X**	**X**	**X**		**X/X**	**0/X**	**X/0**			**X**	**X**		
Mentha Piperita (Peppermint) Leaf	**X**	**X**														**X**															**X**		
Mentha Piperita (Peppermint) Leaf Extract	**X**	**X**																					**X**		**X**						**X**		
Mentha Piperita (Peppermint) Leaf Water	**X**	**X**																							**0/X**		**X/0**		**0/X**				

X = data; 0 = no data*

[Mentha Piperita-derived Ingredients (5/16/2016; 2/5/2017; 7/31/2017; 10/23/2017]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
Mentha Piperita (Peppermint) Oil	8006-90-4 84082-70-2	1/1	164/14	164/11	165/11	1	0	0	0	0	0	0	0	0	0	0	0	
Mentha Piperita (Peppermint) Leaf Extract	84082-70-2	1./1	4/1	1/1	5/2	1	0	0	0	0	0	0	0	0	0	0	0	
Mentha Piperita (Peppermint) Leaf		1/1	197/19	10/3	34/4	1	0	0	0	0	0	0	0	0	0	0	0	
Mentha Piperita (Peppermint) Leaf Water	84082-70-2	1/1	1/1	2/1	4/1	1	0	0	0	0	0	0	0	0	0	0	0	
Mentha Piperita (Peppermint) Extract		1/1	0/1	0/69	0/207	1	0	0	0	0	0	0	0	0	0	0	0	
Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract		1/1	0/1	0/0	0/0	1	0	0	0	0	0	0	0	0	0	0	0	
Mentha Piperita (Peppermint) Flower/Leaf/Stem Water		1/1	0/0	0/0	0/0	0	0	0	0	0	0	0	0	0	0	0	0	
Mentha Piperita (Peppermint) Leaf Cell Extract		1/1	0/12	0/15	0/0	0	0	0	0	0	0	0	0	0	0	0	0	
Mentha Piperita (Peppermint) Leaf Juice		1/1	0/93	0/0	0/0	1	0	0	0	0	0	0	0	0	0	0	0	
Mentha Piperita (Peppermint) Meristem Cell Culture		1/1	0/1	0/0	0/0	0	0	0	0	0	0	0	0	0	0	0	0	

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]

[*identify total # of hits /# hits that were useful or examined for usefulness*]

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

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

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/

RIFM (the Research Institute for Fragrance Materials) should be contacted

Day 2 of the June 3-4, 1996 CIR Expert Panel Meeting

Peppermint Oil

Dr. Schroeter noted that an informal data request on Peppermint Oil was issued at the March 4-5, 1996 Panel meeting. With the exception of the RIFM (Research Institute For Fragrance Materials) monograph on Peppermint Oil that was received, there was no response to the informal data request that was issued. Thus, the Panel voted unanimously in favor of issuing an Insufficient Data Announcement on Peppermint Oil with the following data requests:

(1) Concentration of use
(2) UV absorption; if significantly absorbed in the UVA or UVB range, then a photosensitization study may be needed
(3) Rate of dermal absorption (of either peppermint oil or its principal component, menthol); if significantly absorbed, then a 28-day dermal toxicity study and reproductive and developmental toxicology data are needed
(4) Human dermal irritation and sensitization

The Panel also requested that the present review be expanded to include literature citations on menthol.

Day 2 of the December 16-17, 1996 CIR Expert Panel Meeting

Peppermint (*Mentha piperita*) Oil, Peppermint (*Mentha piperita*) Extract, and Peppermint (*Mentha piperita*) Leaves

Dr. Belsito noted that an Insufficient Data Announcement on this group of ingredients was issued at the June 3-4, 1996 Panel meeting. Also, in considering the data on menthol that were incorporated into the present report after this announcement was issued, the Belsito Team determined that the available data are still insufficient for evaluating the safety of these three ingredients. Dr. Belsito stated his Team's data needs as follows: (1) Concentration of use; (2) Impurities of cosmetic grade Peppermint Oil, specifically pulegone; or, in the absence of impurities data, (3) a 28-day dermal toxicity study on cosmetic grade Peppermint Oil.

Dr. Schroeter recalled that the potential need for 28-day dermal toxicity data is expressed in item #2 of the Insufficient Data Announcement as follows: Rate and extent of dermal absorption of Peppermint Oil or menthol; if there is significant skin penetration, then both a 28-day dermal toxicity study to assess general skin and systemic toxicity and a reproductive and developmental toxicity study are needed.

Drs. Shank and Schroeter noted that if the systemic toxicity resulting from the dermal route is the same (or less) compared to that resulting from oral exposure, then a dermal reproductive and developmental toxicity test will not be needed.

Dr. Klaassen wanted to know which toxic effects observed in oral studies were of concern.

Dr. Carlton noted that spongiform encephalopathy was observed in oral toxicity studies, and that the impurity pulegone was probably responsible for this finding.

Dr. Andersen brought to the Panel's attention that an oral reproductive and developmental toxicity study on menthol is included in the present report on Peppermint Oil. He noted that menthol is a significant component of Peppermint Oil.

Regarding the issue of exposure, especially regarding pulegone as a contaminant of Peppermint Oil, Dr. Bailey said that the Panel may want to consider more accurate skin penetration data relative to Peppermint Oil and/or the contaminant.

Dr. Andersen said that the Panel's concern about the safety of cosmetic grade Peppermint Oil seems to be based on the assumption that it may contain the impurity, pulegone. He also said that if pulegone is not detected in the impurities analysis, then there should be no concern about its absorption and, also, no need for a 28-day dermal toxicity study.

The Panel voted unanimously in favor of issuing a Tentative Report with an insufficient data conclusion. The data needed in order for the Panel to complete its safety assessment of Peppermint Oil, Peppermint Extract, and Peppermint Leaves are listed in the discussion section of the report as follows:

(1) Concentration of use
(2) Impurities (specifically pulegone) in cosmetic grade Peppermint (Mentha Piperita) Oil, Peppermint (Mentha Piperita) Extract, and Peppermint (Mentha Piperita) Leaves or in the absence of impurities data, a 28-day dermal toxicity study using cosmetic grade ingredients. (Note: If changes found following dermal exposure are the same as those reported in existing oral-dosing studies, then there will be no need for reproductive and developmental toxicity studies; if the results are not similar, then there may be a need for dermal reproductive and developmental toxicity studies.)

Day 2 of the June 5-6, 1997 CIR Expert Panel Meeting – Full Panel

Peppermint (Mentha Piperita) Oil
Peppermint (Mentha Piperita) Extract
Peppermint (Mentha Piperita) Leaves

Dr. Schroeter noted that the Panel issued a Tentative Report with an insufficient data conclusion at the December 16-17, 1996 Panel meeting. The data needed in order for the Panel to complete its safety assessment were stated as follows:

(1) Concentration of use
(2) Impurities (especially pulegone) in cosmetic grade Peppermint (Mentha Piperita) Oil, Peppermint (Mentha Piperita) Extract, and Peppermint (Mentha Piperita) Leaves or in the absence of impurities data, a 28-day dermal toxicity study using cosmetic grade ingredients. (Note: If changes found following dermal exposure are the same as those reported in existing oral-dosing studies, then there will be no need for reproductive and developmental toxicity studies; if the results are not similar, then there may be a need for dermal reproductive and develop-mental toxicity studies.)

Dr. Schroeter said that, in response to the Tentative Report, the Panel received impurities data on Peppermint Oil (pulegone detected at concentrations of 1 to 4%) and data indicating use concentrations of Peppermint Oil in the range of 0.02 to 3.0%. Dr. Schroeter noted that, based on the impurities analysis, his Team determined that pulegone is at a level that is not significantly toxic. Thus, the Schroeter Team concluded that Peppermint (Mentha Piperita) Oil, Peppermint (Mentha Piperita) Extract, and Peppermint (Mentha Piperita) Leaves are safe as used in cosmetics.

Dr. Bronaugh noted that the levels of the impurity, pulegone reported by industry fall within the range of the short-term oral toxicity on pages 15-16 of the Tentative Report. The Peppermint Oil sample tested contained 1.7% pulegone, and the no-effect-level for Peppermint Oil in this study was 10 mg/kg body weight.

Dr. Bronaugh also noted that FDA has done an exposure assessment based on some of the new data submitted on a body splash lotion containing 0.2% Peppermint Oil. He said that if one assumes whole-body application of the lotion and 100% absorption (since there are no absorption data on Peppermint Oil), approximately 1 mg of Peppermint Oil per day is absorbed. He also said that the use of a 100-fold safety factor reduces the 10 mg/kg no-effect-level to 0.1 mg/kg. Therefore, without knowing absorption, it is possible that as much as 1 mg of Peppermint Oil/kg will be absorbed if the body splash lotion is applied over the entire body. Dr. Bronaugh noted that there is some concern over the use of Peppermint Oil in cosmetics, not knowing the extent of its dermal absorption.

Dr. Bailey said that Dr. Bronaugh's comments become particularly relevant if one considers that the body splash lotion may be used on infants and children. Dr. Bailey reiterated that a no-effect-level has been determined,

and acknowledged that an extremely conservative exposure estimate was used in the calculation. However, he noted that even if one assumes 10% area and 50% absorption, the safety factor is 180. According to Dr. Bailey, this means that an area in which safety becomes more of a question is being approached. Furthermore, he said that this becomes even more relevant when infants and children are taken into consideration.

Dr. McEwen asked Dr. Bronaugh if, based on his calculation, 1 mg of Peppermint Oil would be applied to the body.

Dr. Bronaugh said that 1 mg of Peppermint Oil/kg would be absorbed per day (by a human) by applying the body splash lotion that reportedly contains 0.2% Peppermint Oil. He also said that 68 mg/day would be absorbed, and, if one divides this by a 60 kg person, this translates into 1.12 mg/kg/day absorption. This estimate assumes 2 mg/cm^2 application over the whole body.

Dr. Andersen wanted to know if the concerns expressed by Drs. Bailey and Bronaugh relate to Peppermint Oil or the pulegone component.

Dr. Bronaugh said that the theory is based on Peppermint Oil. However, he noted that Peppermint Oil tested in the study by Thorup et al., 1983a (pp.15-16 of Tentative Report) contains 1.7% pulegone.

Dr. McEwen said that it would probably be difficult, if not impossible, to apply a body splash at a concentration of 2 mg/cm^2.

Dr. Bronaugh said that 2 mg is approximately 2 μl, which is a small amount.

Dr. Schroeter said that it takes an ounce of content, 28 ml, to cover a total body (for an average adult, this is actually 1.7 m^2). With this in mind, he said that he is also concerned about the data.

Dr. Bergfeld said that the Panel has the option of tabling the Tentative Report on Peppermint Oil, placing it in Teams for further discussion.

The Panel voted unanimously in favor of tabling the Tentative Report until the September 22-23, 1997 Panel meeting.

Dr. Bergfeld asked the Panel to elaborate on additional information that would be needed to address Dr. Bronaugh's concerns regarding Peppermint Oil/pulegone exposure.

Dr. Schroeter said that the Panel needs to review the data on which FDA's calculations are based, as well as the actual calculations.

Dr. Bailey noted that the no-effect-level of 10 mg/kg/day for Peppermint Oil was taken from the Tentative Report. He added that an ADI of 0.1 mg/kg/day has been reported for Peppermint Oil.

Dr. Bailey stated that the Panel will be provided with a copy of FDA's calculations.

Dr. Bergfeld said that because the extent of percutaneous absorption of Peppermint Oil is not known, it would be appropriate for the Panel to informally request any available absorption studies on Peppermint Oil that have not been submitted to CIR.

Day 2 of the September 22-23, 1997 CIR Expert Panel Meeting

Peppermint (Mentha Piperita) Oil,
Peppermint (Mentha Piperita) Extract,
and Peppermint (Mentha Piperita) Leaves

At the June 5-6, 1997 Panel meeting, The Panel voted unanimously in favor of tabling the Tentative Report (insufficient data conclusion issued at December 1996 Panel meeting) on this group of ingredients until the September 22-23, 1997 Panel meeting. [Note: Prior to the June 5-6, 1997 review, the concentration of use and impurities data requested by the Panel were received.] This action resulted from statements made by Drs. Bailey and Bronaugh relating to the fact that FDA had done an exposure assessment of Peppermint Oil based on the

concentration of use data supplied by industry. In this assessment (made available for present meeting), a concentration of 0.2% (reported use concentration in a body splash) was selected, and 100% absorption was assumed per whole body application (2 mg/cm^2). This translated into the absorption of 34 mg Peppermint Oil/day (0.6 mg/kg/day exposure for a 60 kg person).

It was also noted in the exposure assessment that an acceptable daily intake (ADI) of 0.2 mg/kg body weight day for menthol (major constituent of Peppermint Oil) was derived by the Joint Expert Committee on Food Additives, and that the ADI calculated using the data in the CIR report on Peppermint Oil was 0.1 mg/kg body weight/day for this ingredient.

During deliberations at the present meeting, the Panel expressed concern over oral-dosing studies on Peppermint Oil in which cyst-like spaces in the cerebellum of rats were reported, and the difficulty in interpreting these study results (due to inconsistent findings when results were compared). Though the lesions appeared to depend on the pulegone content (a greater NOAEL [no observable adverse effects level] was reported in a 90-day oral toxicity study in which Peppermint Oil containing 1.1% pulegone was tested, compared to a 28-day oral toxicity study in which Peppermint Oil containing 1.7% pulegone was tested), no definitive conclusion could be made.

Given the results for Peppermint Oil containing pulegone in short-term and subchronic oral toxicity studies, Dr. Belsito recommended that pulegone, as an impurity, should be limited to a concentration of 1% in Peppermint Oil, Peppermint Extract, and Peppermint Leaves.

Dr. Bronaugh noted that the toxicity of menthol is similar to that of pulegone.

The Panel also expressed concern over menthol, major component of Peppermint Oil. In the absence of dermal absorption studies on Peppermint Oil, it was noted that its absorption is expected to be rapid, like menthol. Furthermore, there was concern that this rapid rate of absorption may induce systemic toxicity that was not observed following oral exposure. Thus, the Panel decided to limit the cosmetic use of Peppermint Oil and other ingredients in this review such that the menthol content would not exceed the ADI (0.2 mg/kg/day for menthol) that was established by the World Health Organization.

The Panel agreed that the inconsistencies between results from short-term and subchronic oral toxicity studies on Peppermint Oil should be addressed in the report discussion, along with the Panel's basis for using the ADI for menthol in its safety assessment.

The Panel voted unanimously in favor of issuing a Revised Tentative Report with the following conclusion: On the basis of the available data, the CIR Expert Panel concludes that Peppermint (Mentha Piperita) Oil, Peppermint (Mentha Piperita) Extract, and Peppermint (Mentha Piperita) Leaves are safe for use in cosmetic formulations at levels such that the menthol content does not exceed the ADI of 0.2 mg/kg/day. The pulegone level should not exceed 1% in these ingredients.

Day 2 of the March 19-20, 1998 CIR Expert Panel Meeting

Peppermint (Mentha Piperita) Oil,
Peppermint (Mentha Piperita) Extract,
and Peppermint (Mentha Piperita) Leaves

Dr. Schroeter said that questions relating to the menthol component of Peppermint Oil remain. One of the questions raised by the Panel related to whether it would be logical to make an exception in the conclusion regarding the concentration of menthol, that it not exceed the ADI (average daily intake) of 0.2 mg/kg/day. Dr. Schroeter noted that his Team determined that there is no need for any specific limitation on menthol in either the report discussion or conclusion. He said that the issue of the dermal absorption of menthol may be managed by explaining in the discussion that the amount of menthol that may be absorbed through the skin is safe, if compared to the same amount in Peppermint Oil that is absorbed from the gastrointestinal tract, which is already considered a safe amount.

Based on the preceding comments, Dr. Schroeter said that the statement in the report discussion that mentions the ADI of 0.2 mg/kg/day for menthol will be replaced with statements based on the following: The dermal absorption of menthol will be no greater than that of oral Peppermint Oil. The clinical data will provide adequate evidence of safety at current concentrations of use [that is, since oral data are adequate for demonstrating that menthol is equal to or not greater than that absorbed through the skin].

Dr. Bailey wanted to know if clinical data (ingestion data) obviate the need for dermal absorption data.

Dr. Shank said that for systemic toxicity, the oral data are sufficient, because it is believed that the extent of absorption through the skin would not be any greater than the absorption through the GI tract and that the "first pass" consideration is not important. He noted that "first pass" effects were considered, and it was determined that the available data are sufficient. Dr. Shank also said that as far as skin effects are concerned, clinical data support the safety of current concentrations of use.

Dr. Bergfeld confirmed with Dr. Schroeter that the substance of Dr. Shank's explanation will be included in the report discussion.

Dr. Schroeter said that Dr. Shank's explanation is logical, and, therefore, does not limit the concentration.

Dr. McEwen said that it is not that "first pass" kinetics are not the primary argument, but, taking this into consideration, there was a sufficient justification for considering the oral doses administered and assuming that the clinical epidermal doses would not sufficiently increase systemic toxicity.

Dr. Andersen recalled that at the last Panel meeting, FDA expressed concern over a calculation that compared the reported concentrations of menthol that could be present in levels of Peppermint Oil that were actually reported to be used. He said that based on that combination of the concentration of Peppermint Oil and the concentration of menthol in it, it was concluded that those levels approached the reported toxicity that was actually included in the CIR report. Dr. Andersen asked FDA for further comments.

Dr. Bronaugh said that because a limitation on the concentration of pulegone is included in the report discussion, one would think that this is adequate.

Dr. Bergfeld said that the revisions in both the report discussion and conclusion need to be discussed and that the Panel needs to vote on the new conclusion. She also said that the Panel needs to discuss the merit of the conclusion and determine whether the present report needs to be reissued as a Tentative Report.

Dr. Bergfeld asked if there was any further discussion regarding the current revised conclusion and the editorial changes in the report discussion that are being considered. Seeing that there was no further discussion, she called for the vote.

The old conclusion that is being revised reads as follows: On the basis of the available data, the CIR Expert Panel concludes that Peppermint (Mentha Piperita) Oil, Peppermint (Mentha Piperita) Extract, Peppermint (Mentha Piperita) Leaves, and Peppermint (Mentha Piperita) Water are safe for use in cosmetic formulations at levels such that the menthol content does not exceed the ADI of 0.2 mg/kg/day. The Pulegone level should not exceed 1% in these ingredients.

The Panel voted unanimously in favor of issuing a Revised Tentative Report with the following revised conclusion: On the basis of the available data, the CIR Expert Panel concludes that Peppermint (Mentha Piperita) Oil, Peppermint (Mentha Piperita) Extract, Peppermint (Mentha Piperita) Leaves, and Peppermint (Mentha Piperita) Water are safe as used in cosmetic formulations. The concentration of pulegone in these ingredients should not exceed 1%.

Day 2 of the September 10-11, 1998 CIR Expert Panel Meeting

Peppermint (Mentha Piperita) Oil,
Peppermint (Mentha Piperita) Extract,
and Peppermint (Mentha Piperita) Leaves

Dr. Schroeter stated that his Team concluded that these ingredients are safe as used in cosmetic formulations, and that the concentration of pulegone in each should not exceed 1.0%. The restriction on pulegone is based on the sensitization potential of this impurity.

Additionally, Dr. Schroeter noted that the percutaneous absorption of other chemicals is enhanced in the presence of Peppermint Oil, and that this issue should be addressed in the report discussion. He suggested that the

statement addressing this issue in the CIR report on Peanut Oil should be incorporated into the report on Peppermint Oil.

Dr. Belsito read the following statement from the report on Peanut Oil, relating it to Peppermint Oil: The Panel noted the evidence that Peppermint Oil can enhance penetration. Formulators are cautioned that this enhanced penetration can affect the use of other ingredients whose safety assessment was based on their lack of absorption.

Dr. Bergfeld recommended inclusion of the preceding statement, with any necessary modifications, in the Peppermint Oil report discussion.

Dr. Belsito recommended that it be clarified in the last sentence of the report discussion that use of Peppermint Oil at a concentration of ≤ 3% in rinse-off formulations and ≤ 0.2% in leave-on formulations, coupled with the restriction of pulegone to ≤ 1%, alleviates the Panel's concern about pulegone toxicity.

The Panel voted unanimously in favor of issuing a Final Report with the following conclusion: On the basis of the available data, the CIR Expert Panel concludes that Peppermint (Mentha Piperita) Oil, Peppermint (Mentha Piperita) Extract, Peppermint (Mentha Piperita) Leaves, and Peppermint (Mentha Piperita) Water are safe as used in cosmetic formulations. The concentration of pulegone in these ingredients should not exceed 1%.

Day 1 of the April 10-11, 2017 CIR Expert Panel Meeting – Dr. Belsito's Team

DR. BELSITO: Okay, peppermint. Were previously reviewed in 2001 for ingredients safe as used in the concentration of pulegone in these ingredients shouldn't exceed 1 percent. So, we, basically, agreed that the assessment was primarily based off of peppermint oil; that the data was considered relevant to the other reports with some new available data on leaf extract, leaf water were added, as well as NNTP data on culergon and then it was really reopened because six ingredients were proposed for addition to the family, and that's what we're looking at today; and then there was a wave 2 submission on 20 percent peppermint oil in a HRIPT that was pretty good.

DR. SNYDER: 50 percent leaf water.

MR. JOHNSON: By the way, we received those from RIFM.

DR. BELSITO: Yeah. So, the oil I think is okay, but we never really got constituents for the other parts of the plant, so I had a question about whether we need repro and gentox for the leaf; or do we at least need --

DR. LIEBLER: You feel we should reopen?

DR. BELSITO: What?

DR. LIEBLER: You feel we should reopen, right?

DR. BELSITO: If we want to add those ingredients. I don't think we can add the other ingredients without reopening and getting some data.

DR. LIEBLER: I just thought we hadn't taken a

(inaudible). I figure reopening as well to add the new ingredients.

DR. BELSITO: Was that the question at this point?

DR. KLAASSEN: Yeah.

DR. BELSITO: It was, okay. So, we can add the new -- it's not a no-brainer.

DR. ANSELL: Well, this is a re-review; so, there are some new ingredients that are proposed, but there're issues with -- for whatever reason you want to use

(inaudible).

DR. LIEBLER: There almost always some data needs when we reopen for new ingredients anyway; so, I mean, I didn't think this was unreasonable. Maybe no-brainer is not the right term to use.

DR. SNYDER: Well, I thought there was some language related to our -- maybe our initial reasoning for using the oil for the safety of all the leaf stuff was flawed. Wasn't that in here? Didn't we have some language in here about that because there's (inaudible).

MR. JOHNSON: I know with respect to the initial review, the oil was classified as the worst case scenario.

DR. SNYDER: Right; was the basis for the safety of everything.

MR. JOHNSON: Right.

DR. ANSELL: And has now been -- the definition has been revised to be explicit that the oil is the whole plant.

DR. BELSITO: But then when you look on page 18 of the PDF -- it's the major constituents of peppermint oil, terpenes and menthols, yada-yada-yada; and then you get to the leaf extract and it's flavons and flavanones and rosmarinic acid -- these seem to be very different chemicals coming out of different parts of the plant; and then this toxic compound, pennyroyal, in the leaf.

DR. SNYDER: The young leaf.

DR. BELSITO: What?

DR. SNYDER: The young leaf; yeah, you've got to watch out for those young ones.

DR. BELSITO: But, you know, would lead me to believe that, you know, what we're getting out of the -- I didn't pick up the peppermint as the whole plant -- but, if peppermint oil is very different from leaf water and other isolated parts of the plant from which we never had data.

DR. LIEBLER: I think the pennyroyal is the pulegone.

MR. JOHNSON: I checked that publication. As a matter of fact, we received a comment from (inaudible) today, and pennyroyal is basically another species of peppermint plant;

so, really, there's no component of pennyroyal that's a little toxic.

DR. SNYDER: The way you word it and you say the leaf contains a toxic compound, pennyroyal.

MR. JOHNSON: Right; and that's what was stated in the publication, the primary source, but we found that was not correct.

DR. SNYDER: All right; we need to find out what that is.

MR. JOHNSON: That's another peppermint plant.

DR. LIEBLER: Mentha Pulegium, (European) pennyroyal.

DR. SNYDER: The monoturpi?

DR. LIEBLER: No; the plant, Mentha Pulegium.

DR. KLAASSEN: Can't get out of these plants.

DR. LIEBLER: But I know -- I remember because one of our late colleagues getting, Sid Nelson, did all of the really definitive magnistic tox work on pulegone; and I remember how many of the publications talked about, you know, a constituent in pennyroyal oil as being the source of the pulegone that they studied. Anyway, the pennyroyal that they're referring to in this context here, it sounds like they're probably talking about pulegone.

DR. SNYDER: (Inaudible) we already put a limit on it, so.

DR. LIEBLER: And it damages the liver.

DR. SNYDER: Well, I think we need to go with composition for all these conditional ingredients to see if there's any significant differences.

DR. LIEBLER: That was my need too, composition, method of manufacturing impurities.

DR. SNYDER: Yep.

MR. JOHNSON: And that's on all of the ingredients that we're going to be adding --

DR. SNYDER: All the new ingredients.

MR. JOHNSON: New ingredients, right?

DR. BELSITO: So, the oil is okay.

DR. SNYDER: Yeah; I think so.

DR. BELSITO: We're fine with that. So, we want --

DR. ANSELL: I think if you reopen and fill their data needs for the existing materials that's okay; but if you have data needs on the new materials, then they should not be added to this report, and it shouldn't be done through reopening.

DR. BELSITO: Well, that was my question; but I thought some of these materials were in the original report. I'm wondering how we signed off on it.

DR. SNYDER: Well, that's why I was making a comment because we -- the 2001 report is for the oil, the leaf, the leaf extract, and the leaf water.

DR. BELSITO: Right.

DR. SNYDER: So, we used the oil as the margin for everything which was flawed.

DR. BELSITO: Which was so different than what we did; because we hung up rice for three years over the constituents of brand or something. I mean, I think it must have been an impending snowstorm or -- what year was this, 2001? It was 9/11.

DR. SNYDER: 9/11.

DR. LIEBLER: You know, if you've got the oil and the leaf, and the leaf extract already in previous reports, and then you're adding a peppermint extract, which is probably whole plant -- Jay just confirmed for us, I think, if I'm not mistaken --

DR. ANSELL: Yeah.

DR. LIEBLER: -- and then a flower leaf stem extract and a flower leaf stem water, and a leaf cell extract, and a leaf juice, those are all typical of things that are similar enough to what's already been covered that I think we could probably -- if we get (inaudible) --

DR. BELSITO: Well, quite honestly, when I read it, I didn't know why we went safe with this because I didn't think there was data that convinced me that the leaf was the same as the oil. I mean, so that's why I thought we needed to reopen because I'm not even certain that the conclusion we made is the correct one.

DR. LIEBLER: Wasn't this the one where Ron Shank, basically, it was the

Shank Approximation, or whatever we called it -- the Shank Doctrine -- that the oil represented a worst case scenario because it was most enriched with respect to the constituents concerns?

DR. BELSITO: But, when you look at what we're seeing in this report which is some material that we didn't have before, the constituents in the leaf, particularly the leaf water; I mean, now, we're actually talking about waters and oils which are, obviously, going to contain different things are quite different. I mean, I think we need to reopen to clearly look at --

DR. SNYDER: It's a sensitizer.

DR. BELSITO: -- yeah, I think we need to reopen it simply to look at was our original conclusion correct, and during that process I think we can add everything else in.

DR. LIEBLER: So, basically, we're on the same page. I agree we should reopen it. We should add the new ingredients. We do have some data needs for a composition, method of manufacturing impurities. I think, I don't really have any doubt that we can get there for most or all of these ingredients to get sufficient data to draw our conclusions. And the main question I had has to do with having, in the previous conclusion, a 1 percent limit, I think, on the pulegone; and I'm wondering if -- you know, given the way we do things now -- if that's the way we would handle the pulegone issue now or whether we should consider like a QRA approach rather than speaking in numbers?

DR. BELSITO: Well, particularly, in light of the fact that we know that other botanicals contain pulegone and we're restricting those into restricteds, it's the same thing as sensitization. To say that we're going to limit eugenol in this plant based upon the highest level eugenol can be used in, and then, you know, it's supplied and mixed with another botanical that contains eugenol, and suddenly you're passed the standards.

DR. LIEBLER: Yeah. I just think that 1 percent

(inaudible) reflect in a way that the panel can reason through this problem several years ago, but it isn't really applicable the way we handle this certain thing now.

DR. BELSITO: I think it was the first time we dealt with pulegone, and didn't realize it'd be popping up in a lot of other botanical species. I don't know why; but it has; because, I mean, I think now we simply say, you know, chemicals of concern not reaching toxic levels.

DR. KLAASSEN: But how could it be toxic? It's a natural chemical.

(Laughter)

DR. LIEBLER: Revise the minutes -- insert laugh here.

DR. BELSITO: The oil is okay, and we want manufacture and impurities for the other constituents; and if significantly different from the oil; then what?

DR. ANSELL: Then they aren't added.

DR. BELSITO: But they're already in the report, Jay, the original report.

DR. ANSELL: Right. The original one; but if the residuals of the --

DR. BELSITO: If we don't get them or they're significantly different, then I'm not going to be comfortable, you know, saying that the original conclusion was correct and would reopen it to amend the conclusion.

DR. HELDRETH: Yeah; I think our traditional no- brainer rule was to alleviate the burden of just adding things in and making a case more difficult. So, just reopening and having no reason but to add these ingredients, and they're not no-brainers, I can see doing it; but since there seems to be a cause to relook at the ingredients that are already in the report, I don't think the no-brainer clause (inaudible).

DR. BELSITO: No; that's what I'm saying. The other ingredients really belong in here if our conclusion is correct. They don't really differ; that would be a no- brainer; but I'm wondering if our original conclusion was correct and would like to reopen it to get a look at that data.

DR. ANSELL: Right; I absolutely agree with that. It's the part with the add-ons, that if they're significantly different, the answer is not to develop a whole other report to support them; it's that they don't belong in this report.

DR. BELSITO: Right.

DR. LIEBLER: I think the no-brainer thinking works with a series of structures where you've got an extra methylene or ethyl, you know, something like that. Here, with botanicals, it's a different world, different rules; there are no botanical no-brainers.

DR. SNYDER: So, on the use table, Wilbur, under Table 3, so under the peppermint oil, the range we have at the bottom is --

MR. JOHNSON: There's a mistake in there. It should be at 40 percent of leaf water and not, I think, 0.1, yeah. That would be correct.

DR. SNYDER: Okay; because the leaf water -- it says up to 15 percent for dermal, which is quite a bit higher than

percent of the oil, but, okay. So, that's going to be even higher? It's going to be 40 percent?

MR. JOHNSON: Yes; mm-hmm.

DR. SNYDER: Okay. Yes, we had use concentrations that are much higher for the other constituents than

(inaudible).

DR. BELSITO: And then I have a question as to whether we need reproductive and genotoxicity for the leaf; because that would only be if they significantly differ.

DR. SNYDER: Well, I think the first step would be absorption; you know, we need absorption data or a 28-day dermal; and then if it's absorbed, or there's absorption in the 28-day dermal, then we go to (inaudible).

DR. BELSITO: Okay; so, the oil is okay; we need manufacturing impurities and composition for the other constituents; if significantly different, then other data needs would be absorption and 28-day dermal -- and if absorbed, and genotox.

DR. SNYDER: I guess that would be based on our compositions if there's something in there that we have some structure we'd be worried about.

DR. LIEBLER: Well, I think we need genotox anyway.

DR. SNYDER: Okay.

DR. LIEBLER: There are enough interesting organics in this so that --

DR. SNYDER: Yeah.

DR. BELSITO: Okay. Since it takes me forever to talk, the other ingredients are the leaf, the flower --

DR. SNYDER: Flower, leaf, and stem extract?

DR. BELSITO: Leaf, flower, stem, right; so, on the meristem?

DR. SNYDER: Okay.

DR. BELSITO: Okay; so, the other ingredients are they the leaf, the flower, the stem, and the meristem?

DR. SNYDER: Okay; so, now sensitization.

DR. BELSITO: Yeah. I think we're okay with sensitization, now. We waved two.

DR. SNYDER: I thought that was at 20 percent; there's no waive; yeah, that was 20 and 50 percent, but wasn't there one at 22 percent? Or am I thinking of a previous report. I thought I saw one here that was.

MR. JOHNSON: Yeah; there was a 48-hour single application patch test on the cleansing gel -- 50 percent.

DR. BELSITO: (Inaudible)

DR. SNYDER: That was negative, though; leaf water, percent gel?

MR. JOHNSON: Well, there was mild erythema in one subject.

DR. BELSITO: Peppermint leaf water is being used up to 15 percent in (inaudible). It's a concentration; and what page are we on here; because I have nothing about sensitization -- on irritation sensitization; leaf water, negative skin irritation sensitization data on a product containing leaf water in Table 4.

DR. SNYDER: Because there was this case report -- there are several case reports -- at.2 percent.

DR. BELSITO: Yeah, but those are patch tests.

DR. SNYDER: Tests; you're right; okay.

DR. BELSITO: People are already sensitized.

DR. SNYDER: Yeah.

DR. BELSITO: Okay; anything else?

MR. JOHNSON: What are the concerns, skin penetration enhancement?

DR. BELSITO: Yeah; I have that in my discussion. There's going to be a pulegone restriction; a botanical boilerplate, depending upon what we find out about this pennyroyal.

DR. SNYDER: Aerosol.

DR. BELSITO: There are lots of terpenes, so formulated to be non-sensitizing; add penetration enhancement to the discussion. So, those will be the big things so far. The botanical boilerplate, the inhalation and penetration enhancement in the discussion; and then, well, obviously, I have to see the other data that we asked for.

MR. JOHNSON: For the genotoxicity data request, did you want bacterial and mammalian cells, or --

DR. SNYDER: Yes.

MR. JOHNSON: -- both?

DR. BELSITO: And then, the last point I had -- I knew there was something else -- we have an ingredient with no concentrations. This is on page 34; it's just labelled peppermint. There's no definition in the dictionary; there are no reported VCR uses in 2017. There were two -- I'm not sure why that's there. VCRP has no reports; we have no reported concentration; and there was no definition in the dictionary as to what peppermint is. So, why is that in the table?

MR. JOHNSON: I think it was in the published report, peppermint.

DR. BELSITO: But can we get rid of it in the current reports?

MR. JOHNSON: We can.

DR. BELSITO: And say it's not a cosmetic ingredient and no one's saying that they're using it.

DR. HELDRETH: Did it change names or just get deleted?

DR. BELSITO: What?

MR. JOHNSON: It was just there.

DR. HELDRETH: Okay. I was just asking if it changed names or was it simply deleted.

MR. JOHNSON: It was in the old database, but it's not in the current one; so, I guess that's what happened.

DR. BELSITO: And then I guess the only other question I had since we're going through everything is so that this irritation with the peppermint leaf, water at 50 percent in a cleansing gel when the highest reported use we have is 15 percent in a wash-off; so, I was (a) confused about that and, you know, again, it's a cleansing gel, it's a surfactant, it's going to be irritating; but I just wanted to pose the question, do we think we need to say formulated to be non-irritating? I didn't think so, but that data is there.

MR. JOHNSON: I'm sorry, I had made a mistake in the table; actually, the mentha piperita peppermint leaf water is used in face and neck products, not spray products at concentrations up to 40 percent.

DR. BELSITO: So, it's used in leave-on products up to 40 percent?

MR. JOHNSON: That's correct.

DR. BELSITO: Okay; can you tell me where in the table that is?

MR. JOHNSON: Well, actually, it's not in the table. That table needs to be corrected; but if you go to page 60, PDF, page 60, in that table they use concentration data.

DR. BELSITO: 40 percent for the leaf water; face and neck products, not spray; okay. So, it's used in leave- ons up to 40 percent.

MR. JOHNSON: Right.

DR. BELSITO: So, then we have this data on the bath gel at 50 percent that's irritating; so, then, the question becomes, do we need a -- if and when we get around to say --

DR. SNYDER: Not the irritation (inaudible); okay.

DR. BELSITO: -- I mean, I think the irritation is probably more from the gel. Okay.

DR. SNYDER: Did we change the tables? Did the totals used to be at the bottom instead of the top?

MR. JOHNSON: Not on this.

DR. SNYDER: Is that common to all documents? I thought they were always

at the bottom.

MR. JOHNSON: It used to be, but years ago; but it was changed, though.

DR. SNYDER: Because I kept getting confused. I always go to the bottom to see what the ranges are, and then go up; and this -- it was like you supposed to start at the top.

DR. LIEBLER: Is it writer dependent?

DR. SNYDER: That's what I'm asking because I thought we still had some at the bottom.

MR. JOHNSON: I think I was the last holdout on that.

MS. BURNETT: Yeah, they supposed to be at the top.

DR. SNYDER: So, I'm not going crazy. It used to be at the bottom, but we changed it at the top.

DR. LIEBLER: You are crazy.

DR. SNYDER: I am crazy; that's all right.

DR. BELSITO: Okay; anything else on peppermint? Okay.

Next is peppermint. Wilbur, you're up again. Let me see. Also known as menthe piperita I guess is how you pronounce the botanical name. And it is, so, in the expert panel previously had reviewed the oil, the leaf extract, the leaf, and the leaf water. And the conclusion was that these were safe as long as the concentration of pulegone. Am I saying that correct? Should not exceed 1%. This is a re-review of these ingredients. So one of the questions was do we add six more ingredients to the four ingredients which were found to be safe. So, I guess the first question would be, Tom, and Ron, and Ron, should we re- open this? Yes or no? And if we do re-open, do we add the six ingredients? And then lastly, what are the needs if we do that? So, first question, re-open or not?

DR. SHANK: Yes.

DR. MARKS: Okay. Move to re-open. Add the six ingredients?

DR. SHANK: No. Just two. I think we can add the leaf cell extract and the leaf juice. Because these are covered by the leaf extract data. Now, leaf water was tested for skin sensitization at 20%. Apparently it's used up to 40% in face and neck products. So we would require more data for that. And then we don't have any data for flowered leaf stem extract and water. Mera stem cell culture extract. So I wouldn't add those.

DR. MARKS: So, yeah, one of the questions. So that would be one approach. And that's sort of the re-open no- brainer. Or do we add the six ingredients and then issue an insufficient data announcement? And I wanted to get as much as possible info on the six additional ingredients. But Ron and Tom, which approach do you prefer? Do you want to just add the two? As no-brainers?

DR. SLAGA: Yes. It's obviously re-open and add the two because that, leave it with the same conclusion.

DR. HILL: Which two are we adding then?

DR. SHANK: Leaf cell extract and leaf juice.

DR. HILL: Okay. But not leaf extract per say?

DR. MARKS: We have the leaf extract on the original. Approved. Yes.

DR. HILL: Okay. And we don't think we need sensitization on that? Or do we have it formulated to be not sensitizing clause?

DR. MARKS: I have, well

DR. HILL: And I was also wondering about phototox, or photosensitization at least.

DR. MARKS: I have that irritation and sensitization is okay for the oil and leaf water. Let me see my notes here. In wave two. Yeah, we have the oil at 20% as you mentioned.

DR. HILL: So if we got oil at 20% then we feel good about the leaf extract?

DR. SHANK: It's not oil, it's water.

DR. MARKS: No. Yeah, the leaf water. We have an HRIPT at 20%. And the question is, can you carry that over to the other leaf ingredients?

DR. HILL: No. Because if you remember how these leaf waters are made, you don't get much. I don't know if we have full method of manufacture.

DR. MARKS: Then we'd be going back to the original report, of course. Because we approved it before as safe for the leaf extract and the leaf water. And the only thing we had was the sensitization for the leaf water. If I interpret the data correctly.

DR. HILL: That's a good reason to re-open for me.

DR. MARKS: Okay. I agree. So, re-open. At least at this point, add two ingredients, the leaf cell extract and leaf juice. So noted that you would want more sensitization data, particularly on the leaf extract. One presumes if we got the leaf extract. Now the question is, seems like if we want more data, we should do an insufficient data announcement. But

DR. SHANK: Then you can add them all.

DR. MARKS: Exactly. That's where I began, with adding all six and get as much possible on the six additional ingredients. Plus, I'm gonna put, Ron Hill, based on your comments, I think, six additional ingredients and leaf extract. Even though it was in the original report found to be safe. Sensitization. Does that? One of the things that I wanted to hear comments about, the cancer hepatatoxic and nephrotoxic issues that Wilbur brought up in his memo. That's

the second paragraph of his March 17th memo, where he says leaf extract hepatoxicity, the leaf nephrotoxicity, and then obviously, I presume, we'll put the same limitation on pulegone in this one. But the hepatoxicity and nephrotoxicity. Wilbur, do you want to clarify that in your memo?

MR. JOHNSON: Which memo are you talking about?

DR. MARKS: I'm looking at the March 17th memo. So the one that, and then I'm looking at the second paragraph, towards the end of that paragraph. The re-review document contains the following data for the panel's consideration. And then you put leaf extract and in there you have skin penetration enhancement, hepatoxicity. And then under the peppermint, next you say the leaf. And you have in parentheses nephrotoxicity. So it's hard for me to ignore your memo and say we can't address those two.

MR. JOHNSON: Yeah, those data are included in the safety assessment.

DR. MARKS: Yeah, so they're fine. Yeah, okay. So the way the memo read, I was concerned was there nephro and hepatoxicity. Okay. And I assume we're going to need the botanical and pesticide heavy metal boilerplates once we get to the final document. So, tomorrow I'm going to move to re- open, add the six new ingredients, and we will have a insufficient data announcement to get as much as possible information on the six additional ingredients. And particularly the leaf extract sensitization. But, you know, if we do the way we do the other botanicals, we're gonna in the end say, formulate to be non-irritating and non-sensitizing. Maybe we can move on to that now. But I like the idea of an insufficient data announcement. Tom, Ron, Ron, what do you think? We'll see how it plays out tomorrow. But, does that sound reasonable now? I know you, Ron Shank, were gonna move right to the leafs were gonna be safe.

DR. SHANK: Well, I'll go with insufficient.

DR. MARKS: Okay. Let's see where it goes. Any other? Wilbur.

MR. JOHNSON: Just a correction for Table 3. The leaf water is used in concentrations up to 40% in leave-on products. So the table will be corrected.

DR. MARKS: Up to 40%?

MR. JOHNSON: It's up to 40%. Yes.

DR. MARKS: So that's twice as much as we have the HRIPT. I'm glad we're getting as much possible. Not only on the six additional, but on the ones already reviewed. On all the ingredients now. So 40% of the peppermint leaf water.

MR. JOHNSON: Right.

DR. MARKS: Is the number of uses, 15, still the same?

MR. JOHNSON: Yes. This just relates to use concentration, data provided by industry.

DR. MARKS: Right.

MR. JOHNSON: So those uses will be the same.

DR. MARKS: Good.

MR. JOHNSON: Dr. Marks, will you just indicate the data needs associated with the IDA?

DR. MARKS: Well clearly, sensitization.

DR. SLAGA: Irritation.

DR. MARKS: Yeah, irritation, sensitization. Do we need anything other than that? Tom? Ron? Ron?

DR. HILL: I wanted to query Ron Shank specifically. Because I was reading the comments in the memo originally. And the issue was the validity of the oral safety studies. I guess it would be the peppermint oil that I was most interested in. Because there was discussion about absorption from the GI tract versus systemic circulation penetration. And I'm always thinking in terms of, first pass effect, which you specifically mentioned, because that was raised by Dr. Schroeter I believe at the time. And Dr. Bailey was in on that discussion. So, your response was something to the effect that, first pass was taken into account. But I wondered how that was even done, if you weren't looking for specific amounts absorbed. Or maybe they were.

DR. SHANK: So where is this?

DR. HILL: The discussion is on page 12 and 13, way back when, let's see where you were quoted. You were quoted on page 14 actually, near the top.

DR. MARKS: Ron Shank was?

DR. HILL: Yes. That's why I'm asking. The substance of Dr. Shank's

explanation will be included in the report discussion, which I guess there was something in there. Right now, if we're going insufficient, I want to just leave that hanging, unless you want to respond. For closer scrutiny. And the reason I'm bringing it up in part is because when you give a subchronic tox, you're giving relatively lower doses. So if you do acute, you give a high dose in general in the dose ranging. You give a high dose and you're saturating everything in sight, like efflux transporters and metabolizing enzymes and liver and so forth. But longer, slower studies, lower percentages in diet for example, orally, in rodents in particular, which are pretty aggressive first pass metabolizers. I'm not sure we're picking everything up. In that context, if you had the oil in a leave-on at 5%, given the mode of use. I mean, I know we've done in the past a conservative estimate, this percentage of the body is exposed this often to this particular chemical heavily. I mean, I eat peppermint with reckless abandon. I remember smearing the leaf juice on my body numerous times as a kid.

DR. BERGFELD: You're going to die.

DR. HILL: Am I? Well yes, I'm likely going to die.

(laughter)

DR. SHANK: I'd have to go back. That's 19 years ago.

(laughter)

DR. SHANK: Out of context, so

DR. MARKS: Out of context, I like it. So, well this is going to go, tomorrow we're going at least, no matter what the final will of the expert panel is, we're going to be seeing it again. So I'll let Ron Hill, your short term memory will bring it up again. And Ron, your long term memory will clarify it. So tomorrow I'm going to move to re-open, add the six new ingredients, and we'll issue an insufficient data notice to get irritation, sensitization on the six additional ingredients, and from the original report, leaf water. It's now being used at 40% with an HRIPT which is negative at 20%. So we don't have sensitization data at the present use concentration of leaf water. And then also leaf extract, which we have no sensitization data on. And Ron Hill, I agree, that's an important point. Does that sound good?

MR. JOHNSON: Just one more thing, Dr. Marks.

DR. MARKS: Uh oh, Wilbur. That could generate another ten minutes of discussion.

MR. JOHNSON: On page 23, are there any concerns relating to genotoxicity?

DR. MARKS: Tom?

DR. SLAGA: I don't have any.

MR. JOHNSON: Is that positive results?

DR. SLAGA: Well they're both positive and negative.

DR. MARKS: So, this is looking at a potential amended Safety Assessment of mentha peperita. That is peppermint. The ingredients are derived ingredients. So this is a re-review. In 2001, the peppermint oil leaf extract, leaf and leaf water, were evaluated. And a conclusion indicated that these were safe. But limit the concentration of pulegone in these ingredients should not exceed one percent. Our team moves that we re-open this group of ingredients and that we add six new ingredients. We would put out an insufficient data notice to get irritation and sensitization on the six additional ingredients. And the leaf water, which was in the original report, 40 percent use we have now. HRIPT in the previous report was 20 percent. So I'd like to see something closer to the present use concentration. And then also, the leaf extract in the original report. So, re-open. Add the six ingredients. Insufficient data notice for irritation and sensitization.

DR. BERGFELD: Belsito. Comment.

DR. BELSITO: Yeah. We agree with re-opening. We had an interesting discussion, because we didn't think it was a no brainer to open the -- to add the additional ingredients. However, I felt that we really didn't have sufficient data on parts of the plant in the prior report, to say that they were safe. And so I wanted to re-open it to take a look at whether we were correct with the original Safety Assessment. And in that regard, had no problems with adding all of the other ingredients in re-opening.

DR. MARKS: Yeah. And the only other comment, I agree obviously Don, with what you said. And we'll address that at the next time. But, in the 2001 report, the pulegone was not to exceed one percent, partly based on a maximum leave on concentration of 0.2 percent in the original report. Now the oil concentration is five percent.

DR. BELSITO: Yeah.

DR. MARKS: So now, we have issues with that.

DR. BERGFELD: So, basically, we'll re-open and send out an insufficient data announcement, adding all these things about the six new ingredients. A review of the old ingredient. Anything else?

DR. LIEBLER: Just to clarify, for the new ingredients, in particular the method of manufacture --

DR. MARKS: Mm-hmm.

DR. LIEBLER: -- composition and impurities.

DR. BELSITO: Yes.

DR. BERGFELD: Okay.

DR. SNYDER: That also goes to the old report.

DR. BERGFELD: Yes.

DR. SNYDER: Because we have a lot more experience now with how to deal with botanicals. And so bring it up for botanical standards I think.

DR. BERGFELD: Any other additions to the request? Seeing none, we'll move on then and make that insufficient data announcement.

DR. BELSITO: Tom, you had a comment?

MR. JOHNSON: Vote. Do we have to vote?

DR. BERGFELD: I don't think on the re-reviews.

MR. JOHNSON: So the data request is on all of the ingredients except for the oil, is that correct?

DR. BELSITO: No.

DR. MARKS: No.

DR. BELSITO: We need new data on the oil because of the increased concentration of use. Right Jim?

DR. MARKS: Yes.

DR. BELSITO: Data on everything they've got.

DR. BERGFELD: Yeah.

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DR. BELSITO: Okay. Peppermint. So at the April meeting we agreed to reopen and to add six additional peppermint derived ingredients, and then went on to issue an insufficient data announcement. And so what were we asking for?

MR. JOHNSON: Skin irritation and the --

DR. BELSITO: The sensitization --

MR. JOHNSON: -- sensitization data.

DR. BELSITO: -- yeah.

MR. JOHNSON: And a data on opposition, method of manufacturer and impurities.

DR. BELSITO: Right. Okay. Okay, peppermint.

DR. SNYDER: We're seeing everything --

DR. BELSITO: All right.

DR. SNYDER: -- but the stem and the flower.

DR. BELSITO: Pardon?

DR. SNYDER: We received data on the leaf extract, and nothing on the stem or the flower.

DR. BELSITO: Right. Or the meristem.

DR. LIEBLER: I think what we received on the leaf extract, leaf water is really inadequate. It doesn't really describe. There are a couple of verbal descriptions, I mean, a couple sentences, right?

DR. SNYDER: You mean as far as the composition and impurities?

DR. LIEBLER: Yeah. I mean, the oil we've got nice data on.

SPEAKER: Yeah.

DR. LIEBLER: And the idea would be, if we can describe these with respect to the oil, then we could use a lot of the oil data to clear the others. I mean, for the leaf water, for example, which is one of the most widely used, I believe, there's hardly any -- and we also don't have impurities data for the oil, actually.

DR. SNYDER: Well, the oil was already reported in 2001. And we added all these (inaudible).

DR. BELSITO: I know, but if we find that the data is now insufficient, it doesn't mean we can't correct that report. I'm just pointing it out. I'm not concerned. While we're on page 31, under non-cosmetic use, you have leaf juice. Is that the same as leaf water? It's the second paragraph under non-cosmetic PDH31.

MR. JOHNSON: I'm not sure (inaudible).

DR. BELSITO: Okay.

MR. JOHNSON: I'll have to check on the juice.

DR. BELSITO: And then, Paul, are you -- we probably discussed this before but --

MR. JOHNSON: Oh, I'm sorry. Yeah, that was one of the additional six ingredients that was added to the --

DR. BELSITO: The leaf juice isn't one of our ingredients.

DR. SNYDER: It is.

MR. JOHNSON: Yes.

DR. BELSITO: It is?

MR. JOHNSON: Yes.

DR. BELSITO: Oh, okay.

MR. JOHNSON: (Inaudible 0:18:36.) The bladder tumors in the female rats.

DR. BELSITO: Page 36 of the PDF, that there appears to be a dose response for the malignant lymphomas in mice. It's from the old report.

DR. SNYDER: Oh, yeah, yeah, yeah. That's (inaudible).

DR. BELSITO: Is that a mouse strain or --

DR. SNYDER: Yeah, it's very high incident so the historical controls, even though they (inaudible) current controls were a little low, the historical incidence is very high, so

--

DR. BELSITO: Okay.

DR. SNYDER: That's okay. Yeah, so I thought, following up on what Dan said at the beginning, that it was insufficient for composition for all except the oil.

SPEAKER: Right, and I think that --

DR. BELSITO: And then depending upon composition, other toxicity endpoints may be needed. And also insufficient for sensitization and irritation for all except the oil and the leaf water. And the oil is safe when formulated to be non-sensitizing.

DR. SNYDER: We got HRT on the leaf extract.

DR. BELSITO: I know. I know. I said, insufficient for all except leaf water.

DR. SNYDER: I have a leaf extract (inaudible).

DR. BELSITO: I have leaf water. Okay, so where are we here?

MR. JOHNSON: Well, we have skin irritations added on --

DR. SNYDER: Leaf extract.

MR. JOHNSON: -- leaf extract.

DR. SNYDER: (Inaudible 0:20:10.)

MR. JOHNSON: Water, ethanol, leaf extract.

DR. BELSITO: We have just irritation on leaf extract?

MR. JOHNSON: Well, this is peppermint leaf extract.

DR. SNYDER: 10%, 100%.

MR. JOHNSON: Yeah, 10% and 100%, but it's extracted with water/ethanol.

DR. SNYDER: Okay. And then we got H (inaudible) HRIPT --

MR. JOHNSON: That's (inaudible).

DR. SNYDER: -- at 100% on a leaf extract.

MR. JOHNSON: And those are (inaudible).

DR. BELSITO: Are undiluted leaf --

MR. JOHNSON: (Inaudible 0:20:34.)

DR. BELSITO: -- extract. Well, I guess I interpreted that as leaf water. (Inaudible) leaf water, oil. Okay. So we have it for leaf water, leaf oil, and leaf extract.

DR. LIEBLER: In the leaf extract we have measurements of some chemical constituents, as reported on PDF 29. But we don't have data that allow us to say that the leaf extract, how similar it is to the oil for which we've got a lot of analyses for. We don't have most of the constituents of concern enumerated in the leaf extract. Either they are not detectable. The closest we come is flavonoids. You know? Just flavonoids. That's --

DR. BELSITO: Mm-hmm.

DR. LIEBLER: That's not really informative because there are a lot of flavonoids, some of which are problematic and many of which are not. And then we get to leaf extract powder. It just says, contains tannen and terpenoid. Okay? That doesn't get us very far. And then pretty much ditto for the leaf. So the leaf, the leaf extract, and the leaf extract powder, you know, if we had good data on any of them, I think that would clear all of them. But we don't really have good data on any of them.

DR. BELSITO: Mm-hmm.

DR. LIEBLER: The leaf water is also very minimal. It just says it contains essential oil. Well, duh. That's how you make it. Right?

DR. BELSITO: Yeah.

DR. LIEBLER: Steam, distill the leaves. So I think those are still problematic in terms of composition.

DR. BELSITO: Yeah, (inaudible).

DR. LIEBLER: We actually have more data on impurities than on composition.

DR. BELSITO: Mm-hmm. Yeah, so insufficient for all except the oil for composition.

DR. LIEBLER: Yeah.

DR. BELSITO: And insufficient for sensitization and irritation, depending upon the composition for all except the oil, the leaf extract, and the leaf water.

DR. LIEBLER: Yeah. And I think if, you know, even if you could say, if you didn't have to quantify all these constituents of concern but you could say, detectable or not

detectable in these, that would allow us to map this back to the oil. And the oil is, you know, pretty well-documented.

DR. BELSITO: Right.

DR. LIEBLER: And so if we can map these back to the oil and provide some reasonable evidence of similarity, then I think we can clear the whole group. It's just we're just not in the reasonable evidence of similarity place right now.

DR. BELSITO: Right.

MR. JOHNSON: Dr. Belsito, will you go over those data needs again so I can --

DR. BELSITO: So composition for all except the oil. And depending upon composition, sensitization and irritation for all except the oil, the leaf extract, and the leaf water. That's it.

MR. JOHNSON: And, Dr. Belsito, with respect to the skin irritation data and sensitization data on PDF page 72, we did not receive complete summaries, just results in the (inaudible). So are those data going to be sufficient with that in mind?

DR. BELSITO: Yeah. I mean, I, well, yeah, I didn't have a problem with that information. I mean, we didn't actually have the -- 72 is concentration of use. What page are you on, Wilbur? I'm sorry.

MR. JOHNSON: I thought it was on page 72.

DR. BELSITO: PDF 72 is Beth's memo on concentration of use.

MR. JOHNSON: Oh, okay.

DR. BELSITO: And we actually had experimental data, as I recall, on all of those.

MR. JOHNSON: I'm sorry, it was PDF 75.

DR. BELSITO: And then that was fine, particularly when coupled with reports that we actually had data on. I didn't have problems with that.

MR. JOHNSON: Okay.

DR. BELSITO: And the GENE-TOX data on page 35, I presume, none of us had problems with that data.

DR. SNYDER: So we're going to continue to reopen the process then? Because this is kind of getting into a --

DR. BELSITO: Well, yeah, I think --

DR. SNYDER: -- (inaudible).

DR. BELSITO: -- we have to reopen because we originally approved, along with peppermint oil, the leave water and we assumed the compositions were going to be the -- I don't know what we assumed back then when we did it, but we approved more than just the oil.

DR. SNYDER: I was surprised because in the original 2001 report, I didn't catch this, but it had some leaf extract and stuff in there.

DR. BELSITO: Mm-hmm. No, I know.

DR. SNYDER: But the report title said only oil.

DR. BELSITO: Right. But so we said they were safe to use. Now we're saying we don't have the information to say that. So I think we have to continue with reopening it because that could change --

SPEAKER: Plus --

DR. BELSITO: -- our entire conclusion. Remember we --

SPEAKER: (Inaudible 0:27:01.)

DR. BELSITO: -- opened -- what?

SPEAKER: It's the reformed (inaudible) in the original (inaudible).

DR. BELSITO: Yeah.

SPEAKER: Yeah.

DR. BELSITO: Because, yes, we're continuing to --

SPEAKER: That's surprising (inaudible).

DR. BELSITO: reopen.

SPEAKER: Yeah, okay.

DR. BELSITO: So again, my question about the GENE- TOX from (inaudible) aberration on the first paragraph on page 35, I'm assuming that's okay.

DR. LIEBLER: Yeah, I didn't have a problem with it. I think that some of these

tests were complicated and did by cytotoxicity of the test agent.

DR. BELSITO: Do we comment? Should we comment that on -- in a discussion or just ignore it?

DR. LIEBLER: We typically haven't, unless there were really, you know, significantly conflicting data.

DR. SNYDER: Well, a lot of times we won't accept it if they don't have the control data to show that there's cytotoxicity occurred here. We have it. So --

DR. BELSITO: Okay. (Inaudible) that.

DR. LIEBLER: I'd actually like to hear what Tom thinks about it, but I think that, you know, in the results or in describing the studies that we do have notations of where, you know, there's evidence of toxicity or inhibition. You know, like, high concentration. For example, the last agent described or last paragraph. I'm sorry, the second paragraph of PDF 35, the last sentence there, and then in the paragraph right above it, the last sentence of that one, too, describes the toxicity of the high doses.

DR. BELSITO: Okay.

DR. LIEBLER: So that's fine. I don't think it needs to be anything special.

DR. BELSITO: Okay. And then, Wilbur, just one other point. In the document on page -- PDF page 3, the second paragraph, you say, regarding the statement and the final report conclusion that the concentration of pulegone and these ingredients should not exceed 1%. The panel considered whether in hindsight their concerns should have been addressed using a non-sensitizing qualification approach. I'm not sure what you meant by that, because our concern with (inaudible) was carcinogenicity, not sensitization.

MR. JOHNSON: Well, that can be revised.

DR. BELSITO: Yeah, I think it --

MR. JOHNSON: But deleted, yes.

DR. BELSITO: I don't even know why that sentence is there. And then that statement should continue to be present in the discussion in the current report that goes forward, because of the presence of pulegone in some fashion.

JAY ANSELL: Right. But we don't think the 1% limit, based on carcinogenicity should continue through because that cancer study had been reviewed and has been -- the conclusions now being attributed to --

DR. LIEBLER: Methanol (inaudible).

JAY ANSELL: -- one artifact of the fixation method (inaudible).

DR. BELSITO: Fine. But it needs to be moved to the discussion and still brought out --

JAY ANSELL: Yeah.

DR. BELSITO: -- number one. Number two, the issue is carcinogenicity, not sensitization.

MR. JOHNSON: So, Dr. Belsito, what --

SPEAKER: Fixation, cause (inaudible).

MR. JOHNSON: -- statement should be included --

SPEAKER: (Inaudible 0:30:38.)

MR. JOHNSON: -- in the discussion, you know, relating to --

SPEAKER: (Inaudible 0:30:42.)

MR. JOHNSON: -- pulegone?

DR. BELSITO: Well, I mean, I think that, you know, there were concerns about its --

SPEAKER: This is (inaudible).

DR. BELSITO: -- carcinogenicity and then --

SPEAKER: (Inaudible).

DR. BELSITO: -- the findings of the recent --

SPEAKER: (Inaudible 0:30:51.)

DR. BELSITO: This was an anti-pea study? I don't remember the pulegone study that was done. It was a two year --

MR. JOHNSON: (Inaudible) NTP. NTP carcinos study.

DR. BELSITO: Right. The findings were that it was due to -- Paul, help me out.

DR. SNYDER: Well, it said that the bladder cancer was cytotoxicity.

DR. BELSITO: Cytotoxicity.

DR. SNYDER: Yeah.

DR. BELSITO: Yeah. So it --

DR. SNYDER: (Inaudible 0:31:12.)

DR. BELSITO: -- it wasn't --

DR. SNYDER: Yeah.

DR. BELSITO: -- a carcinogenic --

DR. SNYDER: No.

DR. BELSITO: -- factor, it was cytotoxic (inaudible).

DR. SNYDER: Yeah.

MR. JOHNSON: Oh, well, in the NTP report, it indicated that a female rat had increased incidences of urinary bladder tumors.

DR. SNYDER: That were due to cytotoxicity. So it wasn't a --

MR. JOHNSON: And what about the benign and malignant tumors of the liver?

DR. BELSITO: Again, hepatotoxicity.

MR. JOHNSON: Oh, okay.

DR. SNYDER: Yeah, there's no cancer in the liver, just some hyperplasias. A liver (inaudible) male/female.

MR. JOHNSON: Because I know the conclusion, NTP's conclusion, stated that the pulegone caused cancer of the urinary bladder in female rats, and cancer of the liver in male and female mice.

DR. BELSITO: Well, it may cause it, but then the question is, what is the mechanism (inaudible).

DR. SNYDER: That's in the second paragraph there, the subsequent --

DR. BELSITO: Is it a genotoxic --

DR. SNYDER: -- (inaudible).

DR. BELSITO: -- mechanism --

SPEAKER: No.

DR. BELSITO: -- or is it a cytotoxic?

DR. SNYDER: It's regenerative self-(inaudible) mode of action. There on the second paragraph.

DR. BELSITO: Okay.

DR. SNYDER: Yeah. And I guess --

DR. KLAASSEN: This has nothing to do with histopathology.

DR. BELSITO: Right.

DR. KLAASSEN: Artifacts.

DR. BELSITO: Yeah. And I guess I just want to raise one issue because, you know, I sort of had forgotten all the parts of the presentation, the botanical presentation, so I had to go back and look at exactly what meristem was. So meristem is when they harvest the small cells from the plant that are capable of dividing indefinitely and giving rise to the similar plants to the south. So the question came in my mind then is, if you're using material from a meristem cell culture, are the potential components of concern present -- could they be present, in higher amounts than what's being reported when you look at simply flower, leaf, stem, twig, bark?

SPEAKER: Sure.

DR. LIEBLER: They could be, but there would be just as plausible an argument that they could be present in lower amounts. And the problem with these cell cultures is they might be partially dedifferentiated to the extent that they don't produce the same repertoire of natural products. And I think our problem with the meristems is we never had any data on these things.

DR. BELSITO: Right. So I mean that's, that's the issue. So --

DR. LIEBLER: Yeah.

DR. BELSITO: -- I mean, I think meristem is something in particular where we

need composition and we can't infer it from composition of the other parts of the plant.

DR. LIEBLER: No.

MS. FIUME: I have to look back at the presentation as well, but I thought meristem was one that you said is specifically on its own, that you can't --

DR. BELSITO: Right.

MS. FIUME: -- use any of the other information in the report.

SPEAKER: Nope.

DR. BELSITO: Good. Well, I --

MS. FIUME: (Inaudible) stuff.

DR. BELSITO: -- was hoping we said that, because when thinking about it, you know, it's basically a cell culture of this pluripotential cell and God knows what comes out of it.

DR. LIEBLER: Right.

MS. FIUME: Yeah.

DR. BELSITO: It's like stem cell research.

DR. LIEBLER: Is there anybody producing that stuff now? Or is it, you know, a great pitch that lasted for a little while and left some ingredients in the dictionary and that's it?

MS. LORETZ: No idea.

SPEAKER: I don't know.

DR. LIEBLER: Okay.

DR. BELSITO: Okay.

DR. LIEBLER: I think I have my answer.

DR. BELSITO: Anything more on --

SPEAKER: You should stop --

DR. BELSITO: -- peppermint?

SPEAKER: -- thinking (inaudible).

DR. BELSITO: Products? Okay. So basically, Wilbur, the oil is fine.

MR. JOHNSON: Mm-hmm.

DR. BELSITO: All the others are insufficient for composition.

SPEAKER: Yep.

DR. BELSITO: And all of the others, except for the oil, the leaf extract, and the leaf water, are insufficient for sensitization and irritation.

SPEAKER: Okay.

SPEAKER: Mm-hmm.

DR. BELSITO: Okay? Okay dokey.

MR. JOHNSON: That statement relating to carcinos and SD, I see it in the summary but it's not in the discussion relating to the mechanism.

DR. BELSITO: Okay. Well, it should be in the discussion. Paul, would you craft some language or Dan?

DR. LIEBLER: Yeah, we can.

DR. BELSITO: Curt?

DR. SNYDER: I did pull up the original report to check out that liver comment, because I don't see that liver was an issue, but Bob will look at that.

DR. BELSITO: So then I guess it should, at some point, there should be a sentence in the panel, you know, at some point about constituents of concern. You talk about the sensitizing constituents, and probably between that and the heavy metals, talk about the pulegone. So just draft some language to put in there.

SPEAKER: Yep.

DR. BELSITO: And then point out the results of the most recent study and, you know, this is cytotoxicity given the concentration or the use concentrations for these peppermint derived ingredients. We're not concerned that this is not genotoxic. It's clearly a cytotoxic dose response relationship.

DR. KLAASSEN: This liver, (inaudible) has to be explained.

DR. SNYDER: Yeah, but it's probably got the high dose, 150 milligrams. They want it pretty high in this study. I'm trying to get to the data on the report here.

DR. KLAASSEN: And I think we're okay with --

MR. JOHNSON: That was --

DR. KLAASSEN: -- (inaudible).
MR. JOHNSON: That was for the mice.
SPEAKER: Mice, yeah.
MR. JOHNSON: For the rats it was up to 75.
SPEAKER: Yeah.

DR. BELSITO: Okay. Anything else for the peppermint? Okay doke. Okay.

Day 1 of the September 11-12, 2017 Panel Meeting – Dr. Marks' Team

DR. MARKS: Any other comments? If not, let's move on to peppermint. So Wilbur, in the April 2017 meeting, the panel reopened the peppermint document to add six derived ingredients and those are list in your memo of extract, flower leaf stem extract et cetera. That meeting the panel issued an insufficient data announcement and requested skin irritation and sensitization data. A compensation method of manufacturing impurities and then there -- was data received?

MR. JOHNSON: Yes.

DR. MARKS: And um.

MR. JOHNSON: We received a use concentration data on the additional six ingredients that were added to the safety assessment. We received method of manufacture, composition and impurities data on the leaf extract. That's the butylene glycol water extract. Another leaf extract which is the water ethanol extract, leaf powder and peppermint leaf water. We also received a invitro skin irritation data on the leaf extract, that's the water ethanol extract. At concentrations of 10 percent and 100 percent. And an HRIPP on the leaf extract, that's the water ethanol extract at a concentration of 100 percent.

DR. MARKS: Okay. So now let's move on. What do we need for this tentative report -- amended report?

DR. EISENMANN: One thing about the original report, you had a limit of pulegone of percent.

DR. MARKS: Yes.

DR. EISENMANN: Um, the basis of that, I think was this brain lesions. There's one more study on that that looked at in another 28-day study determined the brain lesions were a histological effect. So they did a fixing -- it was an error in fixation. So they did fixation using two different methods and they didn't see the brain lesions. So that 1 percent pulegone limit -- I'm not sure where you want to go with that. If you notice the iso standard generally the pulegone is up to 3 percent in peppermint oil. The extracts apparently, they're all within the less than the 1 percent so those don't matter.

MR. JOHNSON: And I might add that adverse effects on the liver are, you know, are noted in that same study by Mulk.

MS. EISENMANN: Right. Generally, it's liver effects not brain effects that have concern for pulegone.

DR. MARKS: So, yeah in 2001, four ingredients are safe with pulegone not exceed 1 percent limit. And that was presumably for the cancer end point. And now we have 5 percent pulegone in the oil. So that and then the other --

MS. EISENMANN: It's up to 3 percent in the oil.

DR. MARKS: Three? I don't know where I got five then.

MR. JOHNSON: That's for sources outside of the United States. For sources within the U.S. it's 2.5 percent.

DR. MARKS: So it's higher than the 1 percent limit that was before. So should we start with that or should we start under needs. Why don't we start with that, Tom, do you think there should be a limit on the pulegone at this point?

DR. SLAGA: (Inaudible).

DR. MARKS: I thought it was but she said it was 2.5., so it's higher than the 1 percent, both sources. I thought it was -- I don't know where I got the 5 percent, page 25. Let me see what it says there. I thought it was five but...

MR. JOHNSON: I know table 3 says, up to 3 percent. DR. MARKS: Pulegone.

MR. JOHNSON: Right. In peppermint oil.

DR. MARKS: Okay. It's still more.

DR. SLAGA: Do any of you have data to support that? Do we have data to support this (inaudible).

DR. JOHNSON: I don't know. I know in the NTP study it reported the doses that were administered.

DR. SLAGA: Yeah.

DR. JOHNSON: But no concentration.

DR. SLAGA: Well, we usually like to have some data to (inaudible) well beyond the 1 percent. Unless -- if we don't I'll just leave it at 1 percent.

SPEAKER: Right.

DR. EISENMANN: But you know now what the 1 percent was based on with these brain lesions and the 28-day study. And there's this -- they did it on the same group.

DR. SLAGA: (Inaudible) there was a problem with fixation, right?

DR. EISENMANN: Correct. I mean, the title of that study is, Lack of Histological Cerebellar Changes in wistar rats given pulegone for 28-days comparison of emersion and profusion tissue fixation, that's the title of the study.

DR. SHANK: The lesions with one of the fixation and not the other?

DR. EISENMANN: That's what I presume, yes. I didn't read the study, I only read what EMEA said about EMEA said about it.

DR. SHANK: Because if they didn't get an even 1 then there's a problem.

SPEAKER: Definitely a problem.

DR. EISENMANN: And this was from the same group that did the original studies.

DR. SHANK: (Inaudible).

DR. MARKS: So you don't want to make a decision yet about the pulegone until you've reviewed those?

DR. SHANK: That's correct.

SPEAKER: I agree.

DR. SHANK: And there's still insufficiency for separations other than the oil.

DR. MARKS: Yeah, I had methods of manufacturer impurities for the extract. I don't know how. I didn't see that data, did I miss that?

DR. SHANK: No.

DR. MARKS: And then I'm sure you'll have more Ron. So that was where I wanted. Now, I figure if we got it for the extract then we're probably no for the rest of it. Because the extracts the total plant. And then I wanted sensitization on the leaf water at 40 percent. The question of that 20 percent leaf water was okay. The leaf extract which I assume would include what's in the leaf water was okay at 100 percent for sensitization.

So I was questioning whether we really needed the leaf water at 40 percent. I could overlook that since we have the leave extract at 100 percent. The extract itself of the whole plant is 7.9 percent and we don't have any sensitization on that. We have again as I mentioned leaf extract, we have an oil, we have the letter but we don't have the whole thing together. So probably the biggest sensitization for me is sensitization for the extract. Does that sound reasonable team?

DR. SLAGA: Yes.

DR. SHANK: Now, there's more than one kind of extract, is it not?

DR. MARKS: Oh yeah, and that's -- and when I said the extract that was -- it was the add-ons and I used the add-on the extract at 7.9 percent. But there was not I'm not talking about the leaf extract and I'm not talking about the leaf cell extract. I'm talking about the extract which I assume is the whole. That's why I want a method of manufacturing also. I kind of used the extract as the centinel ingredient. And then maybe I missed it but in this spread sheet I didn't see the 6th added ingredients on there. There's not much data on the 6th extra ingredients. Factors little if anything other than method of composition of the flower leaf stem extract.

DR. SLAGA: So that's only sensitization data (inaudible).

DR. MARKS: Yeah, basically, -- well I wanted to have the method of manufacturing of purities for the extract. Because I think we should know what's in the extract assuming that's everything. And then the sensitization for the extract and those were the two I needed. And then we need to clarify the pulegone.

DR. SHANK: Pulegone, yeah.

DR. MARKS: And it's kind of interesting because I say I like data, but with botanicals we always put formulate to be non-sensitizing. So one could say if you have that as your conclusion do you really need this. I would like to see it.

DR. SHANK: But would that apply to pulegone?

DR. MARKS: No. So tomorrow I'm going to move -- shall we --

DR. SHANK: Insufficient.

DR. MARKS: Um-hum. Insufficient data announcement and we want the sensitization. And then how do you want the pulegone? Clarify the pulegone studies or review it or we can just -- that's really not a need.

DR. SHANK: I'll email it to them (inaudible).

SPEAKER: (Inaudible).

DR. MARKS: So I'll put in there pulegone limit question mark 1 percent that's mentioned that. Okay.

DR. SHANK: That's been in several reports is it not? The pulegone (inaudible).

SPEAKER: (Inaudible).

MS. FIUME: Yes.

SPEAKER: They change it.

DR. SHANK: But you can't base it on something that's not real.

DR. SLAG: That's not right.

DR. MARKS: Okay. Any other comments? So on insufficient data announcement I'll move tomorrow. We want the extract method of manufacturing and impurities and sensitization data. And then we want to clarify the pulegone limit of 1 percent.

SPEAKER: Alright.

MR. JOHNSON: Excuse me. Doctor Marks, this will be a tentative report with an insufficient data conclusion. Because an insufficient data announcement was issued at the April meeting. So this would be the tentative report.

DR. MARKS: Thank you.

MR. JOHNSON: You're welcome.

DR. MARKS: I had that before, tentative report.

DR. EISENMANN: Now, should a more comprehensive search be done on pulegone, rather than just um, just a question. I'm not sure you used pulegone as a search term Wilbur.

MR. JOHNSON: No, I did not. No, I did not. I just spoke -- I was aware of the NTP carcinogenicity study. And that's why I included those data in the safety assessment.

DR. EISENMANN: And maybe you don't need necessarily go back. I mean, well except this one study is older. I was just going to say maybe since the NTP bio essay might be helpful to look at if anything new on pulegone.

SPEAKER: When was that study done, the NTP.

MR. JOHNSON: And there's a brief summary of that in the safety assessment.

DR. EISENMANN: It's not too old.

MR. JOHNSON: That was done in 2011.

DR. MARKS: So are we going to -- if we're issuing a tentative report then we're saying it's safe for the other -- what is it nine. Are there ten ingredients total? The original four and then we added six. So safe for nine ingredients and an insufficient for the extract, does that sound reasonable?

DR. SHANK: Yes.

DR. MARKS: And then clarify the pulegone limit. Okay, does that sound -- I see you thinking Ron Shank.

DR. SHANK: Well, I was just wondering should a search be done, specifically for pulegone or with the NTP study always has preliminary data in it so that they can find the dose. For the carcinogenicity study. they always do preliminary short term studies. If that's available that should help us. Because if we find out 1 percent --

SPEAKER: They don't usually like to release it separate --

DR. SLAGA: They did a two week.

SPEAKER: -- because want to look at totality of all of the studies before they -- I don't if the...

DR. EISENMANN: I was just wondering since the NTP bio essay was done if you want to for like, mechanistic type data that might be useful. Rather than the post (inaudible) I was just going to suggest since the NTP bio acid came out that might be helpful.

MR. JOHNSON: They did do a two study and a three- month study prior to the two- year study.

DR. MARKS: And those were oral?
MR. JOHNSON: Oral studies.
DR. MARKS: Um-hum. Any other comments? Okay.

Day 2 of the September 11-12, 2017 Panel Meeting – Full Panel

Moving on to the next ingredient in this group, and that's peppermint, Dr. Marks presenting.

DR. MARKS: So at the April 2017 meeting, the panel agreed to open the peppermint document from 2001 to add six more peppermint-derived ingredients. We issued an insufficient data notice, or announcement, for skin irritation, sensitization, composition, method of manufacture, and impurities.

We did receive some data and our team moves that a tentative report be issued "safe for nine ingredients when formulated to be non-sensitizing" and insufficient for the extract. We wanted the method of manufacture and impurities for the extract. And despite the conclusion to "formulate to be non-sensitizing," we also wanted to see sensitization data on the extract at its use concentration of 7.9 percent. In the discussion, we clarify that a pulegone limit of 1 percent, which was in the original document from 2001.

DR. BERGFELD: And that's a motion?
DR. MARKS: Yes.
DR. BERGFELD: Is there a second, or a discussion?

DR. BELSITO: Yeah. So we looked at this and we were shocked that we actually had allowed the other non-oil ingredients to be found safe as used back then because we have absolutely no composition for any of them except the oil. We have no clue what's in any of them.

So we found it was insufficient for composition for all except the oil. And depending upon the composition, other toxicologic endpoints may be needed. And we thought it was insufficient for sensitization and irritation for all except the oil, the leaf extract, and the leaf water which we had data on.

DR. BERGFELD: Comment.

DR. MARKS: What were that sensitization again? Which ones did you say we have?

DR. BELSITO: We had sensitization and irritation for oil, leaf extract, and leaf water. So those three are fine. But all of the other ingredients in the report -- so the flower leaf stem, flower leaf extract, flower leaf stem water, leaf cell extract, leaf juice, and the meristem cell culture.

DR. MARKS: Yeah. I guess my reasoning was if we have sensitization data on the extract, that would include components from the whole plant, assuming that that's what the extract is. And if we had sensitization data on that which was -- would be --

DR. BELSITO: Well, we have data for the leaf extract and the leaf water.
DR. MARKS: Right.
DR. BELSITO: We don't have data on the stem and --

DR. MARKS: Oh, I agree. We can ask for all that. I would just be reassured if I had the extract that that would include all the other components of the plant and if we had that, we could --

DR. LIEBLER: Depending on whether that's actually true.
DR. MARKS: Exactly. Well, that's why --

DR. LIEBLER: And it's a circular problem. We don't know what the method of manufacture is, we don't know what's in it to make that assumption.

DR. MARKS: That's correct. That's why we asked for that specifically -- method of manufacture. But sure, I think we can go out with your team's request and --

DR. BERGFELD: Can you restate the motion, then?

DR. BELSITO: So it's "insufficient for composition for all except the oil," and depending upon the composition, we got "other toxicologic endpoints may be needed." And "insufficient for sensitization and irritation" for all except the oil, the leaf extract, and the leaf

water.

DR. BERGFELD: So, if this is going to have to go out, it's a draft tentative amended report, so how will we send this out? As an insufficient data report?

DR. HELDRETH: We could send it out as an IPS.

DR. BERGFELD: Okay.

DR. SLAGA: (Inaudible) for insufficient data.

DR. BERGFELD: Yeah. It's -- yeah. Okay. All right. Is there a second on Don's motion? Okay. And Wilbur?

MR. JOHNSON: What are we saying about the prior 1 percent concentration limit on pulegone?

DR. BELSITO: Jim addressed that. We're keeping that in the discussion.

MR. JOHNSON: Okay. Now, I know that was based upon -- in the original report, it was based upon concerns about the regions in the brain and the effect on the liver. Should those concerns be addressed in the discussion?

DR. BELSITO: I mean, it's -- yeah. I mean, those can be addressed, sure.

MR. JOHNSON: What should we be saying about those? And the carcinogenicity of the pulegone?

DR. BELSITO: Right. I mean that, you know, it's been the --

DR. SNYDER: Yeah. (Inaudible) in the rat. And so we can address that in the discussion.

MR. JOHNSON: What should we --

DR. BELSITO: Wilbur's asking specifically the wording for the --

DR. SNYDER: Well, that the endpoints evaluated in the NTP study were attributed to renal toxicity and the liver toxicity. Okay.

DR. SLAGA: Just for the liver, now.

DR. SNYDER: Yeah.

DR. BERGFELD: What did you say, Tom?

DR. SLAGA: Just for the liver. We don't need the brain stuff because of that complication.

MR. JOHNSON: So the cerebellum region should not be mentioned at all in the discussion?

DR. SLAGA: I don't think it's needed.

DR. BERGFELD: Any other comments about the cerebellum brain region? No it's not needed.

So we want to call the question, then, if there are no other comments on an insufficient data report.

All those in favor, indicate by raising your hands. And the list of needs have been stated, I believe.

(The motion passed unanimously.) Okay.

Amended Safety Assessment of *Mentha piperita* (Peppermint)-derived Ingredients as Used in Cosmetics

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The 2017 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, 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 report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Ivan Boyer, Ph.D., former Senior Toxicologist.

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of *Mentha piperita* (peppermint)-derived ingredients; most of the ingredients function as fragrance ingredients and/or skin conditioning agents in cosmetic products. Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. Industry should continue to use good manufacturing practices to limit impurities that could be present in botanical ingredients. The Panel reviewed data relevant to the safety of these ingredients and concluded that Mentha Piperita (Peppermint) Oil is safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-sensitizing, and that the available data are insufficient to make a determination that the remaining ingredients are safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

The safety of four of the cosmetic ingredients named in this safety assessment has been previously reviewed by the Panel; in 2001, the Panel issued a final report with a conclusion stating that Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint) Leaf Water are safe as used in cosmetic formulations.[1] The conclusion also stated that the concentration of pulegone, a constituent of these botanical ingredients, should not exceed 1%. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*), most of these ingredients are reported to function as fragrance ingredients and/or skin conditioning agents in cosmetic products.[2]

Most of the safety test data in the 2001 report are on Mentha Piperita (Peppermint) Oil, and the Panel noted that much of the data on this ingredient are considered relevant to the entire group. The current safety assessment is a re-review of the 4 *Mentha piperita* (peppermint)-derived ingredients that are mentioned above and an initial review of the following 6 related ingredients:

Mentha Piperita (Peppermint) Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Water
Mentha Piperita (Peppermint) Leaf Cell Extract
Mentha Piperita (Peppermint) Leaf Juice
Mentha Piperita (Peppermint) Meristem Cell Culture

Safety test data that have been found in the published literature or those provided by the Personal Care Products Council (Council) as unpublished data since the final report was issued, are included. Some safety test data on menthol, menthone, and pulegone are also included in the original published final report, and in this safety assessment, because these chemicals are components of Mentha Piperita (Peppermint) Oil. These data are presented in Table 1. Considering that a limitation on pulegone is mentioned in the original conclusion, it should be noted that a National Toxicology Program (NTP) oral carcinogenicity study with positive results on pulegone was published in 2011 and that a 1998 publication on the absence of test substance-related histological cerebellar changes in Wistar rats dosed orally with pulegone is available. These studies are also presented in Table 1.[3,4]

The cosmetic ingredient names, according to the *Dictionary*, are written as listed above, capitalized, without italics, and unabbreviated. When referring to the plant from which these ingredients are derived, the standard scientific practice of using italics to identify genus and species will be followed (e.g., *Mentha piperita*).

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 list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates is available on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Excerpts from the 2001 safety assessment on the previously reviewed ingredients are disseminated throughout the text of this re-review document, as appropriate, and are identified by italicized text. For complete and detailed information, please refer to the original report, which is available on the CIR website (https://www.cir-safety.org/ingredients).

CHEMISTRY

Definition and General Characterization

The definitions of *Mentha piperita* (peppermint)-derived ingredients are stated in Table 2.[2]

Chemical and Physical Properties

Properties/specifications relating to Mentha Piperita (Peppermint) Oil and Mentha Piperita (Peppermint) Leaf Extract are presented in Table 3.[1]

Method of Manufacture

Mentha Piperita (Peppermint) Oil

European and American peppermint oil is distilled with steam from the fresh, above-ground parts of the flowering plant Mentha piperita Linne, rectified by distillation and not dementholized.[1] It has been reported that the menthone content decreases while the menthol content increases in peppermint leaves upon storage for 1 to 2 months, at 22˚C to 24˚C. However, the relative menthone to menthol proportion remained practically constant during the total storage time.

According to one source, Mentha Piperita (Peppermint) Oil has been extracted (distilled; water solvent) from the leaves of *Mentha piperita* harvested (first in July and second harvest in September) in Washington state.[5]

Mentha Piperita (Peppermint) Leaf Extract

The following method relates to preparation of the butylene glycol/water extract of Mentha Piperita (Peppermint) Leaf Extract.[6] Dried raw material is extracted with 50 vol% 1,3-butylene glycolic solution. After extraction, the additional steps in the production process include: filtrate → sedimentation → filtrate → adjustment → packaging.

In another method, the preparation of a water/ethanol extract is described.[6] Dried raw material is extracted with 30 vol% ethanolic solution. After extraction, the additional steps in the production process include: filtrate → concentration → adjustment → sedimentation → filtrate → adjustment → packaging**.**

The production method described herein relates to preparation of Mentha Piperita (Peppermint) Leaf Extract (powder form).[6] The preparation of this material may be similar to the preparation of some of the ingredients in this report. According to the method of production, dried raw material is extracted with 30 vol% ethanolic solution. After extraction, the additional steps in the production process include: filtrate → concentration → add exsiccated sodium sulfate as vehicle → drying → packaging.

In the supercritical fluid extraction with natural carbon dioxide production method for Mentha Piperita (Peppermint) Leaf Extract from the dried leaves of *Mentha piperita*, neither additives nor other technical adjuncts are introduced during the production process.[7]

Mentha Piperita (Peppermint) Leaf Water

In the preparation of Mentha Piperita (Peppermint) Leaf Water, dried raw material is subjected to steam distillation.[6] After distillation, the remaining steps in the production process are: water soluble fraction obtained → adjustment → filtrate → packaging**.**

Composition/Impurities

Pulegone is found in young peppermint leaves, and is metabolized to menthol as the leaves mature. It has also been reported that pulegone is found only in Mentha Piperita (Peppermint) Oil from young plants and in trace amounts in "inferior" oils; pulegone is absent from "good quality" Mentha Piperita (Peppermint) Oil.[1] However, a supplier of Mentha Piperita (Peppermint) Oil reported pulegone concentrations of 1% to 4%, depending on the origin of the oil. Published studies that have investigated the pulegone content of Mentha Piperita (Peppermint) Oil also reported a range of <1% to 4% for Mentha Piperita (Peppermint) Oils of a North American origin.

Mentha Piperita (Peppermint) Oil

The major constituents of Mentha Piperita (Peppermint) Oil include the terpenes: (-)-menthol (30-55%), (-)-menthone (14-32%), (+)-isomenthone (1.5-10%), (-)-menthyl acetate (2.8-10%), (+)-menthofuran (1.0–9.0%), and 1,8-cineol (3.5-14%).[8]

Certain trends were observed between oil extracted from first and second harvest leaves, and oil extracted from fresh leaves versus dried leaves.[5] When compared to the second harvest, oils from the first harvest were generally higher in (*Z*)-3-hexenol, 1,8-cineole, α-pinene, β-pinene, sabinene hydrate, isomenthone, menthofuran, pulegone, β-caryophyllene, and germacrene d, but lower in limonene, menthol, and menthone. When compared to oils from dried leaves, oils from fresh

leaves were higher in 1,8-cineole, α-pinene, limonene, isomenthone, menthofuran, menthone, and pulegone and lower in β-caryophyllene, germacrene d, and menthol. Menthyl formate was found in all of the *Mentha piperita* (peppermint) oils (from leaf extraction) that were analyzed.

Regarding the essential oil composition of *Mentha piperita* adult plants (in Poland), menthone, menthol, menthyl acetate, carvone, piperitone, 1,8-cineole, and pulegone have been identified as major components.[9]

According to the United States Pharmacopeial Convention's (USP) Food Ingredients Expert Committee, the acceptance criteria for Mentha Piperita (Peppermint) Oil include not less than 5% total esters (calculated as menthyl acetate) and not less than 50% menthol.[10]

The international standard for Mentha Piperita (Peppermint) Oil, published by the International Organization for Standardization, contains the chromatographic profile for this ingredient that is presented in Table 4.[11] Pulegone and menthofuran were among the chemicals detected. A public statement from the European Medicines Agency on the use of herbal medicinal products containing pulegone and menthofuran indicated that Mentha Piperita (Peppermint) Oil contains a maximum of 4% pulegone and between 1% and 9% menthofuran.[12] It was also noted that the Scientific Committee on Food (SCF) has concluded that pulegone is mainly metabolized through pathways involving menthofuran and that these two substances show similar toxicity.

Mentha Piperita (Peppermint) Leaf Extract

An analysis of Mentha Piperita (Peppermint) Leaf Extract indicated that the leaves principally contained cinnamic acid, caffeic acid, rosmarinic acid, and various flavonoids (flavones and flavanones).[13] The following solvents were used to extract the peppermint leaves: light petroleum, dichloromethane, acetonitrile, ethyl acetate, methanol, *n*-butanol, and water. Eriocitrin (383.3 ± 2.2 mg/g extract) and rosmarinic acid (381.2 ± 1.9 mg/g extract) were the most abundant components identified within the leaves, while naringenin-7-*O*-glucoside (0.8 ± 0.01 mg/g extract) was the least abundant component identified. Kynurenic acid (3.82 ± 0.46 µg/g) has also been detected in Mentha Piperita (Peppermint) Leaf Extract.[14] It should be noted that kynurenic acid is a constituent of human synovial fluid.

Composition data provided by the Council indicate that Mentha Piperita (Peppermint) Leaf Extract (butylene glycol/water extract) contains tannin and terpenoid (which contains 2.8 ppm pulegone) and that Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract) contains essential oil, tannin and terpenoid.[6] Additionally, *Mentha piperita* (peppermint) leaf extract powder (another name for *Mentha piperita* (peppermint) Leaf Extract) contains tannin and terpenoid.[6]

The chromatographic profile for Mentha Piperita (Peppermint) Leaf Extract is presented in Table 4.[15,16]

Mentha Piperita (Peppermint) Leaf

The major monoterpene constituents of Mentha Piperita (Peppermint) Leaf are: (-)-limonene; 1,8-cineole; (+)-pulegone; (-)-menthone; (+)-isomenthone; (+)-menthofuran; (-)-menthol; and (+)-neomenthol.[17] Mentha Piperita (Peppermint) Leaf also contains caffeic acid, rosmarinic acid, and the following flavonoids: apigene-, diosmetin-, and luteolin glycosides, and free lipophile methoxylized flavones such as xanthomicrol and gardenine D.[18]

Mentha Piperita (Peppermint) Leaf Water

Composition data provided by the Council indicate that Mentha Piperita (Peppermint) Leaf Water contains essential oil (menthol).[6]

Mentha Piperita (Peppermint) Leaf Extract

Data on impurities provided by the Council indicate that Mentha Piperita (Peppermint) Leaf Extract (butylene glycol/water extract) contains not more than 10 ppm heavy metals and not more than 2 ppm arsenic.[6] Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract) contains not more than 10 ppm heavy metals and not more than 1 ppm arsenic.

The supercritical fluid extraction with natural carbon dioxide production method for *Mentha piperita* (Peppermint) Leaf Extract from the dried leaves of *Mentha piperita* results in no solvent residues, no inorganic salts, no heavy metals, and no reproducible microorganisms.[7]

According to data provided by the Council, *Mentha piperita* (peppermint) leaf extract powder contains not more than 10 ppm heavy metals and not more than 2 ppm arsenic.[6]

Mentha Piperita (Peppermint) Leaf

The following elemental contaminants have been detected in *Mentha piperita* herbal tea (tea leaves) samples (n = 3) from Serbia: manganese (111.97 mg/kg dry weight), iron (443.90 mg/kg), copper (17.15 mg/kg), and zinc (26.86 mg/kg), molybdenum (2.695 mg/kg), cobalt (0.161 mg/kg), nickel (1.882 mg/kg), selenium (0.107 mg/kg), aluminum (554 mg/kg), and tin (3.66 mg/kg).[19]

It is possible that pesticide residues may be present as impurities in the leaves of *Mentha piperita*. In a study in which Mentha Piperita (Peppermint) Leaves were soaked in pesticides, the dissipation rate of pesticide residues during the drying process was said to have been satisfactory, except for the pirimiphos-ethyl pesticide, because of its high octanol-water partition coefficient and low vapor pressure.[20]

Mentha Piperita (Peppermint) Leaf Water

Data on specifications provided by the Council indicate that Mentha Piperita (Peppermint) Leaf Water contains not more than 10 ppm heavy metals and not more than 1 ppm arsenic.[6]

USE

Cosmetic

The safety of *Mentha piperita* (peppermint)-derived ingredients is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database.[21] Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Council, of maximum reported use concentrations by product category.[22]

According to 2017 VCRP data, the greatest use frequency is being reported for Mentha Piperita (Peppermint) Oil, which is being used in 827 cosmetic products (433 leave-on products + 360 rinse-off products + 34 products diluted for bath use).[21] The results of a concentration of use survey conducted in 2016 indicate that Mentha Piperita (Peppermint) Leaf Water is being used at concentrations up to 40% in leave-on products (face and neck products [not spray]), which is the greatest use concentration that is being reported for *Mentha piperita* (peppermint)-derived ingredients reviewed in this safety assessment.[22] Current and historical use frequency and concentration of use data are presented in Table 5. These data indicate that the highest maximum use concentration of Mentha Piperita (Peppermint) Oil in cosmetics increased from 3% in 1997 to 5% in 2017. Because 1997 use concentration data on the remaining 3 ingredients that were reviewed in the original safety assessment, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint), were not provided, a comparison of 1997 versus 2017 use concentration data cannot be made.

According to VCRP and Council survey data, the following *Mentha piperita* (peppermint)-derived ingredients are not being used in cosmetic products: Mentha Piperita (Peppermint) Flower/Leaf/Stem Water, Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract, Mentha Piperita (Peppermint) Leaf Cell Extract, Mentha Piperita (Peppermint) Leaf Juice, and Mentha Piperita (Peppermint) Meristem Cell Culture.

Cosmetic products containing *Mentha piperita* (peppermint)-derived ingredients may be applied to the skin and hair or, incidentally, may come in contact with the eyes (at maximum use concentrations up to 0.0018 % Mentha Piperita (Peppermint) Leaf Extract in eye lotions) and mucous membranes (at maximum use concentrations up to 3.9% Mentha Piperita (Peppermint) Oil in bath oils, tablets, and salts). Additionally, use in lipstick products (at maximum use concentrations up to 2.9% Mentha Piperita (Peppermint) Oil) is being reported, the application of which may result in incidental ingestion. Products containing *Mentha piperita* (peppermint)-derived ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Mentha Piperita (Peppermint) Oil is being used in both pump hair sprays (maximum use concentrations up to 0.02%) and aerosol hair sprays (maximum use concentrations up to 0.017%) which may result in incidental inhalation exposure. Additionally, use of this ingredient in foot sprays at maximum use concentrations up to 0.5% is being reported. Mentha Piperita (Peppermint) Leaf Extract is also being used in pump and aerosol hair sprays, but at lower maximum use concentrations, and in face and neck/body and hand spray products at maximum use concentrations up to 0.001%. Mentha Piperita (Peppermint) Extract is being used in face and neck sprays at a highest maximum use concentration of 1.3%. In

practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump sprays.[23,24,25,26] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[23,24]

Mentha Piperita (Peppermint) Oil is being used in foot powders at maximum use concentrations up to 1%, and Mentha Piperita (Peppermint) Leaf Extract is being used in face powders at maximum use concentrations up to 0.0018%. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[27,28,29]

Noncosmetic

Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Extract, Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract, and Mentha Piperita (Peppermint) Leaf Juice

Mentha Piperita (Peppermint) Oil is a generally recognized as safe (GRAS) ingredient for use in dietary supplements.[1] *It is described as a naturally occurring carminative that relaxes gastrointestinal smooth muscle. A final ruling by the FDA labeled Mentha Piperita (Peppermint) Oil as safe and effective as an antitussive (topical/inhalant). Final rulings cautioned that Mentha Piperita (Peppermint) Oil is not safe and effective for use as an expectorant in either topical/inhalant or lozenge form, or for use as a nasal decongestant, mouthwash, or digestive aid*.

Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Extract, Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract, and Mentha Piperita (Peppermint) Leaf Juice are generally recognized as safe (GRAS) for use in food for human consumption (21CFR182.20). Mentha Piperita (Peppermint) Oil is an inactive ingredient in drug products that have been approved by the U.S. FDA.[30] A number of active ingredients, Mentha Piperita (Peppermint) Oil included, have been present in over-the-counter (OTC) drug products for various uses.[31] However, the FDA has determined that, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of Mentha Piperita (Peppermint) Oil as an active ingredient in the following drug products: nasal decongestant drug products, digestive aid drug products, insect bite and sting drug products, and astringent drug products.

Mentha Piperita (Peppermint) Oil is on the U.S. Environmental Protection Agency (EPA) list of active ingredients eligible for minimum risk pesticide products.[32]

Mentha Piperita (Peppermint Oil)

According to the European Medicines Agency Committee on Herbal Medicinal Products (HMPC) community herbal monograph on *Mentha x piperita* L., aetheroleum (i.e., peppermint oil; aetheroleum is a term used to describe a preparation made from the above-ground parts of a plant), this herbal medicine is administered orally for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence, and abdominal pain, especially in patients with irritable bowel syndrome.[33] It is also an herbal medicine that is administered cutaneously for the symptomatic relief of mild tension-type headache. These uses have been identified as well-established uses by the HMPC. The highest recommended daily dose in the European Union is 1.2 ml peppermint oil (i.e. 1,080 mg peppermint oil, which contains maximum 140 mg pulegone + menthofuran). For a 60 kg person, this would correspond to a daily intake of 2.3 mg/kg body weight.

TOXICOKINETIC STUDIES

Dermal Penetration

Animal

Mentha Piperita (Peppermint) Oil

Eserine in a Mentha Piperita (Peppermint) Oil vehicle was applied to a 2.2 cm^2 shaved area on the abdomen of mice. The absorption rate for Mentha Piperita (Peppermint) Oil was measured as the latent period between application and appearance of eserine-induced signs.[1] *Mentha Piperita (Peppermint) Oil had a latent period of 58 minutes.*

Penetration Enhancement

Mentha Piperita (Peppermint) Leaf Extract

The skin penetration enhancement potential of Mentha Piperita (Peppermint) Leaf Extract (aqueous ethanol extract) was evaluated using dorsal porcine skin (dermatomed to thickness of 500 µm).[34] A square section of skin was cut to provide a dose area of 1 cm^2 and placed in a flow-through diffusion cell. [^{14}C]-Caffeine (hydrophilic) or [^{14}C]-salicylic acid (hydrophobic) was applied topically with 10% Mentha Piperita (Peppermint) Leaf Extract to porcine skin. Ethanol alone served as the control. When compared to [^{14}C]-caffeine in the presence of ethanol (control), the dermal absorption of [^{14}C]-caffeine was significantly greater ($p > 0.05$; flux and permeability of caffeine increased by over 3-fold) in the presence of Mentha Piperita (Peppermint) Leaf Extract. However, this was not true for [^{14}C]-salicylic acid.

Penetration Inhibition

Mentha Piperita (Peppermint) Oil

Mentha Piperita (Peppermint) Oil and [ring-UL-^{14}C]benzoic acid were applied to full-thickness human skin (breast or abdominal) samples in a static diffusion cell.[35] As the concentration of Mentha Piperita (Peppermint) Oil increased from zero to 5% in the donor phase, the maximal flux of benzoic acid decreased. The differences were significant at 1.0% and 5.0% Mentha Piperita (Peppermint) Oil, where the maximal fluxes were reduced to 81% and 52% of the control, respectively.

Absorption, Distribution, Metabolism, and Excretion

Human

Oral

Mentha Piperita (Peppermint) Oil

The rate of Mentha Piperita (Peppermint) Oil absorption and excretion following oral administration was determined by measuring urinary menthol glucuronide.[1] *Four male volunteers ingested 180 mg of an enteric-coated Mentha Piperita (Peppermint) Oil-coated capsule following a 16-h fast. Menthol was liberated from its glucuronide metabolite by treating the urine with β-D-glucuronidase. It was estimated that between 37 and 116 mg of menthol corresponding to an average 40% recovery of the administered menthol dose was excreted by each panelist within 14 h.*

Mentha Piperita (Peppermint) Oil is relatively rapidly absorbed after oral administration and eliminated mainly via the bile.[8] The major biliary metabolite is menthol glucuronide, which undergoes enterohepatic circulation. The urinary metabolites result from hydroxylation at the C-7 methyl group at C-8 and C-9 of the isopropyl moiety, forming a series of mono- and dihydroxymenthols and carboxylic acids, some of which are excreted, in part, as glucuronic acid conjugates. Studies with tritiated I-menthol in rats indicated approximately equal excretion in the feces and urine. The main metabolite identified was menthol-glucuronide. Additional metabolites are mono- or di-hydroxylated menthol derivatives.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Mentha Piperita (Peppermint) Oil

Mentha Piperita (Peppermint) Oil had a 24-h oral LD_{50} of 4441 mg/kg in fasted Wistar rats; the 48-h LD_{50} was 2426 mg/kg.[1] *In a study involving fasted mice, an LD_{50} of 2410 mg/kg was reported for Mentha Piperita (Peppermint) Oil diluted in olive oil.*

Short-Term Toxicity Studies

Oral

Mentha Piperita (Peppermint) Oil

In 3 of 4 short-term oral toxicity studies (28-day or 5-week studies) involving 20 to 28 rats per group, brain lesions (specifically, cyst-like spaces in the cerebellum) were observed at Mentha Piperita (Peppermint) Oil doses up to 100 mg/kg/day.[1] *In the remaining study (12 rats per group), these lesions were not observed in rats dosed with Mentha Piperita (Peppermint) Oil at doses of 20, 150, or 500 mg/kg/day for 5 weeks.*

Subchronic Toxicity Studies

Oral

Mentha Piperita (Peppermint) Oil

Groups of 28 Wistar rats were given oral doses of 10, 40, and 100 mg/kg Mentha Piperita (Peppermint) Oil (diluted with soybean oil) daily for 90 days.[1] *All hematological and biochemical parameters were within normal range, and there were no significant differences in absolute and relative organ weights. Brain lesions (specifically, cyst-like spaces in the cerebellum) were observed in all dose groups, but these results were classified as significant only for animals of the 100 mg/kg/day dose group. No other lesions of encephalopathy were observed. Nephropathy (hyaline droplet formation) was observed only in male rats of the 100 mg/kg/day dose group, and there was no evidence of epithelial degeneration. The no-observed-adverse-effect level (NOAEL) for Mentha Piperita (Peppermint) Oil was 40 mg/kg/day in this study*.

Chronic Toxicity Studies

Human

Dermal

Exposure Assessment

Mentha Piperita (Peppermint) Oil

The FDA calculated an estimated human exposure from cosmetic use based on the concentration of use information supplied by industry.[1] *Using a body splash product containing 0.2% Mentha Piperita (Peppermint Oil) and assuming 100% absorption over a body surface of 17,000 cm^2 and a daily application of 1 mg/cm^2 (~17 ml of the product), the FDA estimated an exposure of 34 mg/day. For a 60-kg person, this amounted to an estimated daily dose of 0.6 mg/kg/day*.

Risk Assessment

Mentha Piperita (Peppermint) Oil

A maximum dermal use level of 5.4% has been recommended for Mentha Piperita (Peppermint) Oil.[36] This dermal restriction is based on 8% menthofuran (pulegone metabolite) and 3% pulegone content, with limits of 0.5% for menthofuran and of 1.2% for pulegone. The authors also recommended that Mentha Piperita (Peppermint) Oil should be avoided altogether in cases of cardiac fibrillation and in individuals with a glucose-6-phosphate dehydrogenase deficiency. No further information relating to these recommendations is provided.

Oral

Exposure Assessment

Mentha Piperita (Peppermint) Oil

In the European Union, the highest recommended daily dose of Mentha Piperita (Peppermint) Oil is 1.2 ml, i.e., 1080 mg Mentha Piperita (Peppermint) Oil (contains a maximum of 140 mg pulegone + menthofuran).[12] For a 60 kg person, this would correspond to a daily intake of 2.3 mg/kg body weight. This recommended daily dose of Mentha Piperita

(Peppermint) Oil in medicinal products results in pulegone/menthofuran that exceeds the tolerated daily intake (TDI) (0.1 mg/kg) that was established for food by the Committee of Experts on Flavoring Substances (CEFS).

Risk Assessment

Mentha Piperita (Peppermint) Oil and Pulegone (a component of Mentha Piperita (Peppermint) Oil)

The authors of a book entitled ***Essential Oil Safety*** have recommended a maximum daily oral dose of 152 mg Mentha Piperita (Peppermint) Oil.[36] This oral restriction is based on 8% menthofuran and 3% pulegone content, with limits of 0.2 mg/kg/day for menthofuran and 0.5 mg/kg/day for pulegone.

Mentha piperita

A study was performed to characterize data on dietary botanical supplement (DBSs) associated with adverse event reports submitted to the FDA Center for Food Safety and Applied Nutrition's Adverse Event Reporting System (CAERS).[37] FDA obtained CAERS data from 1999 to 2003 involving adverse effects associated with the 6 most frequently used DBSs, including peppermint. No adverse events were reported for single-ingredient peppermint supplements during the study period.

GENOTOXICITY STUDIES

In Vitro

Mentha Piperita (Peppermint) Oil

The mutagenic potential of Mentha Piperita (Peppermint) Oil was investigated using the Salmonella/mammalian microsome test.[1] *The following Salmonella typhimurium strains were used: TA1535, TA100, TA1537, and TA98. The sample tested contained 38.1% menthol, 33.7% menthone, and 1.7% pulegone; the remaining components were not identified. Mentha Piperita (Peppermint) Oil, tested at doses of 6.4, 32, and 160 µg/plate, produced the same number of revertants as the negative control. Toxicity was noted at the next (and maximum) dose of 800 µg/plate. Metabolic activation appeared to have made the oil less toxic to the bacteria. Mentha Piperita (Peppermint) Oil was not genotoxic.*

In an in vitro chromosomal aberration test using a Chinese hamster fibroblast cell line, Mentha Piperita (Peppermint) Oil, at a maximum concentration of 0.25 mg/ml (in ethanol), produced polyploidism in 3% of the cells and structural aberrations in 7% of the cells at 48 h after treatment. The results were considered equivocal, as scores of either ≥ 10% or ≤ 4.9% were necessary for classification as either positive or negative, respectively. The results for Mentha Piperita (Peppermint) Oil (150 µg/ml) were negative in a mouse lymphoma L5178Y TK +/- cell mutagenesis assay. Results were also negative for this ingredient (at 155 µg) in an unscheduled DNA synthesis assay using rat hepatocytes.[1]

The genotoxicity of Mentha Piperita (Peppermint) Oil was evaluated in a chromosome aberration test using human peripheral blood lymphocytes.[38] Lymphocyte cultures were incubated for 24 h with test substance concentrations up to 0.30 µl/ml. When chromosome aberrations (chromatid breaks, chromatid exchanges, chromosome breaks, and chromosome exchanges) were scored, not less than 100 metaphases per culture were analyzed. Mentha Piperita (Peppermint) Oil was the most clastogenic at a concentration of 0.20 µl/ml (8-fold increase over acetone solvent control); the number of aberrant cells decreased at higher concentrations. The authors noted that the dose-response curve for Mentha Piperita (Peppermint) Oil was complicated, with a clear peak response at a concentration of 0.20 µl/ml.

Mentha Piperita (Peppermint) Oil was tested at concentrations up to 0.30 µl/ml in the sister chromatid exchange (SCE) test involving human lymphocytes.[38] The test conditions were essentially the same as those in the preceding chromosome aberration test, with the exception that 5-bromo-2'-deoxyuridine was added (10 µg/ml) to cultures initially. To determine the replicative index, 200 cells were scored. Mentha Piperita (Peppermint) Oil induced SCEs in a dose-independent manner. The authors noted that, seemingly, the saturation of SCE-inducing capacity occurred at high concentrations of Mentha Piperita (Peppermint) Oil. Results also indicated that Mentha Piperita (Peppermint) Oil inhibited cell replicative kinetics, some signs of which were observed at a concentration of 0.15 µl/ml. At concentrations ≥ 0.20 µl/ml, statistically significant inhibition of cell replicative kinetics was evident.

ANTIGENOTOXICITY STUDIES

Mentha Piperita (Peppermint) Leaf Extract

Oral pretreatment with Mentha Piperita (Peppermint) Leaf Extract (aqueous extract) (1 g/kg/day for 3 consecutive days) before exposure to gamma radiation was found to be effective in protecting against chromosomal damage in the bone marrow of Swiss albino mice (number tested not stated).[39] The exposure of mice to 8 gray (Gy), ionizing radiation (1 Gy is equivalent to the absorption of one joule of radiation energy per kilogram of matter), only resulted in chromosomal aberrations in the form of chromatid breaks, chromosome breaks, centric rings, dicentrics, exchanges, and acentric fragments. In mice pretreated with Mentha Piperita (Peppermint) Leaf Extract, there was a significant decrease in the frequency of aberrant cells when compared to the irradiated control. A significant increase in the percentage of chromatid breaks, chromosome breaks, centric rings, dicentrics, exchanges, acentric fragments, total aberrations, and aberrations/ damaged cell was observed at 12 h post-irradiation necropsy time in control animals. However, a significant decrease in the percentage of aberrations of this type was observed in mice pretreated with Mentha Piperita (Peppermint) Leaf Extract.

The modulatory effects of Mentha Piperita (Peppermint) Leaf Extract (aqueous extract) on genotoxicity and lung tumor incidence were evaluated using 4 groups of 30 to 76 Swiss albino mice.[40] Beginning at 3 weeks of age (weaning), the mice received a single subcutaneous injection of benzo[a]pyrene and were then dosed orally (by gavage) with either water (group of 53 mice) or Mentha Piperita (Peppermint) Leaf Extract (1 g/kg; group of 76 mice). The remaining 2 groups of mice in the study were identified as no benzo(a)pyrene or Mentha Piperita (Peppermint) Leaf Extract dosing (30 mice) and Mentha Piperita (Peppermint) Leaf Extract alone (30 mice). When compared to mice in the benzo(a)pyrene only group, Mentha Piperita (Peppermint) Leaf Extract reduced the frequency of chromosomal aberrations and micronuclei in bone marrow cells. Mentha Piperita (Peppermint) Leaf Extract had an antigenotoxic effect in this study. Results relating to the modulatory effect of Mentha Piperita (Peppermint) Leaf Extract on lung tumor formation are included in the Anticarcinogenicity section of the report text.

CARCINOGENICITY STUDIES

Oral

Mentha Piperita (Peppermint) Oil

In a carcinogenicity study of toothpaste and its components, groups of 52 male pathogen-free CFLP (ICI-redefined) mice were dosed by gavage with 4 or 16 mg Mentha Piperita (Peppermint) Oil/kg/day, 6 days per week for 80 weeks. Treatment was followed by a 16- to 24-week observation period. An untreated group of 52 male mice and a vehicle control group of 260 male mice that received the toothpaste base (which did not contain chloroform, eucalyptol, or Mentha Piperita (Peppermint) Oil) were maintained as controls. At least one neoplasm at any site was observed in 73%, 69%, 65%, and 71% of mice of the low-dose, high-dose, untreated control, and vehicle control groups, respectively. The incidence of neoplasms of the lungs and kidneys was comparable among mice of the treated and nontreated groups. Hepatic cell tumor incidence for Mentha Piperita (Peppermint) Oil-dosed mice (25%) was comparable to the incidence for mice of the vehicle control group (27%); the incidence for the untreated group was 19%. Malignant lymphoma was found in 25%, 21%, 10%, and 14% of mice of the low-dose, high-dose, untreated, and vehicle control groups, respectively. The researchers did not discuss whether the differences in tumor incidence were significant.[1]

ANTICARCINOGENICITY STUDIES

Mentha Piperita (Peppermint) Leaf Extract

The modulatory effects of Mentha Piperita (Peppermint) Leaf Extract (aqueous extract) on genotoxicity and lung tumor incidence were evaluated using 4 groups of 30 to 76 Swiss albino mice.[40] Beginning at 3 weeks of age (weaning), the mice received a single subcutaneous injection of benzo[a]pyrene and were then dosed orally (by gavage) with either water (group of 53 mice) or Mentha Piperita (Peppermint) Leaf Extract (1 g/kg; group of 76 mice). The remaining 2 groups of mice in the study were identified as no benzo(a)pyrene or Mentha Piperita (Peppermint) Leaf Extract dosing (30 mice) and Mentha Piperita (Peppermint) Leaf Extract alone (30 mice). The mice were killed at 9 weeks of age and evaluated for lung tumor incidence. Dosing with Mentha Piperita (Peppermint) Leaf Extract caused a significant reduction in the number of lung adenomas from an incidence of 67.92% in mice given benzo[a]pyrene only to 26.31%, which amounted to 61.26% inhibition. Tumor multiplicity was 1.22 in the benzo[a]pyrene only group and 1.15 in the benzo[a]pyrene + Mentha Piperita (Peppermint) Leaf Extract group. Mentha Piperita (Peppermint) Leaf Extract had an inhibitory effect on lung tumor

formation in this study. Results relating to the modulation of genotoxicity are included in the Antigenotoxicity section of the report text.

The anticancer potential of Mentha Piperita (Peppermint) Leaf Extract (double-distilled; water extract) was studied using Swiss albino mice (number not stated).[41] Two stage mouse skin carcinogenesis was initiated by 7,12-dimethyl-benz[a]anthracene (DMBA). Two weeks later, croton oil (promoter) was applied 3 times per week for 14 weeks. The mice were dosed orally with Mentha Piperita (Peppermint) Leaf Extract (800 mg/kg/day) for the same period. At the end of the dosing period, average latent period, tumor incidence, size, burden, weight and cumulative number of papillomas were assessed. Dosing with Mentha Piperita (Peppermint) Leaf Extract caused inhibition of skin papilloma formation induced by DMBA and the application of croton oil, in terms of a significant decrease in the cumulative number of papillomas, tumor burden, and tumor incidence. In the control group, the tumor incidence was 100 percent. However, after dosing with the test substance for 15 days, the tumor incidence was reduced to 64%. There was a significant increase in the latency period for the appearance of papillomas in test animals (11 weeks in control group; 13 weeks in test group).

The possible molecular mechanisms underlying the cytotoxicity and anticarcinogenic potential of Mentha Piperita (Peppermint) Leaf Extract (petroleum ether, benzene, chloroform, ethyl acetate, methanol, or water extract) on 6 human cancer (HeLa, MCF-7, Jurkat, T24, HT-29, MIAPaCa-2) and normal (IMR-90, HEK-293) cell lines were evaluated.[42] In the human cancer cell lines tested with doses of 1 µg/ml, 10 µg/ml, and 100 µg/ml for 6 h, the number of apoptotic cells was incremental with an increase in the dose of *Mentha piperita* extracts. However, of all the extracts tested, the chloroform and ethyl acetate extracts resulted in a significantly higher apoptotic index after 6 hours, and the results were dose-dependent. When compared to the cancer cell lines, no significant changes were observed in normal cells. Similarly, of all of the extracts tested, chloroform and ethyl acetate extracts of *Mentha piperita* had significant dose- and time-dependent anticarcinogenic activity, leading to G1 cell cycle arrest and mitochondrial-mediated apoptosis, perturbation of oxidative balance, upregulation of Bax gene, elevated expression of p53 and p21 in the treated cells, and acquisition of senescence phenotype, while inducing pro-inflammatory cytokines response.

A study was performed to evaluate the antitumor activity of Mentha Piperita (Peppermint) Leaf Extract (methanol extract), using SW-480 human colon adenocarcinoma cells in a relevant cell anti-proliferation assay.[43] Statistically significant ($\alpha = 0.05$) growth inhibition was observed at a concentration of 31µg/ml. An IC_{50} (concentration required for 50% inhibition, µg/ml) of 92.3 µg/ml was reported for Mentha Piperita (Peppermint) Leaf Extract.

OTHER RELEVANT STUDIES

Cytotoxicity

Mentha Piperita (Peppermint) Oil

The cytotoxicity of Mentha Piperita (Peppermint) Oil was evaluated in the (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay using 2 human cancer cell lines, MCF-7 and LNCaP.[44] Mentha Piperita (Peppermint) Oil from plants that were harvested during the summer and winter was tested. The following IC_{50} values were reported: MCF-7 cell line (75.2 ± 2.9 [summer]; 80.8 ± 3.2 [winter]) and LNCaP cell line (90.4 ± 3.7 [summer]; 95.7 ± 4.5 [winter]). IC_{50} values in the 10 to 100 µg/ml range represented a potentially toxic chemical, and IC_{50} values < 10µg/ml represented a potentially very toxic chemical.

In another study, essential oil was extracted from the leaves of *Mentha piperita*.[45] This extract was found to be cytotoxic in the following 4 human cancer cell lines: human lung carcinoma SPC-A1 cells (IC_{50} = 10.89 µg/ml), human leukemia K562 cells (IC_{50} = 16.16 µg/ml) and human gastric cancer SGC-7901 cells (IC_{50} = 38.76 µg/ml). The extract was inactive against human hepatocellular carcinoma BEL-7402 cells.

Mentha piperita

The inhibitory effect of *Mentha piperita* on A549 non-small cell lung adenocarcinoma cells was investigated using the MTT assay.[46] The results indicated that *Mentha piperita* had a moderate toxic effect on the A549 cell line (IC_{50} = 879.52 ± 22.55 µg/ml). The growth of A549 cells was inhibited by *Mentha piperita* in a dose-dependent manner. The inhibitory rate was 54.54% ± 1.38% at the highest concentration tested (1 mg/ml).

Hepatotoxicity

Mentha Piperita (Peppermint) Leaf Extract

Mentha Piperita (Peppermint) Leaf Extract (methanol extract) and other botanical extracts were tested on both human (HepG2/C3A) and rat (MH1C1) hepatoma cells, using a battery of toxicity endpoints.[47] The extract was dissolved in dimethyl sulfoxide (DMSO) and then diluted in culture medium to a final concentration of 1000 µg/ml. The following 8 endpoints covering a variety of biological activities relevant to hepatotoxicity were used for hepatotoxicity evaluation: oxidative stress, mitochondrial membrane permeability, cellular neutral and polar lipid accumulation, CYP1A, 2B, 3A activities, albumin excretion, and total DNA content. Cluster analysis was used to group the phenolics into 4 clusters for each cell type. Two of the clusters were cluster 1 (compounds clustering with the solvent control (DMSO) and cluster 2 (compounds with reported in vivo liver toxicity). Overall and individual liver activity of the phenolics on both human and rat hepatoma cell lines were compared. For HepG2/C3A cells, 100% of the observations for Mentha Piperita (Peppermint) Leaf Extract and thyme extract, 92% for cinnamon extract, and 89% for juniper berry extract were assigned to cluster 1 (control group). For rat MH1C1 cells, 100% of the juniper berry extract and Mentha Piperita (Peppermint) Leaf Extract observations were assigned to cluster 1. The authors noted that because there are currently no reports of liver toxicity associated with peppermint, Mentha Piperita (Peppermint) Leaf Extract is useful as a negative control.

Nephrotoxicity

Mentha Piperita (Peppermint) Leaf Extract (as *Mentha piperita* tea)

The effects of *Mentha piperita* tea on rat kidney tissue were evaluated. The tea (prepared daily) was made by pouring 250 ml of boiling water over one heaped teaspoon (5 g) of the dried leaves of *Mentha piperita* L (grown in Turkey) and steeping for 5 to 10 minutes. Groups of 12 male Wistar albino rats were used. Test animals received *Mentha piperita* tea (20 g/l) in drinking water for 30 days. Control rats were given commercial drinking water during the study. The following histopathological changes, described as slight, were reported for the group dosed with *Mentha piperita* tea: hydropic degeneration of tubular epithelial cells, epithelial cells with pyknotic nuclei and eosinophilic cytoplasm, tubular dilatation and enlargements in Bowman capsules. In conclusion, the results indicate that *Mentha. piperita* does not show nephrotoxicity.[48]

Effect on Histamine Release

Mentha Piperita (Peppermint) Leaf Extract

The 50% ethanol extract of peppermint leaves and stems significantly inhibited histamine release from rat peritoneal mast cells that was induced by compound 48/80 (polymer produced by the condensation of *N*-methyl-*p*-methoxyphenethylamine with formaldehyde) *in vitro*.[49]

Mentha Piperita

In a study involving human basophil cell suspensions, obtained from workers who were exposed to an additive containing penicillin, the cell suspensions were incubated with 10^{-1} to 10^{-3} mg/ml Peppermint (dry aroma). A dose-dependent increase in histamine release was noted, and it was concluded that this release was due to nonimmunological mechanisms.[1]

Immune System Effects

Mentha Piperita (Peppermint) Oil

The results of a host-resistance assay involving groups of 20 mice that had been dosed orally with Mentha Piperita (Peppermint) Oil (up to 1250 mg/kg/day for 5 days) suggested immunosuppression and/or increased susceptibility to bacterial-induced mortality. The results of a plaque-forming assay involving groups of 10 mice that received the same oral doses were negative.[1]

Effect on Hair Growth

In a study involving C57BL/6 mice, the data suggest that 3% Mentha Piperita (Peppermint) Oil (diluted in jojoba oil) facilitates hair growth by promoting the conservation of vascularization of hair dermal papilla, which may contribute to the induction of early anagen stage.[50]

DERMAL IRRITATION AND SENSITZATION STUDIES

Irritation

In Vitro

Mentha Piperita (Peppermint) Leaf Extract

The skin irritation potential of Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract) at concentrations of 10% and 100% was evaluated using the in vitro reconstructed human epidermis test method, and results were negative. This test is summarized in Table 6.

Animal

Mentha Piperita (Peppermint) Oil

Hairless sites on 5 white rabbits were injected intradermally with 0.05 ml Mentha Piperita (Peppermint) Oil. Gross examinations were performed at 24 h and 48 h, at 1 and 2 weeks, and, in some cases, at 1 month after dosing. Dosing was repeated between 5 and 10 times. At microscopic examination of skin samples, moderate reactions characterized by polymorphonuclear leucocytes, lymphocytes, and plasma cells (without necrosis) were observed in 3 rabbits. Severe reactions, which were marked by the above as well as necrosis, were observed in the other 2 rabbits.[1]

Human

Human skin irritation data are summarized in Table 6.

Mentha Piperita (Peppermint) Leaf Extract

The skin irritation potential of a lipstick containing 0.2961% Mentha Piperita (Peppermint) Leaf Extract was evaluated in a 48-h occlusive patch test using the following group of 50 subjects: normal (25), with eczema (4 subjects), with allergy (4 subjects) and with sensitive skin (17 subjects). Results were classified as negative.[51]

Mentha Piperita (Peppermint) Leaf Water

Slight erythema was observed in 1 of 50 subjects after repeated applications of a cleaning gel containing 50% Mentha Piperita (Peppermint) Leaf Water in a product use study. Mild and moderate erythema were observed in 12 and 6 subjects, respectively, patch tested with 50% Mentha Piperita (Peppermint) Leaf Water (10% aqueous solution dilution; effective concentration = 5% Mentha Piperita (Peppermint) Leaf Water). In one of the skin sensitization studies on 20% Mentha Piperita (Peppermint) Oil that is summarized in the following section, it was reported that there was no evidence of skin irritation in the 104 subjects tested.[52,53,54]

Sensitization

Human

In the maximization test, 25 healthy male panelists received five 48-h occlusive induction patch (containing 8% Mentha Piperita (Peppermint) Oil) applications. Pre-treatment was for 24 h with an occlusive patch containing 5% sodium lauryl sulfate (SLS) prior to each exposure. After a 10-day non-treatment period, the subjects were challenged on the back with a 48-h patch (also preceded by SLS treatment). No evidence of sensitization was found.[1]

Human skin sensitization data are summarized in Table 6.

Human repeated insult patch test (HRIPT) results were negative for sensitization in studies involving $\geq$ 101 subjects tested with a face cream containing 20% Mentha Piperita (Peppermint) Leaf Water (1 study) and 20% Mentha Piperita

(Peppermint) Oil (2 studies). HRIPT results for undiluted Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract) in 52 subjects were also negative.[6,54,55,56,57]

Photosensitization/Phototoxicity

Animal

Mentha Piperita (Peppermint) Oil

Undiluted Mentha Piperita (Peppermint) Oil was applied to the backs of 6 Skh:hairless mice. Thirty minutes later, the mice were irradiated for either 1 h with light from a fluorescent blacklight at an integrated UVA of 3 W/m^2, or for 40 minutes with light from a Xenon lamp at a weighted erythema energy of 0.1667 W/m^2. The mice were examined at 4 h, 24 h, 48 h, 72 h, and 96 h after radiation treatment. No effects were noted. In a second experiment, using 2 miniature swine and following the same protocol, no effect was produced by 100% Mentha Piperita (Peppermint) Oil.[1]

OCULAR IRRITATION STUDIES

Human

Mentha Piperita (Peppermint) Leaf Water

The ocular irritation potential of a cleansing gel containing 50% Mentha Piperita (Peppermint) Leaf Water was studied using 50 subjects.[52] The subjects applied the product twice per day for 4 weeks, and were instructed to record any signs felt or observed during product use. Product use did not cause any signs of ocular or palpebral irritation.

CLINICAL STUDIES

Multicenter Studies

Mentha Piperita (Peppermint) Oil

Data from multicenter studies evaluating the skin irritation/sensitization potential of Mentha Piperita (Peppermint) Oil in patients are summarized in Table 6.[57]

A multicenter study involving 13,398 patients was performed by the US/Canadian North American Contact Dermatitis Group (NACDG), whereby 71 patients were patch tested with Mentha Piperita (Peppermint) Oil (2% in petrolatum). A positive reaction prevalence rate of 0.53% was reported for this ingredient (Table 6).[59] In another multicenter study, neither irritant nor allergic reactions were observed in 73 patients patch tested with Mentha Piperita (Peppermint) Oil according to International Contact Dermatitis Research Group (ICDRG) patch test procedures.

Case Reports

Case reports are summarized in Table 6.

Positive patch test reactions to Mentha Piperita (Peppermint) Oil and Mentha Piperita were reported in 8 of 9 case reports on patients with diseased skin.[60,61,62,63,64,65,66] Though positive patch test results were reported in one of the studies on Mentha Piperita (Peppermint) Oil, prick test results in that study were negative. In patients without skin disease, but with peppermint sensitivity, positive prick test reactions to Mentha Piperita (Peppermint) Leaf, Mentha Piperita (Peppermint) Leaf Extract, and Mentha Piperita were reported.[67,68]

Other Clinical Reports

Mentha Piperita (Peppermint) Oil

Positive reactions were observed in 7 of 450 dermatitic patients who were patch tested with 2% Mentha Piperita (Peppermint) Oil in yellow soft paraffin.[1] *In another study, positive reactions to 2% Mentha Piperita (Peppermint) Oil were observed in 6 of 86 dermatitic patients. A patch containing 1% Mentha Piperita (Peppermint) Oil (vehicle unknown) was applied to the backs of 56 patients with chronic urticaria. No reactions were noted after a 1-h or 48-h exposure.*

No reactions were observed in 25 spice factory workers who were patch tested with 2% Mentha Piperita (Peppermint) Oil in petrolatum. It has been reported that the patch testing of individual components of Mentha Piperita (Peppermint) Oil using 3 patients with allergic contact dermatitis established that the allergens were menthol and trace components such as piperitone or pulegone.[1]

Oral

A triple-blind clinical trial involved 96 randomly selected subjects (47 cases and 49 controls; all pregnant women) with a diagnosis of pruritus gravidarum.[69] The case and control subjects were instructed to consume 60 ml of peppermint oil (0.5% in sesame oil) and identical placebos, respectively, twice per day for 2 weeks. The authors noted that Mentha Piperita (Peppermint) Oil did not cause any special side effects in any of the subjects tested.

Each of 6 pediatric patients with irritable bowel syndrome received a single oral dose of Mentha Piperita (Peppermint) Oil (187 mg).[70] Each capsule contained 83 mg of menthol as a constituent of Mentha Piperita (Peppermint) Oil. Each patient drank 125 ml of water after ingestion of the capsule. No adverse events were reported. The delayed appearance of menthol in the plasma was reported; a substantial lag time (range 1 h to 4 h) was observed in all subjects. Thus, an apparent prolonged absorption time was demonstrated. The authors noted that reasons for the delayed time of peak (T_{max}) likely related to formulation-specific factors (i.e., delayed release) and, potentially, enterohepatic recirculation.

SUMMARY

The safety of the following ingredients in cosmetics has been reviewed by the Panel, and a final report with a conclusion stating that these ingredients are safe as used in cosmetic formulations was published in 2001: Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint) Leaf Water. The conclusion also stated that the concentration of pulegone, a constituent of these botanical ingredients, should not exceed 1%. The current safety assessment is, in part, a re-review of the 4 *Mentha piperita* (peppermint)-derived ingredients, and is inclusive of safety test data that have become available since the final report was issued.

The current safety assessment is also an initial review of the following 6 *Mentha piperita* (peppermint)-derived ingredients: Mentha Piperita (Peppermint) Extract, Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract, Mentha Piperita (Peppermint) Flower/Leaf/Stem Water, Mentha Piperita (Peppermint) Leaf Cell Extract, Mentha Piperita (Peppermint) Leaf Juice, and Mentha Piperita (Peppermint) Meristem Cell Culture.

According to 2017 VCRP data, the greatest use frequency is being reported for Mentha Piperita (Peppermint) Oil, which is being used in 827 cosmetic products, mostly leave-on products. The results of a concentration of use survey provided in 2016 indicate that Mentha Piperita (Peppermint) Leaf Water is being used at concentrations up to 40% in leave-on products, which is the greatest use concentration that is being reported for *Mentha piperita* (peppermint)-derived ingredients reviewed in this safety assessment.

Mentha Piperita (Peppermint) Oil is GRAS for use in food for human consumption. It is also an inactive ingredient in drug products that have been approved by the FDA and is on the EPA list of active ingredients eligible for minimum risk pesticide products.

Mentha Piperita (Peppermint) Leaf Extract (10% aqueous ethanol extract) caused a statistically significant increase in the penetration of caffeine, but not salicylic acid, through porcine skin. Mentha Piperita (Peppermint) Oil inhibited the penetration of benzoic acid through human skin.

Following oral administration, Mentha Piperita (Peppermint) Oil is relatively rapidly absorbed and eliminated mainly via the bile. The major biliary metabolite is menthol glucuronide. Additional metabolites are mono- or di-hydroxylated menthol derivatives.

In a 28-day oral toxicity study on pulegone (up to 800 mg/kg/day) involving rats, no significant histopathology of the liver was observed and histological examination revealed no or very few cyst-like spaces in white matter of the cerebellum. The number and severity of cyst-like spaces in this study were not related to dosing with pulegone and were considered comparable to observations that are normally present in historical control Wistar rats at the laboratory where the study was performed. Mentha Piperita (Peppermint) Leaf (as *Mentha piperita* tea**)** was not nephrotoxic to rats when administered (20 g/l) in drinking water daily for 30 days.

No adverse events were reported for single-ingredient peppermint supplements in a study that was performed to characterize data on dietary botanical supplement (DBSs) associated with adverse event reports submitted to the FDA Center for Food Safety and Applied Nutrition's Adverse Event Reporting System (CAERS).

Mentha Piperita (Peppermint) Oil was clastogenic in a chromosome aberration test involving peripheral blood lymphocytes. In a genotoxicity assay involving human lymphocytes, Mentha Piperita (Peppermint) Oil induced sister chromatid exchanges in a dose-dependent manner.

Oral pretreatment with Mentha Piperita (Peppermint) Leaf Extract (aqueous extract) before exposure to gamma radiation was found to be effective in protecting against chromosomal damage in the bone marrow of Swiss albino mice. In another study, the oral administration of Mentha Piperita (Peppermint) Leaf extract had an antigenotoxic (i.e., reduced the frequency of chromosomal aberrations and micronuclei in bone marrow cells) in Swiss albino mice intraperitoneally injected with benzo(a)pyrene.

Carcinogenicity data on pulegone, a constituent of *Mentha piperita* (peppermint)-derived ingredients, are included in this safety assessment (see Table 1), considering that the Panel previously limited the concentration of pulegone in these cosmetic ingredients. In a 2-year bioassay, pulegone (up to 150 mg/kg/day)was administered to groups of 50 male and 50 female F344/N rats and groups of 50 male and 50 female B6C3F1 mice by corn oil gavage (5 days/week). Increased incidences of liver neoplasms in male and female B6C3F1 mice in the study led to the conclusion that there was clear evidence of carcinogenic activity in mice. For female F344/N rats, it was concluded that there was some evidence of carcinogenicity based on an increased incidence of urinary bladder neoplasms. Male rats did not have increased incidences of bladder tumors or neoplasms of other organs. A subsequent study supported the hypothesis that cytotoxicity followed by regenerative cell proliferation is the mode-of-action for pulegone-induced urothelial tumors in female rats.

Oral dosing with Mentha Piperita (Peppermint) Leaf Extract caused a significant reduction in the number of lung adenomas from an incidence of 67.92% in Swiss albino mice intraperitoneally injected with benzo(a)pyrene to 26.31%. Oral dosing with Mentha Piperita (Peppermint) Leaf Extract also caused inhibition of skin papilloma formation induced by DMBA and the application of croton oil, in terms of a significant decrease in the cumulative number of papillomas, tumor burden, and tumor incidence.

In the human cancer cell lines tested with Mentha Piperita (Peppermint) Leaf Extract (various extractants used), the number of apoptotic cells was incremental with an increase in the dose of *Mentha piperita* extracts. Mentha Piperita (Peppermint) Leaf Extract (only from chloroform and ethyl acetate extractants) had significant dose- and time-dependent anticarcinogenic activity, leading to G1 cell cycle arrest and mitochondrial-mediated apoptosis, perturbation of oxidative balance, upregulation of Bax gene, and elevated expression of p53 and p21 in the treated cells. In a study that was performed to evaluate the antitumor activity of Mentha Piperita (Peppermint) Leaf Extract (methanol extract) in an anti-proliferation assay involving SW-480 human colon adenocarcinoma cells, statistically significant growth inhibition was observed.

Results were positive for Mentha Piperita (Peppermint) Oil in cytotoxicity assays involving human cancer cell lines.

Mentha Piperita (Peppermint) Leaf Extract (1000 µg/ml, methanol extract) did not induce hepatotoxicity in in vitro assays involving human (HepG2/C3A) and rat (MH1C1) hepatoma cells.

The 50% ethanol extract of peppermint leaves and stems significantly inhibited compound 48/80-induced histamine release from rat peritoneal mast cells *in vitro*.

In a study involving C57BL/6 mice, it was concluded that 3% Mentha Piperita (Peppermint) Oil (diluted in jojoba oil) facilitated hair growth by promoting the conservation of vascularization of hair dermal papilla.

In a 48-h occlusive patch test, a lipstick product containing 0.2961% Mentha Piperita (Peppermint) Leaf Extract did not cause skin irritation in any of the 50 subjects tested. In an *in vitro* skin irritation study on Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract) involving reconstructed human epidermis, results were negative (MTT > 50%).

A face cream containing 20% Mentha Piperita (Peppermint) Leaf Water did not induce cumulative skin irritation or sensitization in an HRIPT involving 107 subjects. Negative results were also reported for a lipstick product containing 0.2961% Mentha Piperita (Peppermint) Leaf Extract in a 48-h occlusive patch test (skin irritation test) involving 50 subjects. Slight erythema was observed in 1 of 50 subjects who applied a cleansing gel containing 50% Mentha Piperita (Peppermint) Leaf Water twice per day for 4 weeks; there were no signs of ocular or palpebral irritation in any of the subjects. In a 48-h, single-application patch test, the skin irritation potential of a cleansing gel containing 50% Mentha Piperita (Peppermint) Leaf Water (10% aqueous dilution [effective concentration = 5%]) was evaluated using 52 subjects. A score of 1 (mild

erythema) was reported for 12 subjects on day 2 and for 18 subjects on day 3. A score of 2 (moderate erythema) was reported for 2 subjects on day 2 and for 3 subjects on day 3. On day 4, 46 subjects had a score of 0 and 6 had a score of 1. The authors concluded that the skin compatibility of the diluted product was considered good.

The skin irritation and sensitization potential of 20% Mentha Piperita (Peppermint) Oil was evaluated in an HRIPT involving 104 subjects and results were negative. Similarly, there was no evidence of sensitization to 20% Mentha Piperita (Peppermint) Oil in an HRIPT involving 101 subjects. HRIPT results for undiluted Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract) in 52 subjects were also negative.

In a multicenter study, neither irritant nor allergic reactions were observed in 73 patients patch tested with Mentha Piperita (Peppermint) Oil according to International Contact Dermatitis Research Group (ICDRG) patch test procedures. Another multicenter study involving 13,398 patients was performed by the US/Canadian North American Contact Dermatitis Group (NACDG), whereby a segment of this population (number of patients not stated) was tested with Piperita (Peppermint) Oil **(**2% in petrolatum). The prevalence rate for this ingredient was 0.9%.

Mostly positive patch test reactions to Mentha Piperita (Peppermint) Oil (2%in petrolatum) and Mentha Piperita were reported in case reports on patients with diseased skin. In patients without skin disease, but with peppermint sensitivity, positive prick test reactions to Mentha Piperita (Peppermint) Leaf, Mentha Piperita (Peppermint) Leaf Extract, and Mentha Piperita were reported. In other clinical reports, oral dosing with Mentha Piperita (Peppermint) Oil (0.5% in sesame oil, 60 ml) did not cause any side effects in 47 pregnant female patients. A single oral dose of Mentha Piperita (Peppermint) Oil did not cause any adverse events in 6 pediatric patients.

DISCUSSION

The safety of the following cosmetic ingredients has been reviewed by the Panel, and a final report with a conclusion stating that these ingredients are safe as used in cosmetic formulations was published in 2001: Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint) Leaf Water. The conclusion also states that the concentration of pulegone, a constituent of these botanical ingredients, should not exceed 1%. The current safety assessment is a re-review of the safety of these 4 ingredients, and is also an initial safety evaluation of the following 6 related ingredients that were not listed as cosmetic ingredients prior to development of the published safety assessment: Mentha Piperita (Peppermint) Extract, Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract, Mentha Piperita (Peppermint) Flower/Leaf/Stem Water, Mentha Piperita (Peppermint) Leaf Cell Extract, Mentha Piperita (Peppermint) Leaf Juice, and Mentha Piperita (Peppermint) Meristem Cell Culture.

In the 2001 published final safety assessment on *Mentha piperita* (peppermint)-derived ingredients, the Panel expressed concern that rat oral-dosing studies on Mentha Piperita (Peppermint) Oil and pulegone reported cyst-like spaces in the cerebellum that were attributed to pulegone. Therefore, the Panel established a 1% concentration limit on pulegone in *Mentha piperita* (peppermint)-derived ingredients due to toxicity concerns. In these studies, brain sections were fixed by immersion using 4% neutral buffered formaldehyde. Because immersion fixation of nervous tissue might cause artifacts observed as vacuolar retraction spaces around neurons, a study involving rats was performed, using both immersion and perfusion tissue fixation methods, to determine whether the cerebellar lesions observed in earlier studies were caused by dosing with pulegone. Study results for rats dosed with pulegone did not reveal the occurrence of test substance-related, cyst-like spaces in the white matter of the cerebellum using either perfusion or immersion tissue fixation techniques. A possible explanation for the observed dose-dependent cyst-like spaces seen in previous studies could have been due to an interaction between impurities in the test substance and the fixation agent used therein. Given this possibility, the Panel agreed that the brain lesions may have been an artifact of the fixation method, and that the 1% limitation on pulegone may not be warranted.

The Panel also considered the positive effects that were observed in female rats, and in male and female mice, dosed with pulegone in the 2011 National Toxicology Program (NTP) oral carcinogenicity study. However, the Panel did not express concern over these findings relative to pulegone as a component of Mentha Piperita (Peppermint) Oil in cosmetic products, based on the understanding that the cytotoxic dose-response relationship (renal and liver toxicity) that was associated with cancer development would not be relevant to pulegone exposure from a cosmetic product containing Mentha piperita (Peppermint) Oil at current use concentrations.

Also, 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 *Mentha piperita* (peppermint)-derived ingredients, the Panel is concerned about the presence of terpenes (e.g., limonene) and terpenoids (e.g. menthol) in cosmetics, which could result in sensitization.

The Panel 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.

Additionally, the Panel recognized that Mentha Piperita (Peppermint) Leaf Extract can enhance the penetration of other ingredients through the skin. The Panel cautioned that care should be taken in formulating cosmetic products that may contain *Mentha piperita* (peppermint)-derived ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.

The issue of incidental inhalation exposure was discussed by the Panel, as *Mentha piperita* (peppermint)-derived ingredients are being used in products that could possibly be inhaled. For example, Mentha Piperita (Peppermint) Oil is being used in both pump hair sprays (maximum use concentrations up to 0.02%) and aerosol hair sprays (maximum use concentrations up to 0.017%) which may result in incidental inhalation exposure. Additionally, the Panel noted that droplets/particles from spray cosmetic products would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. 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.

Finally, the Panel agreed that the available composition data on Mentha Piperita (Peppermint) Oil are sufficient, but the data relating to composition of the other ingredients, are insufficient. After considering the available skin irritation and sensitization data, the Panel determined that skin sensitization data on all ingredients, except for the Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, and Mentha Piperita (Peppermint) Leaf Water, are insufficient. Thus, the Panel determined that the following additional data are needed in order to evaluate the safety of in cosmetic products:

- Composition data on all ingredients except for Mentha Piperita (Peppermint) Oil.
    - Depending on the composition data that are received, other toxicological endpoints may be needed.

- Skin irritation and sensitization data on all ingredients except Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, and Mentha Piperita (Peppermint) Leaf Water.

Composition data on Mentha Piperita (Peppermint) Leaf Extract and a negative 48-h occlusive patch test on a lipstick product containing 0.2961% Mentha Piperita (Peppermint) Leaf Extract were received. However, no other data were received.

CONCLUSION

The CIR Expert Panel concluded that Mentha Piperita (Peppermint) Oil is safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-sensitizing; and, CIR Expert Panel concluded that the available data are insufficient to make a determination that the following ingredients are safe under the intended conditions of use in cosmetic formulations:

- Mentha Piperita (Peppermint) Leaf
- Mentha Piperita (Peppermint) Leaf Extract
- Mentha Piperita (Peppermint) Leaf Water
- Mentha Piperita (Peppermint) Extract
- Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract*
- Mentha Piperita (Peppermint) Flower/Leaf/Stem Water*
- Mentha Piperita (Peppermint) Leaf Cell Extract*
- Mentha Piperita (Peppermint) Leaf Juice*
- Mentha Piperita (Peppermint) Meristem Cell Culture*

* Not reported to be in current use.

TABLES

Table 1. Toxicity Data on Components of Mentha Piperita (Peppermint)–Derived Ingredients, as described in the original (2001) report.[1]

Study Type/Protocol	Results
Short-Term Oral Toxicity	
Menthone: 28-day study on groups of 20 rats. Doses up to 800 mg/kg/day.	Brain lesions (cyst-like spaces in the cerebellum).[1]
Menthol: 28-day study on groups of 20 rats. Doses up to 800 mg/kg/day	No brain lesions.[1]
Pulegone: 28-day study on groups of 20 rats. Doses up to 160 mg/kg/day	Brain lesions (cyst-like spaces in the cerebellum).[1]
Pulegone: 28-day study on groups of 28 female rats (CrL: (WI)BR, SPF strain). Doses (in soybean oil) of 160 mg/kg/day. Untreated control.	Alopecia. Statistically significant, test substance-related decrease in body weight and food consumption ($p < 0.001$) observed throughout t study. Statistically significant reduction in plasma creatinine. Statistically significant increase in plasma alkaline phosphatase and non-statistically significant increase in alanine aminotransferase. Increased plasma concentrations of alkaline phosphatase and alanine aminotransferase taken together with increased absolute liver weight was non- statistically significant, but increased relative liver weight ($p < 0.05$) was indicative of adverse effect on the liver. However, no significant histopathology of liver observed. Number and severity of cyst-like spaces in cerebellum considered comparable to observations normally present in historical control Wistar rats at laboratory where study was performed. Authors noted that dose-dependent cyst- like spaces in cerebellum observed in previous studies could have been due to interaction between impurities in test substance and fixation agent used. [4]
Developmental and Reproductive Toxicity	
Menthol: Groups of 15 to 23 pregnant animals dosed with Brazilian menthol via oral intubation. Mice received doses up to 185 mg/kg/day on gestation days (GD) 6 to 15. Rats received doses up to 218 mg/kg on GDs 6 to 15. Hamsters received doses up to 405 mg/kg/day on GDs 6 to 10. Artificially inseminated rabbits received doses up to 425 mg/kg/day on GDs 6 to 18. Caesarean sections were performed on all dams.	No teratogenic effects. [1]
Genotoxicity	
Menthol: *Salmonella typhimurium* strains: TA1535, TA100, TA1537, and TA98. Doses of 6.4, 32, 160, and 800 µg/plate in Ames test with or without metabolic activation.	Toxicity at highest dosed; less toxicity with metabolic activation. Same number of revertants reported for test and control cultures exposed to lower doses.[1]
Pulegone: *Salmonella typhimurium* strains: TA1535, TA100, TA1537, and TA98. Doses of 6.4, 32, 160, and 800 µg/plate in Ames test with or without metabolic activation.	Toxicity at highest dose; less toxicity with metabolic activation. Same number of revertants reported for test and control culture exposed to lower doses.[1]
Menthone: *Salmonella typhimurium* strains: TA1535, TA100, TA1537, TA98, and TA97. Doses of 6.4, 32, 160, and 800 µg/plate in Ames test with or without metabolic activation.	Toxicity at highest dose. Statistically significant number of revertants in strain TA1537 at doses of 6.4 and 32 µg/plate without metabolic activation. Further testing with a more sensitive strain (TA98) yielded statistically significant increases in the number of revertants at all doses tested without metabolic activation; results were dose-related.[1]
Menthol (Brazilian): Cytogenetic assay (rats). Doses of 1.45, 14.5, and 145 mg/kg, and, in some instances, doses of 500, 1150, and 3000 mg/kg, or 5000 mg/kg.	Non-genotoxic.[1]
Menthol (Brazilian): Dominant lethal assay (rats). Doses of 1.45, 14.5, and 145 mg/kg, and, in some instances, doses of 500, 1150, and 3000 mg/kg, or 5000 mg/kg.	Non-genotoxic.[1]
Menthol (Brazilian): Host-mediated assay (mice). Doses of 1.45, 14.5, and 145 mg/kg, and, in some instances, doses of 500, 1150, and 3000 mg/kg, or 5000 mg/kg. *Salmonella typhimurium* strain TA1530 and *Saccharomyces* strain D3 tested *in vitro*.	Weakly positive but significant response at high dose in *Salmonella typhimurium* TA1530, and elevated recombinant frequencies noted in *Saccharomyces* strain D3.[1]
Carcinogenicity	
Menthone: National Cancer Institute (NCI) 2-year bioassay. *dl*-menthol administered orally to Fischer 344 rats (3750 ppm or 7500 ppm) or to $B6C3F_1$ mice (2000 ppm or 4000 ppm).	Negative trend in fibroadenomas of the mammary gland observed in female rats (20 of 50 control; 10 of 49 low-dose; 7 of 49 high-dose).[1]

Table 1. Toxicity Data on Components of Mentha Piperita (Peppermint)–Derived Ingredients, as described in the original (2001) report.[1]

Study Type/Protocol	Results
Carcinogenicity	
Pulegone: National Toxicology Program (NTP) 2-year bioassay. Pulegone (in corn oil) administered to groups of 50 male and 50 female F344/N rats and groups of 50 male and 50 female B6C3F1 mice by gavage (5 days/week) for 105 weeks. Male rats received doses of 18.75, 37.5, or 75 mg/kg 5; female rats and male and female mice received doses of 37.5, 75, or 150 mg/kg.	Effects in the kidneys (hyaline glomerulopathy and nephropathy), liver (oval cell hyperplasia, bile duct hyperplasia, hypertrophy, hepatocyte necrosis, and portal fibrosis), nose (olfactory epithelium degeneration, inflammation, and metaplasia), and forestomach (inflammation, hyperplasia, and ulcer) reported. Increased incidences of liver neoplasms in male and female B6C3F1 mice in the study led to the conclusion that there was clear evidence of carcinogenic activity in mice. For female F344/N rats, it was concluded that there was some evidence of carcinogenicity based on an increased incidence of urinary bladder neoplasms. Five of 47 rats in 150 mg/kg female stop-exposure group (gavage with pulegone stopped at week 60 because of severely reduced body weights) diagnosed with papilloma and carcinoma, combined. Male rats did not show increased incidences of bladder tumors or neoplasms of other organs.[3] The International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence in experimental animals for the carcinogenicity of pulegone, and that there is inadequate evidence in humans for the carcinogenicity of pulegone. [71]
Pulegone: Female rats dosed orally (gavage) with 75 or 150 mg/kg for 4 and 6 weeks.	Results supported hypothesis that cytotoxicity followed by regenerative cell proliferation is mode-of-action for pulegone-induced urothelial tumors in female rats.[72]
Anticarcinogenicity	
(-)-Menthol: Rats dosed orally with 1%or 0.5% (-)-menthol for 20 weeks. Dosing initiated 2 weeks prior to dimethylbenzanthracene (DMBA) tumor induction.	Significant inhibition ($p < 0.001$) of DMBA-induced rat mammary gland carcinogenesis following 20 weeks of oral dosing with 1% (-)-menthol. Chemopreventive effect noted when rats dosed with 0.5% menthol for 2 weeks prior to and 1 week after DMBA induction.[1]
Skin Irritation	
Methanol: Two Tiger Balm formulations containing 8% and 10% menthol applied for 23 h, under occlusive patches, to abraded and intact sites on New Zealand white rabbits. Total number of patches applied was 21. A third group was treated with control wax (mixture of hard and soft waxes).	Dermal irritation observed in all treated animals, with the following severity scale: 8% menthol balm < control wax < 10% menthol balm. 8% menthol balm almost innocuous in male rabbits. Irritation observed was not progressive and tolerance developed within 10 days. No severe damage noted at microscopic examination of skin (increased hyperkeratosis noted at treated sites), and no evidence of systemic toxicity.[1]
Skin Sensitization	
Menthol	Because menthol is a predominant component of Mentha Piperita (Peppermint) Oil and Mentha Piperita (Peppermint) Leaf Extract, it should be noted that a review article on the sensitization potential of menthol is available.[58]
Other Clinical Reports	
Menthol: 877 patients with primary contact, atopic, nummular, and stasis dermatitis and eczema were tested with 5% menthol in yellow paraffin	Reactions observed in 1% of the panelists within 96 h.[1]

Table 2. Definitions and Functions of the Ingredients in this Safety Assessment.[2]

Ingredient CAS No.	Definition & Idealized Structures	Function
Mentha Piperita (Peppermint) Oil 8006-90-4 84082-70-2	Mentha Piperita (Peppermint) Oil is a volatile oil obtained from the whole plant *Mentha piperita*. The accepted scientific name for *Mentha piperita* is *Mentha x piperita*.	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Mentha Piperita (Peppermint) Leaf Extract 84082-70-2	Mentha Piperita (Peppermint) Leaf Extract is the extract of the leaves of the peppermint, *Mentha piperita*. The accepted scientific name for *Mentha piperita* is *Mentha x piperita*.	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous; Skin-Conditioning Agents - Occlusive
Mentha Piperita (Peppermint) Leaf	Mentha Piperita (Peppermint) Leaf is the dried leaves of *Mentha piperita*. The accepted scientific name for *Mentha piperita* is *Mentha x piperita*.	Fragrance Ingredients
Mentha Piperita (Peppermint) Leaf Water 84082-70-2	Mentha Piperita (Peppermint) Leaf Water is an aqueous solution of the steam distillate obtained from the leaves of *Mentha piperita*. The accepted scientific name for *Mentha piperita* is *Mentha x piperita*.	Flavoring Agents; Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Mentha Piperita (Peppermint) Extract 84082-70-2	Mentha Piperita (Peppermint) Extract is the extract of the whole plant, *Mentha piperita.* The accepted scientific name for *Mentha piperita* is *Mentha* x *piperita.*	Skin-Conditioning Agents - Miscellaneous
Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract 84082-70-2	Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract is the extract of the flowers, leaves and stems of *Mentha piperita*. The accepted scientific name for *Mentha piperita* is *Mentha* x *piperita.*	Flavoring Agents; Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Mentha Piperita (Peppermint) Flower/Leaf/Stem Water 84082-70-2	Mentha Piperita (Peppermint) Flower/Leaf/Stem Water is the aqueous solution of the steam distillates obtained from the flowers, leaves and stems of *Mentha piperita.* The accepted scientific name for *Mentha piperita* is *Mentha* x *piperita*.	Fragrance Ingredients
Mentha Piperita (Peppermint) Leaf Cell Extract	Mentha Piperita (Peppermint) Leaf Cell Extract is the extract of a culture of the leaf cells of *Mentha piperita.* The accepted scientific name for *Mentha piperita* is *Mentha* x *piperita.*	Antioxidants; Skin Protectants
Mentha Piperita (Peppermint) Leaf Juice 84082-70-2	Mentha Piperita (Peppermint) Leaf Juice is the juice expressed from the leaves of *Mentha piperita.* The accepted scientific name for *Mentha piperita* is *Mentha* x *piperita.*	Skin-Conditioning Agents - Miscellaneous
Mentha Piperita (Peppermint) Meristem Cell Culture	Mentha Piperita (Peppermint) Meristem Cell Culture is a suspension of the cultured meristem cells of *Mentha piperita.* The accepted scientific name for *Mentha piperita* is *Mentha* x *piperita.*	Skin-Conditioning Agents - Miscellaneous

Table 3. Physical and Chemical Properties of Mentha Piperita (Peppermint) Oil and Mentha Piperita (Peppermint) Leaf Extract

Property	Value	Reference
Mentha Piperita (Peppermint) Oil		
Form	Colorless or pale yellow liquid	1
Angular rotation (˚C)	Between -18 and 32	1
Refractive index (at 20˚C)	Between 1.459 and 1.465	1
Specific gravity	Between 0.896 and 0.908	1
Assay for total esters	Not less than 5% of esters, calculated as menthyl acetate	1
Assay for total menthol	Not less than 50% of menthol	1
Dimethyl sulfide	Passes test (rectified); fails test (natural)	1
Heavy metals (as Pb)	Passes test (limit of 0.004%)	1
Solubility	Soluble in alcohol: Passes test (1 volume dissolves in 3 volumes of 70% alcohol); Soluble in most vegetable oils; insoluble in propylene glycol	1, 10
Mentha Piperita (Peppermint) Leaf Extract		
Form	Yellow to light brown, clear oil	15
Refractive index (at 20˚C)	1459-1469	15
Density (at 20˚C)	0.890-0.910	15

Table 4. Chromatographic Profiles for Mentha Piperita (Peppermint) Oil[11,16] and Mentha Piperita (Peppermint) Leaf Extract.[15]

	Origins Other Than U.S.		U.S. Type	
Components	**Min. (%)**	**Max. (%)**	**Min. (%)**	**Max. (%)**
Mentha Piperita (Peppermint) Oil				
3-Octanol	0.1	0.5	0.1	0.4
1,8-Cineole	3.0	8.0	4.0	6.0
Limonene[a]	1.0	3.0	1.0	2.5
trans-Sabinene Hydrate	0.5	2.0	0.5	2.3
Menthone	13.0	28.0	15.0	25.0
Isomenthone	2.0	8.0	2.0	4.5
Menthofuran	1.0	8.0	1.5	6.0
Neomenthol	2.0	6.0	2.5	4.5
Menthol	32.0	49.0	36.0	46.0
Pulegone	0.5	3.0	0.5	2.5
Menthyl Acetate[b]	2.0	8.0	3.0	6.5
β-Caryophyllene	1.0	3.5	1.0	2.5
	Origin Not Stated			
Mentha Piperita (Peppermint) Leaf Extract				
Essential Oil[c]	80	90		
Essential Oil[d]		> 65		
Water		Not specified		
Volatile Compounds[e]				
Limonene		< 2		
1,8-Cineol		not specified		
L-Menthone	20	40		
Menthofuran		< 2		
Isomenthone		Not specified		
Isomenthol		Not specified		
Neomenthol		Not specified		
L-Menthol	25	40		
Pulegone		< 3		
Menthyl Acetate	5	15		
beta Caryophyllene		Not specified		
Germacrene		Not specified		
Allergen Compounds[f]				
Eugenol		< 0.05		
Linalool		< 0.3		
d-Limonene		< 1		

[a]The limonene is regarded to be predominantly L-limonene based on physical tests. It is believed that there might be a small amount of D-limonene present, but the exact quantity is unknown

[b]The menthyl acetate is regarded to be predominantly L-menthyl acetate based on the physical tests. It is believed that there might be a small amount of D-menthyl acetate present, but the exact quantity is unknown.

[C]Gravimetric distillation detection method used

[d]Volumetric distillation detection method used

[e]Gas chromatography-mass spectrometry detection method used

[f]Allergen compounds present are subject to declaration if the concentration exceeds 0.001% in leave-on and 0.01% in rinse-off products. However, values < 0.01% are not mentioned.

Table 5. Frequency and Concentration of Use of *Mentha piperita* (peppermint)-derived Ingredients According to Duration and Exposure. [1,21,22]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Mentha Piperita (Peppermint) Oil				**Mentha Piperita (Peppermint) Leaf Extract**			
	2017	**1998**	**2017**	**1997**	**2017**	**1998**	**2017**	**1997**
Totals*	**827**	**102**	**0.0001-5**	**0.1-3**	**198**	**35**	**0.000075-0.5**	**NR**
Duration of Use								
Leave-On	*433*	*52*	*0.0006-5*	*0.2-2*	*118*	*10*	*0.000075-0.5*	*NR*
Rinse-Off	*360*	*44*	*0.0001-1.9*	*0.1-3*	*79*	*24*	*0.0001-0.2*	*NR*
Diluted for (Bath) Use	*34*	*6*	*0.018-3.9*	*NR*	*1*	*1*	*NR*	*NR*
Exposure Type								
Eye Area	4	NR	0.00094	NR	4	NR	0.0018	NR
Incidental Ingestion	214	24	0.05-2.9	0.2-1.2	7	NR	0.00075-0.5	NR
Incidental Inhalation-Spray	19;120[a]	NR;23[a]	0.017-1;0.002-1.1[a]	NR	5;34[a]	NR;2[a]	0.00041-0.0046;0.00057-0.026[a]	NR
Incidental Inhalation-Powder	1	NR	0.01-1	NR	3	NR	0.0018	NR
Dermal Contact	458	75	0.0006-5	0.1-2	139	22	0.000075-0.2	NR
Deodorant (underarm)	2	NR	NR	NR	NR	NR	0.0018	NR
Hair - Non-Coloring	148	1	0.0001-0.96	3	50	13	0.00018-0.2	NR
Hair-Coloring	NR	NR	0.0024	NR	NR	NR	0.032	NR
Nail	7	2	0.00064-1.5	NR	2	NR	NR	NR
Mucous Membrane	317	30	0.0025-3.9	0.2-1.2	8	6	0.00075-0.5	NR
Baby Products	1	NR	0.2	NR	NR	NR	NR	NR
	Mentha Piperita (Peppermint) Leaf				**Mentha Piperita (Peppermint) Leaf Water**			
	2017	**1998**	**2017**	**1997**	**2017**	**1998**	**2017**	**1997**
Totals*	**NR**	**NR**	**0.0002-1.6**	**NR**	**15**	**NR**	**0.00013-40**	**NR**
Duration of Use								
Leave-On	*NR*	*NR*	*0.001*	*NR*	*9*	*NR*	*0.00013-40*	*NR*
Rinse-Off	*NR*	*NR*	*0.0002-1.6*	*NR*	*6*	*NR*	*0.00021-0.00067*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	***NR***	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	2	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR;0.001[a]	NR	NR;4[a]	NR	NR;0.00043-10[a]	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	0.001-1.6	NR	13	NR	0.00013-40	NR
Deodorant (underarm)	NR	NR	NR	NR	1	NR	15	NR
Hair - Non-Coloring	NR	NR	0.0002-0.023	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	0.001-0.16	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Mentha Piperita (Peppermint) Extract							
	2017		**2017**					
Totals*	**71**		**0.00006-7.9**					
Duration of Use								
Leave-On	*43*		*0.00006-7.9*					
Rinse-Off	*27*		*0.0001-1*					
Diluted for (Bath) Use	*1*		*1*					
Exposure Type								
Eye Area	NR		NR					
Incidental Ingestion	4		0.0099-3.4					
Incidental Inhalation-Spray	10; 21[a]		1.3; 0.005-1[a]					
Incidental Inhalation-Powder	NR		NR					
Dermal Contact	63		0.00006-7.9					
Deodorant (underarm)	1		1					
Hair - Non-Coloring	4		0.0004-1					
Hair-Coloring	NR		NR					
Nail	NR		NR					
Mucous Membrane	3		0.0099-3.4					
Baby Products	NR		NR					

*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.

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

NR - no reported use

Table 6. Dermal Irritation and Sensitization Data

Ingredient	Subjects/Cell Type	Protocol	Results
Irritation Studies			
In Vitro			
Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract) (10% and 100%)	Reconstructed human epidermis	*In vitro* reconstructed human epidermis test method. In this test, the reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) in test material-treated tissues is expressed as a percentage relative to negative control-treated cultures.	Negative (MTT > 50%).[6]
Human			
Lipstick containing 0.2961% Mentha Piperita (Peppermint) Leaf Extract	50 subjects, described as follows: normal (25), with eczema (4 subjects), with allergy (4 subjects) and with sensitive skin (17 subjects).	In occlusive patch test, product (~ 20 mg) applied in a square test chamber (8 mm x 8 mm) to the back of each subject for 48 h. Reactions scored 30 minutes after patch removal and at 72 h post-application. Sodium dodecyl sulfate (1% in water) and water served as the positive and negative controls, respectively.	Product and negative control did not cause skin irritation in any of the subjects tested and product was classified as harmless. Positive control caused positive reactions in 12 subjects.[51]
50% Mentha Piperita (Peppermint) Leaf Water in a cleansing gel	50 subjects	Subjects applied product twice per day for 4 weeks, and were instructed to record any signs felt or observed during product use.	Slight erythema was observed in one subject.[52]
50% Mentha Piperita (Peppermint) Leaf Water in a cleansing gel (10% aqueous dilution [effective concentration = 5%])	52 subjects	Diluted product applied, under occlusive patch, to the skin for 48 h. Reactions scored up to 48 ± 4 h after patch removal (day 4).	A score of 1 (mild erythema) was reported for 12 subjects on day 2 and for 18 subjects on day 3. A score of 2 (moderate erythema) was reported for 2 subjects on day 2 and for 3 subjects on day 3. On day 4, 46 subjects had a score of 0 and 6 had a score of 1. Skin compatibility of diluted product considered good.[53]
Sensitization Studies			
100% Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract)	52 subjects	HRIPT (protocol details not included).	Negative results.[6]
20% Mentha Piperita (Peppermint) Leaf Water in a face cream	107 subjects (96 women, 11 men) with no history of atopy	In HRIPT, product applied (0.02 ml) to the back using occlusive patch (small Finn chamber), and 9 induction applications made over 3-week period. For 1st, 2nd, 5th, 7th, and 8th applications, duration of exposure was 48 ± 4 h. Duration of exposure was 72 ± 4 h for 3rd, 6th, and 9th applications. Challenge phase consisted of single application to new site and a previously treated site for 48 ± 4 h.	Product did not induce cumulative irritation or sensitization.[56]

Table 6. Dermal Irritation and Sensitization Data

Ingredient	Subjects/Cell Type	Protocol	Results
20% Mentha Piperita (Peppermint) Oil	104 male and female subjects	In HRIPT, test substance applied (0.2 ml) for 24 h to upper back (between scapulae) using 3/4" x 3/4" semi-occlusive patch. Application repeated 3 times per week for total of 9 induction applications. 24-h challenge patch applied after 2-week non-treatment period, and reactions scored at 24 h and 72 h.	No evidence of irritation or sensitization.[54]
20% Mentha Piperita (Peppermint) Oil	101 male and female subjects	In HRIPT, nine 24-h applications of test substance (0.2 ml) made to back using semi-occlusive patches (dimensions not stated). 24-h challenge patch applied after 10- to 15-day non-treatment period.	No evidence of sensitization.[55]
Multicenter Studies			
Mentha Piperita (Peppermint) Oil (concentration not stated)	73 patients	Patients patch tested according to International Contact Dermatitis Research Group (ICDRG) patch test procedures during 1994 to 1998	Neither irritant nor allergic reactions reported.[57]
Mentha Piperita (Peppermint) Oil (2% in petrolatum)	13,398 patients in study (71 patch tested with ingredient)	Patients patch tested during years 2009 to 2014 to determine frequency of positive patch test reactions to essential oils. Study used a retrospective analysis of patch test results and relevant demographical/clinical data that were collected electronically by the US/Canadian North American Contact Dermatitis Group (NACDG) and other networks.	Positive reaction prevalence rate of 0.53% reported for Mentha Piperita (Peppermint) Oil.[59]
Case Reports			
Mentha Piperita (Peppermint) Oil (2% in petrolatum)	Male patient with orofacial granulomatosis mainly affecting lower lip	Patch test	Allergic positive reaction.[60]
Mentha Piperita (Peppermint) Oil (concentration not stated)	Female patient with lichenoid eruption on oral mucosa	Patch and prick tests	Positive patch test reaction, i.e., itching, erythema, and swelling, beginning at day 5; ++ reaction by day 7. Prick test results negative.[61]
Mentha Piperita (Peppermint) Oil (2% in petrolatum)	Male patient with history of hand eczema and sensitization to tixocortol pivalate. Presented with severe eczematous contact dermatitis after repeated applications of a local action transcutaneous (LAT) patch for lumbar pain containing Mentha Piperita (Peppermint) Oil.	Patch test	Strong positive reactions to LAT patch and to Mentha Piperita (Peppermint) Oil (2% in petrolatum).[62]

Table 6. Dermal Irritation and Sensitization Data

Ingredient	Subjects/Cell Type	Protocol	Results
Mentha Piperita (Peppermint) Oil (2% in petrolatum)	Female patient with allergic contact dermatitis after consuming herbal tea containing Mentha Piperita (Peppermint) Oil.	Patch test. Reactions evaluated at 2, 3 and 7 days according to ICDRG procedures.	Positive patch test reaction (+ reaction) observed on days 2 and 3.[63]
Mentha Piperita (Peppermint) Oil (concentration not stated)	4 patients with allergic contact cheilitis (lips and perioral skin), secondary to exposure to lip balm that contained Mentha Piperita (Peppermint) Oil	Patch test. Reactions evaluated at 48 h and 96 h.	Positive patch test reactions to lip balm and to Mentha Piperita (Peppermint) Oil.[64]
Mentha Piperita (Peppermint) Leaf and Peppermint (concentration not stated)	Male patient with IgE-mediated anaphylaxis to peppermint (*Mentha piperita*) after sucking on peppermint candy. 5 healthy controls	Skin prick and prick-to-prick tests	Patient had strongly positive prick test reaction to slurry of peppermint candy and fresh peppermint leaf. Prick testing of patient with saline slurry of peppermint candy caused wheal and flare, with largest diameters of 10 mm and 35 mm (W10/F25), respectively. Prick-to-prick test with fresh peppermint leaf revealed skin test response of W25/F50. All prick tests on 5 controls negative.[67]
Mentha Piperita (Peppermint) Leaf Extract (concentration not stated)	Female patient became symptomatic with dyspnea when near peppermint (*Mentha piperita*) scent	Skin prick test	Positive skin prick test reaction to commercial Mentha Piperita (Peppermint) Leaf Extract.[68]
Mentha Piperita (Peppermint) (concentration not stated)	Male patient with severe cheilitis	Patch test	Negative reaction..[65]
Mentha Piperita (Peppermint) fragrance (1:50, 2% in petrolatum)	Female patient with recurrent irritant rash after applying a Mentha Piperita (Peppermint) foot spray	Patch test	+ reaction on days 2 and 4.[66]

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2017 FDA VCRP Data

Mentha Piperita (Peppermint) Oil

01B - Baby Lotions, Oils, Powders, and Creams	1
02A - Bath Oils, Tablets, and Salts	24
02B - Bubble Baths	2
02D - Other Bath Preparations	8
03G - Other Eye Makeup Preparations	4
04B - Perfumes	1
04E - Other Fragrance Preparation	17
05A - Hair Conditioner	43
05B - Hair Spray (aerosol fixatives)	1
05F - Shampoos (non-coloring)	57
05G - Tonics, Dressings, and Other Hair Grooming Aids	31
05H - Wave Sets	1
05I - Other Hair Preparations	15
07E - Lipstick	88
07I - Other Makeup Preparations	34
08B - Cuticle Softeners	2
08E - Nail Polish and Enamel	2
08G - Other Manicuring Preparations	3
09A - Dentifrices	34
09B - Mouthwashes and Breath Fresheners	19
09C - Other Oral Hygiene Products	73
10A - Bath Soaps and Detergents	43
10B - Deodorants (underarm)	2
10E - Other Personal Cleanliness Products	26
11A - Aftershave Lotion	3
11B - Beard Softeners	2
11D - Preshave Lotions (all types)	2
11E - Shaving Cream	10
11G - Other Shaving Preparation Products	2
12A - Cleansing	33
12C - Face and Neck (exc shave)	30
12D - Body and Hand (exc shave)	45
12E - Foot Powders and Sprays	9
12F - Moisturizing	56
12G - Night	1
12H - Paste Masks (mud packs)	17
12I - Skin Fresheners	13
12J - Other Skin Care Preps	73
Total	**827**

Mentha Piperita (Peppermint) Leaf (No Posting)

Mentha Piperita (Peppermint) Leaf Extract

02D - Other Bath Preparations	1
03D - Eye Lotion	4

04C - Powders (dusting and talcum, excluding aftershave talc)	1
04E - Other Fragrance Preparation	4
05A - Hair Conditioner	23
05B - Hair Spray (aerosol fixatives)	1
05F - Shampoos (non-coloring)	18
05G - Tonics, Dressings, and Other Hair Grooming Aids	3
05I - Other Hair Preparations	5
07B - Face Powders	2
07C - Foundations	2
07D - Leg and Body Paints	1
07E - Lipstick	5
07I - Other Makeup Preparations	2
08F - Nail Polish and Enamel Removers	1
08G - Other Manicuring Preparations	1
09A - Dentifrices	1
09B - Mouthwashes and Breath Fresheners	1
10A - Bath Soaps and Detergents	6
10E - Other Personal Cleanliness Products	6
11A - Aftershave Lotion	3
11G - Other Shaving Preparation Products	1
12A - Cleansing	14
12C - Face and Neck (exc shave)	24
12D - Body and Hand (exc shave)	5
12E - Foot Powders and Sprays	1
12F - Moisturizing	17
12G - Night	2
12H - Paste Masks (mud packs)	8
12I - Skin Fresheners	10
12J - Other Skin Care Preps	24
13A - Suntan Gels, Creams, and Liquids	1
Total	**198**

Mentha Piperita (Peppermint) Leaf Water

03G - Other Eye Makeup Preparations	2
10A - Bath Soaps and Detergents	1
10B - Deodorants (underarm)	1
11G - Other Shaving Preparation Products	1
12A - Cleansing	3
12C - Face and Neck (exc shave)	1
12F - Moisturizing	3
12H - Paste Masks (mud packs)	1
12I - Skin Fresheners	1
12J - Other Skin Care Preps	1
Total	**15**

Mentha Piperita (Peppermint) Extract

02A - Bath Oils, Tablets, and Salts	1
05A - Hair Conditioner	1
05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
07E - Lipstick	2
07I - Other Makeup Preparations	2
09B - Mouthwashes and Breath Fresheners	2
10A - Bath Soaps and Detergents	2
10B - Deodorants (underarm)	1
10E - Other Personal Cleanliness Products	3
11A - Aftershave Lotion	1
11E - Shaving Cream	3
12A - Cleansing	4
12C - Face and Neck (exc shave)	10
12D - Body and Hand (exc shave)	2
12E - Foot Powders and Sprays	3
12F - Moisturizing	17
12H - Paste Masks (mud packs)	10
12I - Skin Fresheners	1
12J - Other Skin Care Preps	3
Total	**71**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 21, 2017

SUBJECT: Mentha Piperita (Peppermint) Leaf Extract

Derma Consult GmbH. 2015. Human patch test of a lipstick containing 0.2961% Mentha Piperita (Peppermint) Leaf Extract.

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E-mail: info@dermaconsult.com
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Date: 20.07.2015

Expertise

Examination of the Product

100146/001
Concentration: undiluted
by Human Patch Test (Cosmetic Trial)

Performing Laboratory
Derma Consult GmbH
Brunnenstr. 61
53347 Alfter
Germany

Study Details

Type of study.....: Determination of irritating effects to the skin with an occlusive patch test.
Study Period.....: July 2015
Study Director....: Dr. med. H. Prieur
Test subjects.....: 50 (22-70 years; sex distribution non-standardized)
25 normal healthy, 4 eczema, 4 allergy and 17 subjects with sensitive skin
Test site.....: Back
Concentration.....: Undiluted Lipstick contains 0,2 %l % Mentha Piperita (Peppermint) Leaf Extract
Controls.....: SDS (1% in water), water

Summary Results

All participants completed the study. Under the test conditions, SDS (1% in water) caused positive reactions in 12 subjects. The negative control water showed no reactions. None of the subjects showed any reaction to the test product. On the basis of the test results and under the test conditions, the product

is to be classified as 'harmless' as regards the possibility of skin irritation.

Signature:

Dr. med. H. Prieur
Dermatologist - Allergist

Signature:

Dr. J. Nissen
Pharmacist - M.D.R.A.

Methodology

Introduction

The epicutaneous patch test allows us to assess the primary skin irritation potential of cosmetic-finished products and raw materials.

Description

All the work described in this expertise was conducted in accordance with the guidelines by COLIPA (Walker A.P. et al: Test Guidelines for Assessment of Skin Compatibility of Cosmetic Finished Products in Man. Food and Chemical Toxicology 34, 1996, 651-660). Because it was a study with humans, it was carried out in accordance with the Declaration of Helsinki (1964) and subsequent revisions.
Experiments were carried out on 50 volunteers (25 normal healthy subjects, 4 eczema patients, 4 allergy patients, 17 subjects with sensitive skin) between the ages of 22 to 70. Sex distribution was not standardized. The volunteers were clearly informed, verbally and in writing, regarding the nature of the study, the timetable, constraints and possible risks. They gave their written informed consent before participating in the study.
Participants could withdraw from the study at any time without giving reason. During the test period, the subjects refrained from using other substances on the test areas.

Inclusion criteria

- informed volunteers
- age ≥ 18 years

Exclusion criteria

- pregnant or lactating women
- blemishes or marks (tattoos, sunburn) which interfere with scoring
- any skin disease that may interfere with the aim of the study

Procedure

Dose for patch testing is approximately 20mg

The product was applied in a concentration as outlined above in square test-chambers (allergEAZE® clear Patch Test Chambers; SmartPractice®, Phoenix, AZ) to the backs of the panellists for a period of 48 hours. Proper adherence of the test patches was assured by the inclusion of sodium dodecyl sulphate (SDS) in one concentration (1%) as positive control. Water was used as a negative control.

chamber size 8mm X 8mm

The treatment sites were assessed for the presence of irritation by a trained evaluator using a 5 point visual scoring scale at 48 h (30 min after patch removal) and 72 h after patch application.

Scoring scale

Erythema	0: no E., 1: slight E., 2: significant E., 3: pronounced E., 4: strong E.
Fissure	0: no F., 1: minimal F., 2: significantly perceptible F., 3: pronounced F., 4: ulceration
Scaling	0: no Sc., 1: minimal Sc., 2: moderate Sc., 3: significant Sc., 4: closed scale crust

Results

The test results outlining the data for erythema, scaling and fissure formation on a per subject base for the test product are attached in tabulated form.

Literature

Jan E. Wahlberg, Magnus Lindberg:
"Patch Testing" in
P.J. Frosch, T. Menné & J.-P. Lepoittevin (eds.),
Contact Dermatitis 4th Edition
Springer-Verlag, Berlin Heidelberg, Germany (2006), pp. 365-390

Appendix: test protocol

No.	Type	after 48 h			after 72 h		
		E	F	S	E	F	S
1	S	0	0	0	0	0	0
2	A	0	0	0	0	0	0
3	S	0	0	0	0	0	0
4		0	0	0	0	0	0
5	S	0	0	0	0	0	0
6		0	0	0	0	0	0
7		0	0	0	0	0	0
8	E	0	0	0	0	0	0
9		0	0	0	0	0	0
10	S	0	0	0	0	0	0
11		0	0	0	0	0	0
12		0	0	0	0	0	0
13	S	0	0	0	0	0	0
14		0	0	0	0	0	0
15	A	0	0	0	0	0	0
16	S	0	0	0	0	0	0
17	S	0	0	0	0	0	0
18		0	0	0	0	0	0
19	S	0	0	0	0	0	0
20		0	0	0	0	0	0
21	E	0	0	0	0	0	0
22		0	0	0	0	0	0
23	S	0	0	0	0	0	0
24	S	0	0	0	0	0	0
25	S	0	0	0	0	0	0
26	E	0	0	0	0	0	0
27		0	0	0	0	0	0
28	S	0	0	0	0	0	0
29		0	0	0	0	0	0
30	E	0	0	0	0	0	0
31		0	0	0	0	0	0
32		0	0	0	0	0	0
33	A	0	0	0	0	0	0
34		0	0	0	0	0	0
35		0	0	0	0	0	0
36		0	0	0	0	0	0
37	A	0	0	0	0	0	0
38	S	0	0	0	0	0	0
39		0	0	0	0	0	0
40		0	0	0	0	0	0
41	S	0	0	0	0	0	0
42		0	0	0	0	0	0
43		0	0	0	0	0	0
44		0	0	0	0	0	0
45	S	0	0	0	0	0	0
46		0	0	0	0	0	0
47	S	0	0	0	0	0	0
48	S	0	0	0	0	0	0
49		0	0	0	0	0	0
50		0	0	0	0	0	0
SUM		0,0	0,0	0,0	0,0	0,0	0,0

Erythema (E): no E.: 0, slight E.: 1, clear E.: 2, severe E.: 3, very severe E.: 4
Fissures (F): no F.: 0, minimal F.: 1, clearly visible F.: 2, distinct F.: 3, ulceration: 4
Scales (S): no S.: 0, minimal S.: 1, clearly visible S.: 2, moderate S.: 3, distinct S.: 4

S: subjects with sensitive skin
E: patients with eczema
A: patients with allergy

16.07.2015
PROTOCOL

Product: Water

No.	Type	after 48 h			after 72 h		
		E	F	S	E	F	S
1	S	0	0	0	0	0	0
2	A	0	0	0	0	0	0
3	S	0	0	0	0	0	0
4		0	0	0	0	0	0
5	S	0	0	0	0	0	0
6		0	0	0	0	0	0
7		0	0	0	0	0	0
8	E	0	0	0	0	0	0
9		0	0	0	0	0	0
10	S	0	0	0	0	0	0
11		0	0	0	0	0	0
12		0	0	0	0	0	0
13	S	0	0	0	0	0	0
14		0	0	0	0	0	0
15	A	0	0	0	0	0	0
16	S	0	0	0	0	0	0
17	S	0	0	0	0	0	0
18		0	0	0	0	0	0
19	S	0	0	0	0	0	0
20		0	0	0	0	0	0
21	E	0	0	0	0	0	0
22		0	0	0	0	0	0
23	S	0	0	0	0	0	0
24	S	0	0	0	0	0	0
25	S	0	0	0	0	0	0
26	E	0	0	0	0	0	0
27		0	0	0	0	0	0
28	S	0	0	0	0	0	0
29		0	0	0	0	0	0
30	E	0	0	0	0	0	0
31		0	0	0	0	0	0
32		0	0	0	0	0	0
33	A	0	0	0	0	0	0
34		0	0	0	0	0	0
35		0	0	0	0	0	0
36		0	0	0	0	0	0
37	A	0	0	0	0	0	0
38	S	0	0	0	0	0	0
39		0	0	0	0	0	0
40		0	0	0	0	0	0
41	S	0	0	0	0	0	0
42		0	0	0	0	0	0
43		0	0	0	0	0	0
44		0	0	0	0	0	0
45	S	0	0	0	0	0	0
46		0	0	0	0	0	0
47	S	0	0	0	0	0	0
48	S	0	0	0	0	0	0
49		0	0	0	0	0	0
50		0	0	0	0	0	0
SUM		0,0	0,0	0,0	0,0	0,0	0,0

Erythema (E): no E.: 0, slight E.: 1, clear E.: 2, severe E.: 3, very severe E.: 4
Fissures (F): no F.: 0, minimal F.: 1, clearly visible F.: 2, distinct F.: 3, ulceration: 4
Scales (S): no S.: 0, minimal S.: 1, clearly visible S.: 2, moderate S.: 3, distinct S.: 4

S: subjects with sensitive skin
E: patients with eczema
A: patients with allergy

16.07.2015
PROTOCOL

Product: SDS (1% in water)

No.	Type	after 48 h			after 72 h		
		E	F	S	E	F	S
1	S	0	0	0	0	0	0
2	A	0	0	0	0	0	0
3	S	1	0	1	1	0	1
4		0	0	0	0	0	0
5	S	0	0	0	0	0	0
6		0	0	0	0	0	0
7		0	0	0	0	0	0
8	E	0	0	0	0	0	0
9		0	0	0	0	0	0
10	S	0	0	0	0	0	0
11		0	0	0	0	0	0
12		0	0	0	0	0	0
13	S	0	0	0	0	0	0
14		0	0	0	0	0	0
15	A	0	0	0	0	0	0
16	S	1	0	0	1	0	0
17	S	1	0	1	1	0	0
18		0	0	0	0	0	0
19	S	2	0	0	2	0	0
20		0	0	0	0	0	0
21	E	0	0	0	0	0	0
22		0	0	0	0	0	0
23	S	1	0	0	1	0	0
24	S	0	0	0	0	0	0
25	S	0	0	0	0	0	0
26	E	1	0	1	1	0	1
27		0	0	0	0	0	0
28	S	0	0	0	0	0	0
29		0	0	0	1	0	0
30	E	1	0	1	1	0	1
31		0	0	0	0	0	0
32		0	0	0	0	0	0
33	A	0	0	0	0	0	0
34		0	0	0	0	0	0
35		0	0	0	0	0	0
36		0	0	0	0	0	0
37	A	1	0	0	1	0	0
38	S	0	0	0	0	0	0
39		0	0	0	0	0	0
40		0	0	0	0	0	0
41	S	0	0	0	0	0	0
42		1	0	1	2	0	2
43		0	0	0	0	0	0
44		0	0	0	0	0	0
45	S	0	0	0	0	0	0
46		0	0	0	0	0	0
47	S	1	0	0	1	0	0
48	S	1	0	0	0	0	0
49		0	0	0	0	0	0
50		0	0	0	0	0	0
SUM		0,24	0,0	0,1	0,26	0,0	0,1

Erythema (E): no E.: 0, slight E.: 1, clear E.: 2, severe E.: 3, very severe E.: 4
Fissures (F): no F.: 0, minimal F.: 1, clearly visible F.: 2, distinct F.: 3, ulceration: 4
Scales (S): no S.: 0, minimal S.: 1, clearly visible S.: 2, moderate S.: 3, distinct S.: 4

S: subjects with sensitive skin
E: patients with eczema
A: patients with allergy

FABER-CASTELL
since 1761
COSMETICS

INGREDIENTS

13.01.2017
Formula Reference: 100146/001 **Version: 1**

Texture: Composite Bulk Texture MSE with plant actives last update: 17.06.2015 14:01: operator: AKU
Group: Sonderprodukte

declaration	CTFA/INCI	percentage
	VP/HEXADECENE COPOLYMER	22,0000
	POLYISOBUTENE	21,6570
	MICROCRYSTALLINE WAX / CERA MICROCRISTALLINA	14,0000
	VEGETABLE (OLUS) OIL	10,4400
	HYDROGENATED COCO-GLYCERIDES	9,0000
	MYRISTYL LACTATE	7,1100
	MICA	3,4000
	TITANIUM DIOXIDE (CI 77891)	2,3350
	MYRISTYL ALCOHOL	1,8900
	RED 6 (CI 15850)	1,5000
	CALCIUM SODIUM BOROSILICATE	1,3575
	RED 7 LAKE (CI 15850)	1,2500
	HYDROGENATED VEGETABLE OIL	1,2000
	ETHYLHEXYL PALMITATE	0,7400
	TOCOPHERYL ACETATE	0,5000
	ZINGIBER OFFICINALE (GINGER) ROOT EXTRACT	0,4740
	EUPHORBIA CERIFERA (CANDELILLA) WAX / EUPHORBIA CERIFERA CERA	0,3600
	MENTHA PIPERITA (PEPPERMINT) LEAF EXTRACT	0,2961
	TRIBEHENIN	0,2000
	HELIANTHUS ANNUUS (SUNFLOWER) SEED OIL	0,0950
	TOCOPHEROL	0,0750
	SORBITAN ISOSTEARATE	0,0500
	ASCORBYL PALMITATE	0,0180
	CITRAL	0,0150
	LACTIC ACID	0,0090
	LIMONENE	0,0080
	TIN OXIDE	0,0075
	CAPSICUM FRUTESCENS FRUIT EXTRACT	0,0050
	LINALOOL	0,0044
	CITRONELLOL	0,0015
	GERANIOL	0,0010
	PALMITOYL TRIPEPTIDE-1	0,0010
		100,0000

A. W. Faber-Castell Cosmetics GmbH • Nürnberger Str. 2 • D-90546 Stein • Germany

Personal Care Products Council
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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 26, 2017

SUBJECT: Mentha Piperita (Peppermint) Leaf Extract

Flavex Naturextrakte GmbH. 2015. Peppermint Leaf CO2-se extract.

Flavex Naturextrakte GmbH. 2015. Analytical Specification Peppermint Leaf CO2-se extract.

Flavex Naturextrakte GmbH. 2015. Allergen compounds according to Cosmetic EU Regulation 1223/2009: Peppermint Leaf CO2-se extract.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Peppermint Leaf CO2-se extract
Type no. 036.001

Raw material:	*Mentha piperita* - Leaves, dried
Production:	By supercritical fluid extraction with natural carbon dioxide no solvent residues, no inorganic salts, no heavy metals, no reproducible microorganisms [1].
Description:	Contains mainly volatile components. Yellow to light brown, clear oil with menthol like odor.
D/E - ratio:	44 - 55 kg raw material yield 1 kg product.
Declaration:	INCI-Name (CTFA): Mentha Piperita (Peppermint) Leaf Extract, CAS-No. 84082-70-2, EINECS-No. 282-015-4
Halal - Status:	Certified by Halal Certification Services (HCS) The certification is marked with the Halal Logo on the product.
Kosher - Status:	Certified by London Beth Din Kashrut Division (KLBD) The certification is marked with the Kosher logo on the product.
Transport:	No dangerous good in the sense of the transport regulations.
Ingredients:	80 - 90 % essential oil, 25 - 40 % menthol, 20 - 40 % menthone, 5 - 15 % menthyl acetate, < 2 % menthofurane.
Application:	In cosmetic industry for flavouring of tooth-paste and mouth wash, in food industry in chewing gum, sweets and liqueurs, in aromatherapy, natural medicines, in perfumery.
Naturalness:	The product is manufactured from the named raw material. It contains no additives and no other technical adjuncts, it is not blended and not formulated. The product is 100 % natural and corresponds to the EC Flavouring Regulation No. 1334/2008 for flavouring preparations.
Stability:	Unopened container under cool and dry storage conditions and exclusion of light at least 5 years.

References: [1] Manninen P., Häivälä E., Sarimo S., Kallio H. : Z. Lebens Unters Forsch A (1997) 204: 202-205

FLAVEX®
Naturextrakte

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CO_2-Extraction Authentic Quality secured by FLAVEX

CO_2 EXTRACTION

Version 66.034.08, 27.03.2015

Hochdruckextraktion mit CO_2

FLAVEX®
Naturextrakte GmbH

version no. 16.157.04, 27.03.2015

Analytical Specification

Peppermint Leaf CO2-se extract, type no. 036.001

raw material: *Mentha piperita* - Leaves, dried

Sensory Check

feature	reference
Appearance:	yellow to light brown, clear oil
Odour:	menthol like odor

Analytical Check

feature	method	limits	unit
Content of essential oil	21.006.01, Distillation, gravimetric	80 - 90	% (g/ 100g)
Content of essential oil	Destillation, volumetric, Ph. Eur. 7.0, 2.8.12	> 65	% (ml/ 100g)
Composition of the volatile compounds in extract:	GCMS, 100 % Method		
Limonene	GC, peppermint.met	< 2	%
1,8 Cineol	GC, peppermint.met	n.s.	%
L-Menthone	GC, peppermint.met	20 - 40	%
Mentholuran	GC, peppermint.met	< 2	%
Isomenthone	GC, peppermint.met	n.s.	%
Isomenthol	GC, peppermint.met	n.s.	%
Neomenthol	GC, peppermint.met	n.s.	%
L-Menthol	GC, peppermint.met	25 - 40	%
Pulegone	GC, peppermint.met	< 3	%
Menthyl acetate	GC, peppermint.met	5 - 15	%
beta Caryophyllene	GC, peppermint.met	n.s.	%

n.s. = not specified n.d. = not detectable

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Hochdruckextraktion mit CO_2

FLAVEX®
Naturextrakte GmbH

version no. 16.157.04, 27.03.2015

Analytical Specification

Peppermint Leaf CO2-se extract, type no. 036.001

raw material: *Mentha piperita* - Leaves, dried

Analytical Check

feature	method	limits	unit
Germacrene	GC, peppermint.met	n.s.	%
Refractive index (20°C)	Abbe-Refractometer	1,459 - 1,469	
Density (20°C)	21.024.02, Pycnometer	0,890 - 0,910	g/cm³
Content of water	Karl Fischer Titr.	n.s.	%

n.s. = not specified n.d. = not detectable

stability: Unopened container under cool storage conditions and exclusion of light at least 5 years.

Computer print-out, valid without signature, the original is in our documents.

created: Dipl. Ing. Anja Cawelius
quality control

Rehlingen, 27.03.2015

approved: Dr. K. W. Quirin
chief executive officer

CO_2-Extraction Authentic Quality secured by FLAVEX

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Allergen Compounds according Cosmetic EU Regulation 1223/2009

Peppermint Leaf CO2-se extract

Type no.: 036.001

Chemical name	CAS no.	Concentration typically found in extract	
Amyl cinnamal	122-40-7	-	%
Benzyl alcohol	100-51-6	-	%
Cinnamyl alcohol	104-54-1	-	%
Citral	5392-40-5	-	%
Eugenol	97-53-0	< 0,05	%
Hydroxy-citronellal	107-75-5	-	%
Isoeugenol	97-54-1	-	%
Amyl cinnamyl alcohol	101-85-9	-	%
Benzyl salicylate	118-58-1	-	%
Cinnamal	104-55-2	-	%
Coumarin	91-64-5	-	%
Geraniol	106-24-1	-	%
Hydroxy-methylpentylcyclohexenecarboxaldehyde	31906-04-4	-	%
Anisyl alcohol	105-13-5	-	%
Benzyl cinnamate	103-41-3	-	%
Farnesol	4602-84-0	-	%
2-(4-tert-Butylbenzyl)propionaldehyde	80-54-6	-	%
Linalool	78-70-6	< 0,3	%
Benzyl benzoate	120-51-4	-	%
Citronellol	106-22-9	-	%
Hexyl cinnam-aldehyde	101-86-0	-	%
d-Limonene	5989-27-5	< 1	%
Methyl heptin carbonate	111-12-6	-	%
3-Methyl-4-(2,6,6-tri-methyl-2-cyclohexen-1-yl)-3-buten-2-one	127-51-5	-	%
Oak moss extract	90028-68-5	-	%
Treemoss extract	90028-67-4	-	%

The substances listed are subject to declaration if concentration exceeds 0.001 % in leave-on and 0.01 % in rinse-off products.

Mean values are indicated according to available statistical data. Values < 0.01 % are not mentioned. This is not needed since the dose of extract in the cosmetic product is normally < 0.5 %, in any case however < 5 %. In case of change FLAVEX will inform the costumers.

FLAVEX®
Naturextrakte

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CO_2 EXTRACTION

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Version 12.090.03

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D., Executive Director
COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 16, 2017

SUBJECT: Concentration of Use by FDA Product Category: Peppermint-Derived Ingredients

Concentration of Use by FDA Product Category – Peppermint-Derived Ingredients

Mentha Piperita (Peppermint) Oil
Mentha Piperita (Peppermint) Leaf
Mentha Piperita (Peppermint) Leaf Extract
Mentha Piperita (Peppermint) Leaf Water

Ingredient	Product Category	Maximum Concentration of Use
Mentha Piperita (Peppermint) Oil	Baby lotions, oils and creams (1B) Not powder	 0.2%
Mentha Piperita (Peppermint) Oil	Bath oils, tablets and salts (2A)	3.9%
Mentha Piperita (Peppermint) Oil	Other bath preparations (2D)	0.018%
Mentha Piperita (Peppermint) Oil	Eye lotions (3D)	0.00094%
Mentha Piperita (Peppermint) Oil	Hair conditioners (5A)	0.0001-0.33%
Mentha Piperita (Peppermint) Oil	Hair sprays (5B) Aerosol Pump spray	 0.017% 0.017-0.02%
Mentha Piperita (Peppermint) Oil	Rinses (noncoloring) (5E)	0.02%
Mentha Piperita (Peppermint) Oil	Shampoos (noncoloring) (5F)	0.0001-0.75%
Mentha Piperita (Peppermint) Oil	Tonics, dressings and other hair grooming aids (5G)	0.002-0.96%
Mentha Piperita (Peppermint) Oil	Wave sets (5H)	0.01%
Mentha Piperita (Peppermint) Oil	Other hair preparations (noncoloring) (5I)	0.0033-0.05%
Mentha Piperita (Peppermint) Oil	Hair dyes and colors (6A)	0.0024%
Mentha Piperita (Peppermint) Oil	Foundations (7C)	0.0006%
Mentha Piperita (Peppermint) Oil	Lipstick (7E)	0.05-2.9%
Mentha Piperita (Peppermint) Oil	Makeup bases (7F)	0.005%
Mentha Piperita (Peppermint) Oil	Basecoats and undercoats (8A)	0.00064%
Mentha Piperita (Peppermint) Oil	Cuticle softeners (8B)	1.5%
Mentha Piperita (Peppermint) Oil	Other manicuring preparations (8G)	0.2-0.45%
Mentha Piperita (Peppermint) Oil	Dentifrices (9A)	0.95%
Mentha Piperita (Peppermint) Oil	Mouth washes and breath fresheners (9B)	0.11-1.1%
Mentha Piperita (Peppermint) Oil	Other oral hygiene products (9C)	0.22-1.3%
Mentha Piperita (Peppermint) Oil	Bath soaps and detergents (10A)	0.0034-1.9%
Mentha Piperita (Peppermint) Oil	Other personal cleanliness products (10E)	0.0025-1.1%
Mentha Piperita (Peppermint) Oil	Aftershave lotions (11A)	0.003%
Mentha Piperita (Peppermint) Oil	Shaving cream (11E)	0.4-0.7%
Mentha Piperita (Peppermint) Oil	Skin cleansing (cold creams, cleansing lotions, liquids and pads) (12A)	0.015-0.25%
Mentha Piperita (Peppermint) Oil	Face and neck products (12C) Not spray	 0.01-5%
Mentha Piperita (Peppermint) Oil	Body and hand products (12D) Not spray Spray	 0.05-2.3% 0.006-0.3%
Mentha Piperita (Peppermint) Oil	Foot powders and sprays (12E) Spray	0.01-1% 0.5%
Mentha Piperita (Peppermint) Oil	Moisturizing products (12F) Not spray	 0.006%

Mentha Piperita (Peppermint) Oil	Paste masks and mud packs (12H)	0.01-0.011%
Mentha Piperita (Peppermint) Oil	Skin fresheners (12I)	0.1-0.12%
Mentha Piperita (Peppermint) Oil	Other skin care preparations (12J)	0.1-0.22%
Mentha Piperita (Peppermint) Leaf Extract	Eye lotions (3D)	0.0018%
Mentha Piperita (Peppermint) Leaf Extract	Hair conditioners (5A)	0.0005-0.2%
Mentha Piperita (Peppermint) Leaf Extract	Hair sprays (5B) Aerosol Pump	 0.00041% 0.0046%
Mentha Piperita (Peppermint) Leaf Extract	Rinses (noncoloring) (5E)	0.00088%
Mentha Piperita (Peppermint) Leaf Extract	Shampoos (noncoloring) (5F)	0.00018-0.2%
Mentha Piperita (Peppermint) Leaf Extract	Tonics, dressings and other hair grooming aids (5G)	0.00057-0.001%
Mentha Piperita (Peppermint) Leaf Extract	Hair tints (6B)	0.032%
Mentha Piperita (Peppermint) Leaf Extract	Face powders (7B)	0.0018%
Mentha Piperita (Peppermint) Leaf Extract	Foundations (7C)	0.0018%
Mentha Piperita (Peppermint) Leaf Extract	Lipstick (7E)	0.3-0.5%
Mentha Piperita (Peppermint) Leaf Extract	Makeup bases (7F)	0.00018%
Mentha Piperita (Peppermint) Leaf Extract	Mouth wash and breath fresheners (9B)	0.00075%
Mentha Piperita (Peppermint) Leaf Extract	Bath soaps and detergents (10A)	0.0018%
Mentha Piperita (Peppermint) Leaf Extract	Deodorants (10B) Pump spray	 0.0018%
Mentha Piperita (Peppermint) Leaf Extract	Other personal cleanliness products (10E)	0.002%
Mentha Piperita (Peppermint) Leaf Extract	Aftershave lotions (11A)	0.0018%
Mentha Piperita (Peppermint) Leaf Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads) (12A)	0.0001-0.18%
Mentha Piperita (Peppermint) Leaf Extract	Face and neck products (12C) Not spray Spray	 0.000075-0.05% 0.001%
Mentha Piperita (Peppermint) Leaf Extract	Body and hand products (12D) Not spray Spray	 0.0018-0.2% 0.001%
Mentha Piperita (Peppermint) Leaf Extract	Moisturizing products (12F) Not spray	 0.00088-0.00092%
Mentha Piperita (Peppermint) Leaf	Other skin care preparations (12J)	0.0012%

Extract		
Mentha Piperita (Peppermint) Leaf Extract	Indoor tanning preparations (13B)	0.026%
Mentha Piperita (Peppermint) Leaf	Hair conditioners (5A)	0.023%
Mentha Piperita (Peppermint) Leaf	Shampoos (noncoloring) (5F)	0.0002%
Mentha Piperita (Peppermint) Leaf	Tonics, dressings and other hair grooming aids (5G)	0.001%
Mentha Piperita (Peppermint) Leaf	Bath soaps and detergents (10A)	0.001-0.16%
Mentha Piperita (Peppermint) Leaf	Face and neck products (12C) Not spray	0.001%
Mentha Piperita (Peppermint) Leaf	Paste masks and mud packs (12H)	1.6%
Mentha Piperita (Peppermint) Leaf Water	Foundations (7C)	0.00013%
Mentha Piperita (Peppermint) Leaf Water	Deodorants (10B) Not spray	15%
Mentha Piperita (Peppermint) Leaf Water	Shaving cream (11E)	0.00021%
Mentha Piperita (Peppermint) Leaf Water	Skin cleansing (cold creams, cleansing lotions, liquids and pads) (12A)	0.00067%
Mentha Piperita (Peppermint) Leaf Water	Face and neck products (12C) Not spray	0.00067-40%
Mentha Piperita (Peppermint) Leaf Water	Body and hand products (12D) Not spray	0.00018-15%
Mentha Piperita (Peppermint) Leaf Water	Moisturizing products (12F) Not spray	10%
Mentha Piperita (Peppermint) Leaf Water	Indoor tanning preparations (13B)	0.00043%

Information collected 2015-2016

Table prepared February 29, 2016

Revised October 16, 2017: Mentha Piperita (Peppermint) Leaf Extract added low concentration 0.3% to lipstick

Concentration of Use by FDA Product Category – Additional Peppermint-Derived Ingredients*

Mentha Piperita (Peppermint) Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Water
Mentha Piperita (Peppermint) Leaf Cell Extract
Mentha Piperita (Peppermint) Leaf Juice
Mentha Piperita (Peppermint) Meristem Cell Culture

Ingredient	Product Category	Maximum Concentration of Use
Mentha Piperita (Peppermint) Extract	Other bath preparations (2D)	1%
Mentha Piperita (Peppermint) Extract	Hair conditioners (5A)	1%
Mentha Piperita (Peppermint) Extract	Rinses (noncoloring) (5E)	1%
Mentha Piperita (Peppermint) Extract	Shampoos (noncoloring) (5F)	0.0004-1%
Mentha Piperita (Peppermint) Extract	Tonics, dressings and other hair grooming aids (5G)	0.005-1%
Mentha Piperita (Peppermint) Extract	Lipstick (7E)	0.0099-3.4%
Mentha Piperita (Peppermint) Extract	Bath soaps and detergents (10A)	0.0001-0.00021%
Mentha Piperita (Peppermint) Extract	Deodorants (10B) Not spray	 1%
Mentha Piperita (Peppermint) Extract	Aftershave lotions (11A)	0.062-1%
Mentha Piperita (Peppermint) Extract	Preshave lotions (11D)	0.025-1%
Mentha Piperita (Peppermint) Extract	Shaving cream (11E)	0.074-0.4%
Mentha Piperita (Peppermint) Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads) (12A)	1%
Mentha Piperita (Peppermint) Extract	Face and neck products (12C) Not spray Spray	 0.06-7.9% 1.3%
Mentha Piperita (Peppermint) Extract	Body and hand products (12D) Not spray	 1-1.3%
Mentha Piperita (Peppermint) Extract	Foot products (12E)	0.0098%
Mentha Piperita (Peppermint) Extract	Moisturizing products (12F) Not spray	 0.18%
Mentha Piperita (Peppermint) Extract	Paste masks and mud packs (12H)	0.0075%
Mentha Piperita (Peppermint) Extract	Skin fresheners (12I)	1%
Mentha Piperita (Peppermint) Extract	Other skin care preparations (12J)	0.00006%

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

Information collected in 2017
Table prepared: July 6, 2017
Revised October 16, 2017: Deleted Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract

Personal Care Products Council
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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 4, 2017

SUBJECT: Re-review: Amended Safety Assessment of *Mentha piperita* (Peppermint)-Derived Ingredients as Used In Cosmetics (draft prepared for the April 10-11, 2017 CIR Expert Panel Meeting)

Key Issue

Please consider adding the reference Tisserand R, Young R. 2014. Essential Oil Safety, 2nd ed. (in Carol's office). The monograph on peppermint essential oil in this book cites additional references, including the ISO standards for composition. It also provides the authors' maximum use recommendations (maximum adult daily oral dose: 152 mg; maximum dermal use level: 5.4%) based on 8% menthofuran and 3% pulegone content. They also recommend that peppermint oil be avoided by people with glucose-6-phosphate dehydrogenase (G6PD) deficiency. This book also includes monographs of a number of components of peppermint essential oil.

Additional Considerations

Composition, Mentha Piperita (Peppermint) Leaf Extract - What solvent was used to extract the leaves (reference 8)?

Composition, Mentha Piperita (Peppermint) Leaf - Pennyroyal is not a "toxic compound". Pennyroyal is a common name for another plant, *Mentha pulegium*. Based on the information in Tisserand and Young (2014), pennyroyal essential oil may contain 67.6-86.7% pulegone.

Cosmetic Use, Table 3 - Please state the specific product category in which the maximum use concentration was reported. Rather than 15% Mentha Piperita (Peppermint) Leaf Water in non-spray body and hand products, the actual maximum use concentration reported is 40% Mentha Piperita (Peppermint) Leaf Water in non-spray face and neck products.

Dermal Penetration - As peppermint essential oil is a mixture, what were they actually measuring in the dermal penetration study from the original report? Please correct "serine" to "Eserine" (appears to be a discontinued ophthalmic preparation of physostigmine).

Absorption, Distribution, Metabolism and Excretion, new information - Did they (reference 4) examine anything other than the absorption and excretion of menthol from peppermint oil?

Genotoxicity, In Vitro, original report summary - It is not clear which compounds were less toxic following "metabolic activation" (if the compounds were less toxic, they were not "activated").

Genotoxicity, new information - Based on the title, reference 32 may also include a genotoxicity study in fruit flies (*Drosophila melanogaster*) that is not yet mentioned in the CIR report.

Carcinogenicity, Pulegone, Summary - Please provide more information about the mechanistic study in female rats. What doses and route of exposure were used in this study? The mechanistic study should also be mentioned in the Summary.

Anticarcinogenicity - What solvent was used to extract the leaves for the extract used in reference 36?

Summary - Please correct the following sentence: "Results were positive for Mentha Piperita (Peppermint) Oil was in cytotoxicity assays involving human cancer cell lines."

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Memorandum

TO: Bart Heldreth, Ph.D.
Interim Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 7, 2017

SUBJECT: Draft Tentative Report: Amended Safety Assessment of *Mentha piperita* (Peppermint)-derived Ingredients as Used in Cosmetics (draft prepared for the September 11-12, 2017 CIR Expert Panel Meeting)

Key Issues

Reference 10 of the CIR report (the 2014 EMEA statement on products containing pulegone and menthofuran) states: "The first reports on brain toxicity of pulegone appear to have been erroneous." As the CIR 1% limit on pulegone is based on these studies, it is not clear why the key study[1] cited in the 2005 EMEA statement (available on the I drive in the CIR peppermint folder) that the brain effects "may have arisen from inadequate tissue fixation procedures" is not included in the CIR report. If the brain effects were not a result of pulegone exposure, what is the basis of the 1% limit for pulegone in ingredients? It would be helpful if the limit was for the amount of pulegone in finished products rather than in ingredients. Perhaps pulegone should be used as a search term.

The dermal and oral limits from the book *Essential Oil Safety* should be presented in a risk assessment section not under "Exposure Assessment". The basis of these limits (hepatotoxicity, estimated rat NOAEL of 5 mg/kg for pulegone and menthofuran considered twice as toxic as pulegone) should also be stated in the CIR report. The EMEA (2014) interim recommendation for pulegone and menthofuran should also be included in a risk assessment section. EMEA stated: "As an interim recommendation, the HMPC suggests that an acceptable exposure limit is 0.07 mg/kg bw per day, which is close to the current ADI value of 0.1 mg/kg bw per day. This limit value should be reviewed when adequate genotoxicity studies are available and relevance of rodent tumours to human carcinogenicity has been assessed." The interim acceptable exposure

[1]Molck, A-M., Poulsen, M., Lauridsen, S.T., Olsen, P. 1998. Lack of histological cerebellar changes in Wistar rats given pulegone for 28 days. Comparison of immersion and perfusion tissue fixation. *Toxicol. Lett.* 95, 117-122.

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limit is based on a 20 mg/kg/day LOAEL from the NTP bioassay of pulegone and a safety factor of 300.

Additional Considerations

Method of Manufacture, *Mentha piperita* (peppermint) leaf extract powder - Dried plant extracts, or powders of plant extracts do not get separate INCI names. The information on the trade name material called peppermint leaf extract powder came from a manufacturer of cosmetic ingredients. Therefore, the information should be presented under the INCI name Mentha Piperita (Peppermint) Leaf Extract and the statement "and likely cannot be referred to as a cosmetic ingredient name for any of the ingredients that are being reviewed in this safety assessment" should be deleted.

Composition, Mentha Piperita (Peppermint) Leaf Extract - What solvent was used to extract the peppermint leaves (reference 11)?

Composition, *Mentha piperita* (peppermint) leaf extract powder - As this is a peppermint leaf extract, this information should be presented under the INCI name "Mentha Piperita (Peppermint) Leaf Extract".

Noncosmetic use - Please define "aetheroleum" (a term used to describe a preparation made from the above-ground parts of a plant).

Multicenter Studies, Summary, Table 5 - Please check the numbers of subjects and the prevalence rates stated for reference 55. A total of 13,398 patients were tested by the NACDG, the number of patients tested with peppermint oil was actually much smaller. Also the prevalence rate for sensitization to peppermint oil stated in the abstract of the paper (0.9%) is different than that stated in a table later in the paper (0.53%).

Other Clinical Reports - The information about plasma levels of menthol following dosing with peppermint oil (reference 66) should be in the ADME section of the report.

Reference 8 - Why is the 8th edition of the Food Chemical Codex included in the reference section when the 10th edition is in Carol's office?

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 23, 2017

SUBJECT: Tentative Report: Amended Safety Assessment of *Mentha piperita* (Peppermint)-derived Ingredients as Used in Cosmetics

Key Issues

Additional composition information on peppermint leaves can be found in the PDR for Herbal Medicines, 4th edition (in Carol's office). This reference indicates that in addition to the volatile oil components, the leaves contain caffeic acid, rosmaric acid and flavonoids. As stated in the report, suppliers of leaf derived ingredients indicate that they contain tannins and terpenoids in addition to components found in the essential oil. The CO_2 extract of peppermint leaves (unpublished data that still needs to be added to the report) has a composition similar to the essential oil.

Peppermint leaves are commonly used as a tea and peppermint "essential oils, oleoresins (solvent-free), and natural extractives (including distillates)" are generally recognized as safe. Based on long history of food use, additional systemic data on leaf preparations should not be necessary. No additional dermal irritation and sensitization data were requested for the leaf extract or the leaf water. Therefore, it is not clear why the data on the leaf, leaf extract and leaf water remain insufficient.

The logic for including some studies about components, e.g., menthol, pulegone, in some sections of the report but not other sections of the report is not clear. For example, rather than individual case studies, perhaps the following review on the sensitization potential of menthol may be helpful.
Ale SO, Hostynek JJ, Maibach HL. 2002. Menthol: A review of its sensitization potential. *Exog Dermatol* 1: 74-80.

It would be helpful to cite the 2016 IARC monograph (found at https://monographs.iarc.fr/ENG/Monographs/vol108/mono108-05.pdf) on pulegone in this report.

Additional Considerations

Abstract, Conclusion - For the insufficient data ingredients, it is not clear what is meant by "intended conditions of use". Generally, the CIR Expert Panel considers whether the ingredients are safe for use in cosmetics with uses as reported to the VCRP and the Council's concentration of use surveys. It is not clear why ingredients are considered "safe in cosmetics in the present practices

of use and concentration", while insufficient data ingredients considered "under the intended conditions of use in cosmetics".

Introduction - If much of the data on Mentha Piperita (Peppermint) Oil "are considered relevant to the entire group", it is not clear why the data are sufficient for Mentha Piperita (Peppermint) Oil, but insufficient for the remaining ingredients.

Chemical and Physical Properties - There are additional chemical and physical properties on Mentha Piperita (Peppermint) Leaf Extract in submissions 4 and 9 from the Council.

Noncosmetic Use - Please add some information about the typical daily dose for peppermint when it is used as a dietary supplement/herbal medicine. Please add that peppermint leaves are commonly used as a tea.

Short-term, Pulegone - Please correct: "auricle o the heart"

Chronic, Risk Assessment - Why do Tisserand and Young (2014) recommend that Mentha Piperita (Peppermint) Oil be avoided by persons with a glucose-6-phosphate dehydrogenase (G6PD) deficiency? (G6PD is the major detoxification pathway for menthol.)

Genotoxicity, Menthol, old report summary - Rather than stating "subacute and acute" it would be helpful to state the actual durations of the studies included in the original report.

Antigenotoxicity Studies - Please correct "Menta"

Carcinogenicity, Pulegone - Please state the doses that were used in the NTP bioassay of pulegone.

Cytotoxicity - Please provide the units for the IC_{50} values (reference 43). What was the maximum concentration at which Mentha Piperita (Peppermint) Oil was inactive in BEL-7402 cells? What was tested in reference 45? The title of reference 45 suggests that polysaccharides isolated from peppermint were tested.

Hepatotoxicity - What concentration/doses were tested in the studies completed in reference 46?

Sensitization - Perhaps if the references were placed with the information that came from the reference it would have been recognized that the last sentence of this section ["HRIPT results for undiluted Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract) in 52 subjects were also negative."] was already presented in the previous paragraph.

Multicenter Studies, Summary, Table 5 - Please review reference 56 again. There is a table in this paper that indicates that 71 persons were tested with peppermint essential oil with a prevalence rate of 0.53% reported (0.9% was the prevalence rate stated in the abstract).

Case Reports - What is meant by "Mostly", (8 of 9 cases found)?

Summary - The doses or concentrations of peppermint ingredients need to be included in the Summary. This information needs to be added to the following paragraphs: penetration enhancement, 28-day oral toxicity studies of pulegone, genotoxicity studies, carcinogenicity of pulegone, cytotoxicity assays and heptotoxicity assays.

Table 1 - CAS numbers should be added to the first column of this table which is titled "Ingredient CAS No.".

Table 3 - In the title of this table, please correct "menthe"