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

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Status: Draft Tentative Amended Report for Panel Review

Release Date: August 18, 2017

Panel Date: September 11-12, 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 Interim Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Ivan Boyer, Ph.D., Toxicologist.

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Memorandum

To: CIR Expert Panel Members and Liaisons  
From: Wilbur Johnson, Jr.  
Senior Scientific Analyst  
Date: August 18, 2017  
Subject: Draft Tentative Amended Report of *Mentha piperita* (Peppermint)-derived Ingredients

At the April 2017 meeting, the Panel agreed that the safety assessment 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) Leaf Cell Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract	Mentha Piperita (Peppermint) Leaf Juice
Mentha Piperita (Peppermint) Flower/Leaf/Stem Water	Mentha Piperita (Peppermint) Meristem Cell Culture

At that meeting, 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

The following data were received in response to the Panel's IDA: (1) use concentration data on the 6 ingredients that are being added (*pepper092017data1* and *pepper092017data2*); (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.] (*pepper092017data3*); and (3) *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%) (*pepper092017data3*). These unpublished data have been added and are indicated using borders in the report text, and the same is true for published data that have been added. The reopened safety assessment also contains a draft discussion, based on comments made by the Panel at the April meeting, and the Panel should determine whether text from the published final report discussion (also in the report) should be added.

Also included in this package for your review is the Draft Tentative Amended Report (*pepper092017rep*), the CIR report history (*pepper092017hist*), Literature search strategy (*pepper092017strat*), Ingredient Data profile (*pepper092017prof*), 2017 FDA VCRP data (*pepper092017FDA*), the 2001 published Final Report on *Mentha piperita* (peppermint)-derived ingredients (*pepper092017prev*), minutes from the April 2017 Panel meeting (*pepper092017min*), and comments that were received from the Council (*pepper092017pcpc*), which have been addressed.

The Panel noted that most of the data in the 2001 published final report are on Mentha Piperita (Peppermint) Oil, and recalled their decision that Mentha Piperita (Peppermint) Oil is considered to present the "worst case scenario" because of its many constituents and that data on the oil were considered relevant to the entire group of ingredients. However, after

reviewing the limited composition data in the current safety assessment that were available initially, the Panel noted that it is possible that data on *Mentha Piperita* (Peppermint) Oil may not have been sufficient for evaluating the safety of all of the *Mentha piperita* (peppermint)-derived ingredients that were being reviewed (e.g., the major components of the oil versus the leaf extract appear to be different) in the original safety assessment. Thus, the Panel recognized the possibility that sufficient data for evaluating the safety of ingredients derived from different parts of the plant may not have been available in the initial safety assessment, and this was the basis, in part, for determining that the report should be reopened. As stated previously, the Panel agreed that 6 additional *Mentha piperita* (peppermint)-derived ingredients should be added to the reopened safety assessment.

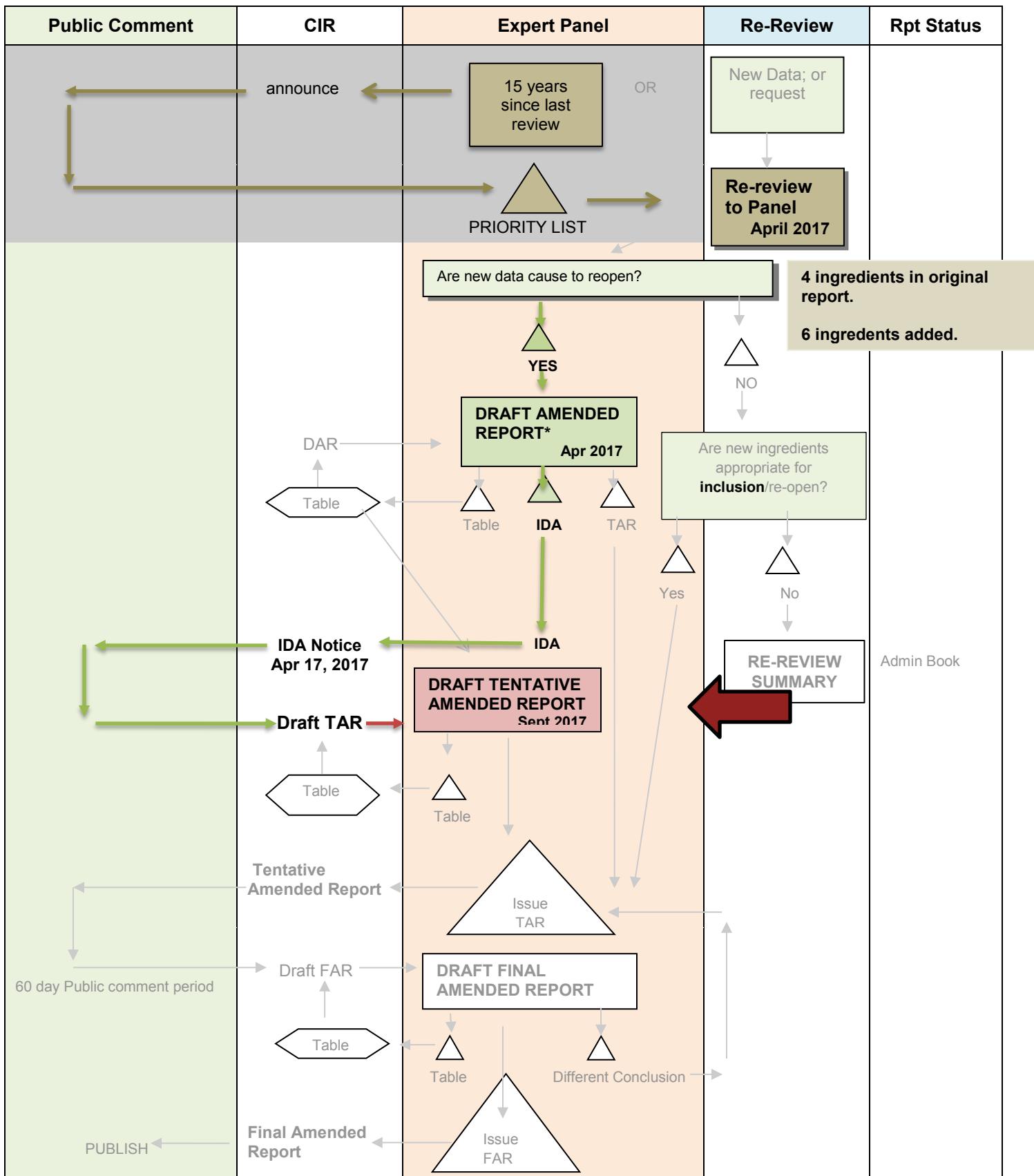
Regarding the statement in the final report conclusion that the concentration of pulegone in these ingredients should not exceed 1%, the Panel considered whether, in hindsight, their concern should have been addressed using a non-sensitizing-qualification approach (which may be based on a QRA). Furthermore, it was noted that the 1% concentration limit on pulegone was based, in part, on maximum leave-on product concentrations of 0.2% - 2% *Mentha Piperita* (Peppermint) Oil, but that the oil is now being used at concentrations up to 5% in leave-on products.

Taking into consideration that skin irritation was observed in subjects after application of a cleansing gel containing 50% *Mentha Piperita* (Peppermint) Leaf Water (diluted to 5% concentration of the leaf water) and that *Mentha Piperita* (Peppermint) Leaf Water is being used at concentrations up to 40% in leave-on products, the Panel considered the possibility of issuing a conclusion stating that products containing *Mentha piperita* (peppermint)-derived ingredients should be formulated to be non-irritating. Furthermore, given the terpene content of these ingredients, addition of the safe when formulated to be non-sensitizing qualification to the conclusion that will be developed was further considered.

Ultimately, the Panel should determine whether the data provided satisfy all of the data needs, and, if not, be prepared to state the additional needs that are needed to make a determination of safety, and consider issuing a tentative amended report with an insufficient data conclusion. However, if the data that were received addresses all concerns, the Panel should determine whether a safe as used, safe with qualifications, or unsafe conclusion should be issued.

# RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Mentha Piperita (Peppermint)-Derived Ingredients  
 MEETING Sept 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%).

Mentha piperita-derived Ingredients Data Profile for September 11 <sup>th</sup> -12 <sup>th</sup> , 2017 Panel – Wilbur Johnson														
	Epidemiology Studies	Human												
	Case Reports	Human-Oral												
	Human-Dermal	X												
Mentha Piperita (Peppermint) Oil														
Mentha Piperita (Peppermint) Leaf	X	X												
Mentha Piperita (Peppermint) Leaf Extract	X	X												
Mentha Piperita (Peppermint) Leaf Water	X	X												
	Dermal Penetration	ADME	Acute Toxicity	DART	Carcinogenicity	Dermal Irritation*	Dermal Sensitization*/Phototoxicity*	Ocular Irritation*	Clinical Studies	Case Reports	Epidemiology Studies	Human	Human-Oral	Human-Dermal
	Nail Penetration													
	Penetration Enhancement													
	In Vitro-Human													
	In Vivo-Human													
	In Vitro-Human													
	In Vivo-Animal													
	Safety Data Available?													
	Used in Cosmetics?	X	X	X										

X = data; 0 = no data\*

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

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>

SciFinder (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/](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/](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.ifra.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 developmental 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<sup>2</sup> 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<sup>2</sup>.

Dr. Bronaugh said that 2 mg is approximately 2  $\mu$ l, 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<sup>2</sup>). 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 ( $2 \text{ mg/cm}^2$ ). 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  $\leq 3\%$  in rinse-off formulations and  $\leq 0.2\%$  in leave-on formulations, coupled with the restriction of pulegone to  $\leq 1\%$ , 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 magnetic 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.

## Day 1 of the April 10-11, 2017 CIR Expert Panel Meeting – Dr. Marks’ Team

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 hepatotoxic 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 hepatotoxicity, the leaf nephrotoxicity, and then obviously, I presume, we'll put the same limitation on pulegone in this one. But the hepatotoxicity 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, hepatotoxicity. 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 hepatotoxicity. 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.

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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.

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

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Status: Draft Tentative Amended Report for Panel Review

Release Date: August 18, 2017

Panel Date: September 11-12, 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 Interim Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Ivan Boyer, Ph.D., Toxicologist.

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**ABSTRACT:** The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of *Mentha piperita* (peppermint)-derived ingredients, which function mostly as fragrance ingredients and 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 this ingredient, and a conclusion will be forthcoming.

## **INTRODUCTION**

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.<sup>1</sup> The conclusion also contains a statement indicating that the concentration of pulegone, a constituent of these botanical ingredients, should not exceed 1%. According to the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), these ingredients function mostly as fragrance ingredients and skin conditioning agents in cosmetic products.<sup>2</sup>

Most of the safety test data in the 2001 report are on *Mentha Piperita* (Peppermint) Oil, and the Panel noted that 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 published final report and in this report because these chemicals are components of *Mentha Piperita* (Peppermint) Oil. Considering that a limitation on pulegone is mentioned in the original conclusion, it should be noted that a National Toxicology Program (NTP) carcinogenicity study with positive results on pulegone was published in 2011 and is summarized in the report text.<sup>3</sup>

The 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 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 (<http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <http://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

## **CHEMISTRY**

### **Definition and General Characterization**

The definitions of *Mentha Piperita* (peppermint)-derived ingredients are stated in Table 1.<sup>2</sup>

## Chemical and Physical Properties

*Properties/specifications relating to Mentha Piperita (Peppermint) Oil are presented in Table 2.<sup>1</sup>*

### 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.<sup>1</sup> 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.<sup>4</sup>

#### **Mentha Piperita (Peppermint) Leaf Extract**

The following method relates to preparation of the butylene glycol/water extract.<sup>5</sup> 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.<sup>5</sup> 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.

#### ***Mentha piperita* (peppermint) leaf extract powder**

The production method described herein relates to preparation of *Mentha piperita* (peppermint) leaf extract powder,<sup>5</sup> which is not a name found in the *Dictionary* (and likely cannot be referred to as a cosmetic ingredient name for any of the ingredients that are being reviewed in this safety assessment). However, 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.

#### **Mentha Piperita (Peppermint) Leaf Water**

In the preparation of *Mentha Piperita (Peppermint) Leaf Water*, dried raw material is subjected to steam distillation.<sup>5</sup> After distillation, the remaining steps in the production process are: water soluble fraction obtained → adjustment → filtrate → packaging.

## Composition

*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.<sup>1</sup> 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%).<sup>6</sup>

Certain trends were observed between oil extracted from first and second harvest leaves, and oil extracted from fresh leaves versus dried leaves.<sup>4</sup> When compared to the second harvest, oils from the first harvest were generally higher in (Z)-3-hexenol, 1,8-cineole,  $\alpha$ -pinene,  $\beta$ -pinene, sabinene hydrate, isomenthone, menthofuran, pulegone,  $\beta$ -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,  $\alpha$ -pinene, limonene, isomenthone, menthofuran, menthone, pulegone and lower in  $\beta$ -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.<sup>7</sup>

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.<sup>8</sup>

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 3.<sup>9</sup> 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 has indicated that *Mentha Piperita* (Peppermint) Oil contains a maximum of 4% pulegone and between 1% and 9% menthofuran.<sup>10</sup> 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 the cinnamic acid caffeic acid, the depside rosmarinic acid, and flavonoids (flavones and flavanones).<sup>11</sup> Eriocitrin ( $383.3 \pm 2.2$  mg/g extract) and rosmarinic acid ( $381.2 \pm 1.9$  mg/g extract) were the most abundant components identified within the leaves, while naringenin-7-O-glucoside ( $0.8 \pm 0.01$  mg/g extract) was the least abundant component identified. Kynurenic acid ( $3.82 \pm 0.46$   $\mu$ g/g) has also been detected in *Mentha Piperita* (Peppermint) Leaf Extract.<sup>12</sup> 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.<sup>5</sup>

### ***Mentha piperita* (peppermint) leaf extract powder**

According to composition data provided by the Council, *Mentha piperita* (peppermint) leaf extract powder (not a cosmetic ingredient name) contains tannin and terpenoid.<sup>5</sup>

### ***Mentha Piperita* (Peppermint) Leaf**

The major monoterpene constituents of *Mentha Piperita* (Peppermint) Leaf are as follows: (-)-limonene; 1,8-cineole; (+)-pulegone; (-)-menthone; (+)-isomenthone; (+)-menthofuran; (-)-menthol; and (+)-neomenthol.<sup>13</sup>

### ***Mentha Piperita* (Peppermint) Leaf Water**

Composition data provided by the Personal Care Products Council indicate that *Mentha Piperita* (Peppermint) Leaf Water contains essential oil (menthol).<sup>5</sup>

## **Impurities**

### ***Mentha Piperita* (Peppermint) Leaf Extract**

Data on impurities provided by the Personal Care Products 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.<sup>5</sup> *Mentha Piperita* (Peppermint) Leaf Extract (water/ethanol extract) contains not more than 10 ppm heavy metals and not more than 1 ppm arsenic.

### ***Mentha piperita* (peppermint) leaf extract powder**

According to data provided by the Personal Care Products Council, *Mentha piperita* (peppermint) leaf extract powder contains not more than 10 ppm heavy metals and not more than 2 ppm arsenic.<sup>5</sup>

### **Mentha Piperita (Peppermint) Leaf**

The following microelements 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).<sup>14</sup>

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.<sup>15</sup>

### **Mentha Piperita (Peppermint) Leaf Water**

Data on impurities provided by the Personal Care Products Council indicate that Mentha Piperita (Peppermint) Leaf Water contains not more than 10 ppm heavy metals and not more than 1 ppm arsenic.<sup>5</sup>

## 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.<sup>16</sup> 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.<sup>17,18</sup>

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).<sup>16</sup> 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.<sup>17,18</sup> Current and historical use frequency and concentration of use data are presented in Table 4. 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) 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.<sup>19,20,21,22</sup> 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.<sup>19,20</sup>

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.<sup>23,24,25</sup>

#### **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.<sup>1</sup> 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.<sup>26</sup> Mentha Piperita (Peppermint) Oil is an inactive ingredient in drug products that have been approved by the U.S. FDA.<sup>27</sup> A number of active ingredients, Mentha Piperita (Peppermint) Oil included, have been present in over-the-counter (OTC) drug products for various uses.<sup>28</sup> 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.<sup>29</sup>

#### **Mentha Piperita**

According to the European Medicines Agency Committee on Herbal Medicinal Products (HMPC) community herbal monograph on *Mentha x piperita* L., aetheroleum, 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.<sup>30</sup> 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.

#### **TOXICOKINETIC STUDIES**

##### **Dermal Penetration**

##### **Animal**

##### **Mentha Piperita (Peppermint) Oil**

*Eserine in a Mentha Piperita (Peppermint) Oil vehicle was applied to a 2.2 cm<sup>2</sup> 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.<sup>1</sup> Mentha Piperita (Peppermint) Oil had a latent period of 58 minutes.*

**Dermal****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).<sup>31</sup> A square section of skin was cut to provide a dose area of 1 cm<sup>2</sup> and placed in a flow-through diffusion cell. <sup>14</sup>C-Caffeine (hydrophilic) or <sup>14</sup>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 <sup>14</sup>C-caffeine in the presence of ethanol (control), the dermal absorption of <sup>14</sup>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 <sup>14</sup>C-salicylic acid.

**Penetration Inhibition****Mentha Piperita (Peppermint) Oil**

*Mentha Piperita* (Peppermint) Oil and [ring-UL-<sup>14</sup>C]benzoic acid were applied to full-thickness human skin (breast or abdominal) samples in a static diffusion cell.<sup>32</sup> 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.<sup>1</sup> 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.<sup>6</sup> 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<sub>50</sub> of 4441 mg/kg in fasted Wistar rats; the 48-h LD<sub>50</sub> was 2426 mg/kg.<sup>1</sup> In a study involving fasted mice, an LD<sub>50</sub> of 2410 mg/kg was reported for *Mentha Piperita* (Peppermint) Oil diluted in olive oil.

## Short-Term Toxicity Studies

### **Oral**

#### **Mentha Piperita (Peppermint) Oil and Components**

*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.<sup>1</sup> 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. In short-term oral toxicity studies (28-day studies; 20 rats per group) on components of Mentha Piperita (Peppermint) Oil, brain lesions (specifically, cyst-like spaces in the cerebellum) were also observed in rats given pulegone doses up to 160 mg/kg/day and menthone doses up to 800 mg/kg/day. These lesions were not observed in groups of 20 rats given oral doses of menthol up to 800 mg/kg/day for 28 days.*

## 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.<sup>1</sup> 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

### **Dermal**

### **Human**

#### **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.<sup>1</sup> Using a body splash product containing 0.2% Mentha Piperita (Peppermint Oil) and assuming 100% absorption over a body surface of 17,000 cm<sup>2</sup> and a daily application of 1 mg/cm<sup>2</sup> (~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.*

The authors of a book entitled ***Essential Oil Safety*** have recommended a maximum dermal use level of 5.4% Mentha Piperita (Peppermint) Oil.<sup>34</sup> This dermal restriction is based on 8% menthofuran 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.

### **Oral**

### **Human**

#### **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).<sup>10</sup> 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).

The authors of a book entitled ***Essential Oil Safety*** have recommended a maximum daily oral dose of 152 mg *Mentha Piperita* (Peppermint) Oil.<sup>34</sup> 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).<sup>35</sup> 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.

## **DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES**

### **Oral**

### **Animal**

### **Menthol**

Developmental toxicity data on menthol, a component of *Mentha Piperita* (Peppermint) Oil (may contain up to 55% menthol), are included in this section in the absence of developmental and reproductive toxicity data on *Mentha piperita* (peppermint)-derived ingredients.

*Groups of 15 to 23 pregnant animals were dosed by oral intubation with natural Brazilian menthol.<sup>1</sup> The mice were dosed with up to 185 mg/kg/day on gestation days (GD) 6 to 15; pregnant rats were given doses up to 218 mg/kg on GDs 6 to 15; pregnant hamsters were given doses up to 405 mg/kg/day on GDs 6 to 10; and artificially inseminated rabbits were given doses up to 425 mg/kg/day on GDs 6 to 18. Maternal body weight was recorded regularly. Caesarean sections were performed on all dams. No teratogenic effects were observed.*

## **GENOTOXICITY STUDIES**

### **In Vitro**

### ***Mentha Piperita* (Peppermint) Oil and component parts**

*The mutagenic potential of *Mentha Piperita* (Peppermint) Oil and its components was investigated using the Salmonella/mammalian microsome test.<sup>1</sup> 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, menthol, and pulegone, all 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 compounds less toxic to the bacteria. In contrast, menthone, induced a statistically significant number of revertants in strain TA1537 at doses of 6.4 and 32 µg/plate without metabolic activation. Menthone was further tested using the more sensitive TA97 strain. Statistically significant increases in the number of revertants were noted at all doses tested without metabolic activation; the results were dose-related (though toxicity was observed at a dose of 800 µg/plate). The researchers remarked on the unexpected results – menthone was mutagenic, but *Mentha Piperita* (Peppermint) Oil, which contained 33.7% menthone, was not.*

*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.<sup>1</sup>*

The genotoxicity of *Mentha Piperita* (Peppermint) Oil was evaluated in a chromosome aberration test using human peripheral blood lymphocytes.<sup>36</sup> 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.<sup>36</sup> 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.

## Menthol

Genotoxicity data on menthol, a component of *Mentha Piperita* (Peppermint) Oil (may contain up to 55% menthol), are included in this section as a supplement to the available genotoxicity data on *Mentha piperita* (peppermint)-derived ingredients.

*The mutagenic potential of natural Brazilian menthol was tested in the cytogenetic assay (rats), the host-mediated assay (mice), and the dominant lethal assay (rats).*<sup>1</sup> *The assays were performed with menthol doses of 1.45, 14.5, and 145 mg/kg, and, in some instances, subacute and acute studies were performed with doses of 500, 1150, and 3000 mg/kg, or 5000 mg/kg. In the host-mediated assay, a weakly positive but significant response was noted with the acute high dose against *Salmonella typhimurium* TA1530, and elevated recombinant frequencies were noted with the subacute doses against *Saccharomyces* strain D3. All of the other assay results were negative.*

## 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).<sup>37</sup> The exposure of mice to 8 Gy gamma radiation 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.<sup>38</sup> 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.<sup>1</sup>

**Menthol**

Carcinogenicity data on menthol, a component of *Mentha Piperita* (Peppermint) Oil (may contain up to 55% menthol), are included in this section as a supplement to the available carcinogenicity data on *Mentha piperita* (peppermint)-derived ingredients.

A 2-year oral dosing study by the National Cancer Institute found no evidence of carcinogenicity after Fischer 344 rats were dosed with 3750 ppm or 7500 ppm d,l-menthol or after B6C3F<sub>1</sub> mice were dosed with 2000 ppm or 4000 ppm d,l-menthol. A negative trend in fibroadenomas of the mammary gland was observed in female rats (20 of 50 control; 10 of 49 low-dose; 7 of 49 high-dose).<sup>1</sup>

**Pulegone**

Carcinogenicity data on pulegone, a constituent of *Mentha piperita* (peppermint)-derived ingredients, are included in this section, considering that the Panel previously limited the concentration of pulegone in these cosmetic ingredients.

In a 2-year bioassay, the administration of pulegone in corn oil 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) showed high morbidity and mortality at high doses in rats and decreased body weight gains in rats and mice.<sup>3,39</sup> 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) were 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 the 150 mg/kg female stop-exposure group (gavage with pulegone stopped at week 60 because of severely reduced body weights) were diagnosed with papilloma and carcinoma, combined. Male rats did not show 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.<sup>39</sup> In this study, pulegone was administered by gavage at a dose of 75 or 150 mg/kg body weight to female rats for 4 and 6 weeks.

**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.<sup>38</sup> 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).<sup>40</sup> 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.<sup>41</sup> 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.<sup>42</sup> Statistically significant ( $\alpha = 0.05$ ) growth inhibition was observed at a concentration of 31 µg/ml. An IC<sub>50</sub> (concentration required for 50% inhibition, µg/ml) of 92.3 µg/ml was reported for *Mentha Piperita* (Peppermint) Leaf Extract.

## **Menthol**

Anticarcinogenicity data on menthol, a component of *Mentha Piperita* (Peppermint) Oil (may contain up to 55% menthol), are included in this section as a supplement to the available carcinogenicity data on *Mentha piperita* (peppermint)-derived ingredients.

*Significant inhibition ( $p < 0.001$ ) of DMBA-induced rat mammary gland carcinogenesis following 20 weeks of oral dosing with 1% (-)-menthol.<sup>1</sup> Dosing with menthol began 2 weeks prior to DMBA tumor induction. A chemopreventive effect was noted when rats were dosed with 0.5% menthol for 2 weeks prior to and 1 week after DMBA induction.*

## **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.<sup>43</sup> *Mentha Piperita* (Peppermint) Oil from plants that were harvested during the summer and winter was tested. The following IC<sub>50</sub> values were reported: MCF-7 cell line ( $75.2 \pm 2.9$  [summer];  $80.8 \pm 3.2$  [winter]) and LNCaP cell line ( $90.4 \pm 3.7$  [summer];  $95.7 \pm 4.5$  [winter]). IC<sub>50</sub> values in the 10 to 100 µg/ml range represented a potentially toxic chemical, and IC<sub>50</sub> values < 10 µg/ml represented a potentially very toxic chemical.

In another study, essential oil was extracted from the leaves of *Mentha piperita*.<sup>44</sup> This extract was found to be cytotoxic in the following following 4 human cancer cell lines: human lung carcinoma SPC-A1 cells ( $IC_{50} = 10.89 \mu\text{g/ml}$ ), human leukemia K562 cells ( $IC_{50} = 16.16 \mu\text{g/ml}$ ) and human gastric cancer SGC-7901 cells ( $IC_{50} = 38.76 \mu\text{g/ml}$ ). 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.<sup>45</sup> The results indicated that *Mentha piperita* had a moderate toxic effect on the A549 cell line ( $IC_{50} = 879.52 \pm 22.55 \mu\text{g/ml}$ ). The growth of A549 cells was inhibited by *Mentha piperita* in a dose-dependent manner. The inhibitory rate was  $54.54\% \pm 1.38\%$  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.<sup>46</sup> 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 (dimethyl sulfoxide) 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.<sup>33</sup>

### **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.<sup>47</sup>

### **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.*<sup>1</sup>

## 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.<sup>1</sup>*

### **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.<sup>48</sup>

## **DERMAL IRRITATION AND SENSITIZATION 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 5.

#### **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.<sup>1</sup>*

#### **Menthol**

Skin irritation data on menthol, a component of Mentha Piperita (Peppermint) Oil (may contain up to 55% menthol), are included in this section as a supplement to the available skin irritation data on *Mentha piperita* (peppermint)-derived ingredients.

*Two Tiger Balm formulations containing 8% and 10% menthol were applied for 23 h under occlusive patches to abraded and intact sites on New Zealand white rabbits. The total number of patches applied was 21. A third group was treated with a control wax (mixture of hard and soft waxes). Untreated sites on each animal served as negative controls. Irritation was scored using the Draize scale. Dermal irritation was observed in all treated animals with the following severity scale: 8% menthol balm < control wax < 10% menthol balm. The 8% menthol balm was almost innocuous in male rabbits. The irritation observed was not progressive and tolerance developed within 10 days. No severe damage was noted at microscopic examination of the skin (increased hyperkeratosis was noted at treated sites) and no evidence of systemic toxicity was noted. The investigators noted that the balm contained "irritants" such as clove oil, camphor, and menthol and remarked that the irritation observed was unexpected.<sup>1</sup>*

#### **Human**

##### **Mentha Piperita (Peppermint) Leaf Water**

Human skin irritation data are summarized in Table 5.

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.<sup>49,50,51</sup>

## **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.<sup>1</sup>*

Human skin sensitization data are summarized in Table 5.

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.<sup>5,51,52,53,54</sup>

HRIPT results for undiluted Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract) in 52 subjects were also negative.<sup>5</sup>

## **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<sup>2</sup>, or for 40 minutes with light from a Xenon lamp at a weighted erythema energy of 0.1667 W/m<sup>2</sup>. 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.<sup>1</sup>*

## **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.<sup>49</sup> 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 5.<sup>54</sup>

In a multicenter study in which the US/Canadian North American Contact Dermatitis Group (NACDG) tested 13,398 patients with *Mentha Piperita* (Peppermint) Oil (2% in petrolatum), the prevalence rate for this ingredient was 0.9% (Table 5).<sup>55</sup>

## Case Reports

Case reports are summarized in Table 5.

Mostly positive patch test reactions to *Mentha Piperita* (Peppermint) Oil and *Mentha Piperita* were reported in case reports on patients with diseased skin.<sup>56,57,58,59,60,61,62</sup> 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.<sup>63,64</sup>

## 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.<sup>1</sup> 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.<sup>1</sup>*

### **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.<sup>65</sup> 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).<sup>66</sup> 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 (Tmax) likely related to formulation-specific factors (ie, delayed release) and, potentially, enterohepatic recirculation.

### **Menthol**

A clinical report on menthol, a component of *Mentha Piperita* (Peppermint) Oil (may contain up to 55% menthol), are included in this section as a supplement to the available clinical data on *Mentha piperita* (peppermint)-derived ingredients.

*When 877 patients with primary contact, atopic, nummular, and stasis dermatitis and eczema were tested with 5% menthol in yellow paraffin, reactions were observed in 1% of the panelists within 96 h.<sup>1</sup>*

## **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 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 (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.

*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 dietarDBSs associated with adverse event reports submitted to the FDA 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, considering that the Panel previously limited the concentration of pulegone in these cosmetic ingredients. In a 2-year bioassay, pulegone 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 (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.

A face cream containing 20% *Mentha Piperita* (Peppermint) Leaf Water did not induce cumulative skin irritation or sensitization in an HRIPT involving 107 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. 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%).

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. In another multicenter study in which the US/Canadian North American Contact Dermatitis Group (NACDG) tested 13,398 patients with *Mentha 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 (From 2001 Final Report)**

*In assessing the safety of *Mentha Piperita* (Peppermint) Oil, *Mentha Piperita* (Peppermint) Extract, *Mentha Piperita* (Peppermint) Leaves, and *Mentha Piperita* (Peppermint) Water, the CIR Expert Panel was concerned about oral-dosing studies that reported cyst-like spaces in the cerebellum of rats. The results of these studies were difficult to interpret. The findings were not consistent among studies (lesions were noted in some studies but not others), and though the lesions appeared to depend on the pulegone content, no definitive conclusion could be made (a greater NOAEL was reported in a 90-day study using a Peppermint Oil containing 1.1% pulegone versus a 28-day study that tested a Peppermint Oil containing 1.7% pulegone). The Panel also noted that the large differences between doses within each study made it impossible to pinpoint exactly the dose at which changes first appeared.*

*Noting the lack of dermal exposure studies on Peppermint Oil, the Panel expected its absorption would be rapid, following that of menthol, a major component. Dermal absorption, however, was not expected to be greater than absorption through the gastrointestinal tract. Metabolism from either route of exposure would be similar – phase I metabolism followed by transport to the liver. The Panel was of the opinion that the oral-dose data contained in this report were sufficient to address concerns resulting from the expected rapid absorption. However, the Panel noted the evidence that menthol 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.*

*Clinical dermal testing demonstrated that 8% Peppermint Oil was not a sensitizer, and that 2% Peppermint Oil produced a small number of positive reactions in dermatitis patients.*

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

## **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.<sup>1</sup> The conclusion also contains a statement indicating 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.

Because final product formulations may contain multiple botanicals, each possibly 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. For *Mentha piperita* (peppermint)-derived ingredients, the Panel was concerned about the presence of terpenes in cosmetics, which could result in sensitization. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

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.

Finally, the Panel discussed the issue of incidental inhalation exposure, 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>.

## **CONCLUSION – To be determined.**

**Table 1. Definitions and Functions of the Ingredients in this Safety Assessment.<sup>2</sup>**

<b>Ingredient CAS No.</b>	<b>Definition &amp; Idealized Structures</b>	<b>Function</b>
Mentha Piperita (Peppermint) Oil	Mentha Piperita (Peppermint) Oil is a volatile oil obtained from the whole plant <i>Mentha piperita</i> . The accepted scientific name for <i>Mentha piperita</i> is <i>Mentha x piperita</i> .	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Mentha Piperita (Peppermint) Leaf Extract	Mentha Piperita (Peppermint) Leaf Extract is the extract of the leaves of the peppermint, <i>Mentha piperita</i> . The accepted scientific name for <i>Mentha piperita</i> is <i>Mentha x piperita</i> .	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous; Skin-Conditioning Agents - Occlusive
Mentha Piperita (Peppermint) Leaf	Mentha Piperita (Peppermint) Leaf is the dried leaves of <i>Mentha piperita</i> . The accepted scientific name for <i>Mentha piperita</i> is <i>Mentha x piperita</i> .	Fragrance Ingredients
Mentha Piperita (Peppermint) Leaf Water	Mentha Piperita (Peppermint) Leaf Water is an aqueous solution of the steam distillate obtained from the leaves of <i>Mentha piperita</i> . The accepted scientific name for <i>Mentha piperita</i> is <i>Mentha x piperita</i> .	Flavoring Agents; Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Mentha Piperita (Peppermint) Extract	Mentha Piperita (Peppermint) Extract is the extract of the whole plant, <i>Mentha piperita</i> . The accepted scientific name for <i>Mentha piperita</i> is <i>Mentha x piperita</i> .	Skin-Conditioning Agents - Miscellaneous
Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract	Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract is the extract of the flowers, leaves and stems of <i>Mentha piperita</i> . The accepted scientific name for <i>Mentha piperita</i> is <i>Mentha x piperita</i> .	Flavoring Agents; Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Mentha Piperita (Peppermint) Flower/Leaf/Stem Water	Mentha Piperita (Peppermint) Flower/Leaf/Stem Water is the aqueous solution of the steam distillates obtained from the flowers, leaves and stems of <i>Mentha piperita</i> . The accepted scientific name for <i>Mentha piperita</i> is <i>Mentha x piperita</i> .	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 <i>Mentha piperita</i> . The accepted scientific name for <i>Mentha piperita</i> is <i>Mentha x piperita</i> .	Antioxidants; Skin Protectants
Mentha Piperita (Peppermint) Leaf Juice	Mentha Piperita (Peppermint) Leaf Juice is the juice expressed from the leaves of <i>Mentha piperita</i> . The accepted scientific name for <i>Mentha piperita</i> is <i>Mentha x piperita</i> .	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 <i>Mentha piperita</i> . The accepted scientific name for <i>Mentha piperita</i> is <i>Mentha x piperita</i> .	Skin-Conditioning Agents - Miscellaneous

**Table 2. Physical and Chemical Properties of *Mentha Piperita* (Peppermint) Oil**

<b>Property</b>	<b>Value</b>	<b>Reference</b>
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 8

**Table 3. Chromatographic Profile for *menthe Piperita* (Peppermint) Oil.<sup>9</sup>**

<b>Components</b>	<b>Origins Other Than U.S.</b>		<b>U.S. Type</b>	
	<b>Min. (%)</b>	<b>Max. (%)</b>	<b>Min. (%)</b>	<b>Max. (%)</b>
3-Octanol	0.1	0.5	0.1	0.4
1,8-Cineole	3.0	8.0	4.0	6.0
Limonene <sup>a</sup>	1.0	3.0	1.0	2.5
<i>trans</i> -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 <sup>b</sup>	2.0	8.0	3.0	6.5
β-Caryophyllene	1.0	3.5	1.0	2.5

<sup>a</sup>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

<sup>b</sup>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.

**Table 4. Frequency and Concentration of Use of *Mentha piperita* (peppermint)-derived Ingredients According to Duration and Exposure.<sup>1,16,17,18</sup>**

	# 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
<b>Totals*</b>	<b>827</b>	<b>102</b>	<b>0.0001-5</b>	<b>0.1-3</b>	<b>198</b>	<b>35</b>	<b>0.000075-0.5</b>	<b>NR</b>
<b>Duration of Use</b>								
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
<b>Exposure Type</b>								
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 <sup>a</sup>	NR;23 <sup>a</sup>	0.017-1;0.002-1.1 <sup>a</sup>	NR	5;34 <sup>a</sup>	NR;2 <sup>a</sup>	0.00041-0.0046;0.00057-0.026 <sup>a</sup>	NR
Incidental Inhalation-Powder	1 <sup>a</sup>	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
<b>Mentha Piperita (Peppermint) Leaf</b>				<b>Mentha Piperita (Peppermint) Leaf Water</b>				
	2017	1998	2017	1997	2017	1998	2017	1997
<b>Totals*</b>	<b>NR</b>	<b>NR</b>	<b>0.0002-1.6</b>	<b>NR</b>	<b>15</b>	<b>NR</b>	<b>0.00013-40</b>	<b>NR</b>
<b>Duration of Use</b>								
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
<b>Exposure Type</b>								
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 <sup>a</sup>	NR	NR;4 <sup>a</sup>	NR	NR;0.00043-10 <sup>a</sup>	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
<b>Mentha Piperita (Peppermint) Extract</b>				<b>Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract</b>				
	2017	2017		2017	2017		2017	
<b>Totals*</b>	<b>71</b>	<b>0.00006-7.9</b>		<b>NR</b>			<b>0.3</b>	
<b>Duration of Use</b>								
Leave-On	43		0.00006-7.9		NR		0.3	
Rinse-Off	27		0.0004-1		NR		NR	
Diluted for (Bath) Use	1		1		NR		NR	
<b>Exposure Type</b>								
Eye Area	NR		NR		NR		NR	
Incidental Ingestion	4		0.0099-3.4		NR		0.3	
Incidental Inhalation-Spray	10; 21 <sup>a</sup>		1.3; 0.005-1 <sup>a</sup>		NR		NR	
Incidental Inhalation-Powder	NR		NR		NR		NR	
Dermal Contact	63		0.00006-7.9		NR		NR	
Deodorant (underarm)	1		1		NR		NR	
Hair - Non-Coloring	4		0.0004-1		NR		NR	
Hair-Coloring	NR		NR		NR		NR	
Nail	NR		NR		NR		NR	
Mucous Membrane	3		0.0099-3.4		NR		0.3	
Baby Products	NR		NR		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.

<sup>a</sup> It is possible these products are sprays, but it is not specified whether the reported uses are sprays..

NR - no reported use

**Table 5. Dermal Irritation and Sensitization Data**

Ingredient	Subjects/Cell Type	Protocol	Results
<b>Irritation Studies</b>			
Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract) (10% and 100%)	Reconstructed human epidermis	<i>In vitro</i> 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%). <sup>5</sup>
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. <sup>49</sup>
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 $48 \pm 4$ 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. <sup>50</sup>
<b>Sensitization Studies</b>			
100% Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract)	52 subjects	HRIPT (protocol details not included).	Negative results. <sup>5</sup>
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 $48 \pm 4$ h. Duration of exposure was $72 \pm$ $4$ h for 3rd, 6th, and 9th applications. Challenge phase consisted of single application to new site and a previously treated site for $48 \pm 4$ h.	Product did not induce cumulative irritation or sensitization. <sup>53</sup>
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. <sup>51</sup>
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. <sup>52</sup>

**Table 5. Dermal Irritation and Sensitization Data**

Ingredient	Subjects/Cell Type	Protocol	Results
<b>Multicenter Studies</b>			
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. <sup>54</sup>
Mentha Piperita (Peppermint) Oil (2% in petrolatum)	13,398 patients	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.	Prevalence rate for Mentha Piperita (Peppermint) Oil was 0.9%. <sup>55</sup>
<b>Case Reports</b>			
Mentha Piperita (Peppermint) Oil (2% in petrolatum)	Male patient with orofacial granulomatosis mainly affecting lower lip	Patch test	Allergic positive reaction. <sup>56</sup>
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. <sup>57</sup>
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). <sup>58</sup>
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. <sup>59</sup>
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. <sup>60</sup>

**Table 5. Dermal Irritation and Sensitization Data**

Ingredient	Subjects/Cell Type	Protocol	Results
Mentha Piperita (Peppermint) Leaf and Peppermint (concentration not stated)	Male patient with IgE- mediated anaphylaxis to peppermint ( <i>Mentha piperita</i> ) 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. <sup>63</sup>
Mentha Piperita (Peppermint) Leaf Extract (concentration not stated)	Female patient became symptomatic with dyspnea when near peppermint ( <i>Mentha piperita</i> ) scent	Skin prick test	Positive skin prick test reaction to commercial Mentha Piperita (Peppermint) Leaf Extract. <sup>64</sup>
Mentha Piperita (Peppermint) (concentration not stated)	Male patient with severe cheilitis	Patch test	Negative reaction.. <sup>61</sup>
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. <sup>62</sup>

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# Final Report on the Safety Assessment of *Mentha Piperita* (Peppermint) Oil, *Mentha Piperita* (Peppermint) Leaf Extract, *Mentha Piperita* (Peppermint) Leaf, and *Mentha Piperita* (Peppermint) Leaf Water<sup>1</sup>

*Mentha Piperita* (Peppermint) Oil, *Mentha Piperita* (Peppermint) Leaf Extract, *Mentha Piperita* (Peppermint) Leaf, *Mentha Piperita* (Peppermint) Leaf Water are obtained from the *Mentha piperita* plant. The oil is currently used in cosmetic formulations as a fragrance component, but previously had been also described as a denaturant. The extract and leaves are described as biological additives, but only the extract is reported to be used. Peppermint Water is described as a flavoring agent or fragrance component, but is not currently in use. Peppermint Oil is used at a concentration of  $\leq 3\%$  in rinse-off formulations and  $\leq 0.2\%$  in leave-on formulations. Peppermint Oil is composed primarily of menthol and menthone. Other possible constituents include pulegone, menthofuran, and limone. Most of the safety test data concern Peppermint Oil. The oil is considered to present the "worst case scenario" because of its many constituents, so data on the oil were considered relevant to the entire group of ingredients. Peppermint Oil was minimally toxic in acute oral studies. Short-term and subchronic oral studies reported cystlike lesions in the cerebellum in rats that were given doses of Peppermint Oil containing pulegone, pulegone alone, or large amounts ( $>200$  mg/kg/day) of menthone. Pulegone is also a recognized hepatotoxin. Repeated intradermal dosing with Peppermint Oil produced moderate and severe reactions in rabbits, although Peppermint Oil did not appear to be phototoxic. Peppermint Oil was negative in the Ames test and a mouse lymphoma mutagenesis assay but gave equivocal results in a Chinese hamster fibroblast cell chromosome aberration assay. In a carcinogenicity study of toothpaste and its components, no apparent differences were noted between mice treated with Peppermint Oil and those treated with the toothpaste base. Isolated clinical cases of irritation and/or sensitization to Peppermint Oil and/or its constituents have been reported, but Peppermint Oil (8%) was not a sensitizer when tested using a maximization protocol. It was expected that dermal absorption of Peppermint Oil would be rapid, following that of menthol, a major component, but in no case would be greater than absorption through the gastrointestinal tract. Because of the toxicity of pulegone, the safe concentration of this constituent was limited to  $\leq 1\%$ . This concentration was achievable both by controlling the time of harvest and processing technique. There is evidence that menthol can enhance penetration of other

agents. Formulators were cautioned that this enhanced penetration can affect the use of other ingredients whose safety assessment was based on their lack of absorption. With the limitation that the concentration of pulegone in these ingredients should not exceed 1%, it was concluded that *Mentha Piperita* (Peppermint) Oil, *Mentha Piperita* (Peppermint) Extract, *Mentha Piperita* (Peppermint) Leaves, *Mentha Piperita* (Peppermint) Water are safe as used in cosmetic formulations.

## INTRODUCTION

The following is a compilation of studies concerning *Mentha Piperita* (Peppermint) Oil (CAS No. 8006-90-4), *Mentha Piperita* (Peppermint) Leaf Extract (CAS No. 84082-70-2), *Mentha Piperita* (Peppermint) Leaf, *Mentha Piperita* (Peppermint) Leaf Water. (Note: recently, cosmetic ingredient terminology for these ingredients has changed. For example, *Mentha Piperita* [Peppermint] Oil previously was called Peppermint [Mentha Piperita] Oil (Wenninger and McEwen 1997).) For brevity, these ingredients are identified as Peppermint Oil, Peppermint Extract, Peppermint Leaves, and Peppermint Water in this report. Most of the information concerns Peppermint Oil. Data on the Oil were considered relevant to the entire group of ingredients.

## CHEMISTRY

### Definition and Structure

Peppermint United States Pharmacopeia, (USP) is defined as the "dried leaves and flowering tops of *Mentha piperita* L. (Labiatae), having carminative, gastric stimulant, and counter-irritant properties; used as an oil, spirit, or water extract as a flavored vehicles for drugs" (Taylor 1988).

*Mentha Piperita* (Peppermint) Oil is a volatile oil obtained from the plant *Mentha piperita*. Synonyms include Mentha Oil, *Mentha Piperita* Oil, Oil of Peppermint, and Peppermint Oil (Wenninger, Canterbury, and McEwen 2000).

*Mentha Piperita* (Peppermint) Leaf Extract is an extract of the leaves of the peppermint, *Mentha piperita*. Synonyms include Extract of *Mentha Piperita*, Extract of Peppermint, Extract of Peppermint Leaves, *Mentha Piperita* Extract, Peppermint

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Extract, and Peppermint Leaf Extract (Wenninger, Canterbury, and McEwen 2000).

*Mentha Piperita* (Peppermint) Leaf is the cosmetic ingredient made from the dried leaves and tops of the peppermint, *Mentha piperita*. Synonyms include Leaf, Mentha Piperita; Leaf, Peppermint; Mentha Piperita Leaves; Peppermint Leaf, and Peppermint Leaves (Wenninger, Canterbury, and McEwen 2000).

*Mentha Piperita* (Peppermint) Leaf Water is an aqueous solution of the odoriferous principles of the leaves of *Mentha piperita*. Synonyms include Peppermint Water and Peppermint Leaf Water (Wenninger, Canterbury, and McEwen 2000).

### Physical and Chemical Properties

One supplier noted that cosmetic Peppermint Oil is natural and of food grade quality (Ungerer and Company 1997).

Peppermint Oil is described as a colorless or pale yellow liquid having a strong, penetrating odor of peppermint and a pungent taste, followed by the sensation of coldness when air is drawn into the mouth (National Academy of Sciences 1981). Table 1 lists some properties and specifications.

Peppermint Oil has over 30 known components. It is comprised mainly of menthol (35% to 60%), and menthone (15% to 30%) (Sang 1982; Thorup et al. 1983a; Madsen, Würtzen, and Carstensen 1986; Saito and Oka 1990; Bowen and Cubbin 1992). Because it is the primary component, menthol is further examined in the next section of this report.

Menthyl acetate (4% to 14%) and small amounts of cineole and other terpenes are also found in Peppermint Oil. Other identified components are acetaldehyde, amyl alcohol, menthyl esters, limone, pinene, phellandrene, cadinene, and dimethyl sulfide (Dooms-Goossens et al. 1977; Andersen 1978). In addition, Lawrence (1972) and Baslas, Singh, and Baslas (1973) identified several trace constituents including  $\alpha$ -pinene, *p*-menthane, sabinene, terpinolene, ocimene, gamma-terpinene, fenchene,

**TABLE 1**  
Chemical/physical properties and specifications of  
Peppermint Oil (National Academy of Sciences 1981;  
National Formulary 1995)

Property	
Angular rotation	Between $-18^{\circ}\text{C}$ and $32^{\circ}\text{C}$
Refractive index	Between 1.459 and 1.465 at $20^{\circ}$
Specific gravity	Between 0.896 and 0.908
Assay for total esters	Not less than 5.0% of esters, calculated as menthyl acetate
Assay for total menthol	Not less than 50.0% of menthol
Dimethyl sulfide	Passes test (rectified); fails test (natural)
Heavy metals (as Pb)	Passes test (limit of 0.004%)
Solubility in alcohol	Passes test (1 volume dissolves in 3 volumes of 70% alcohol)

$\alpha$ -thujone,  $\beta$ -thujone, citronellol,  $\alpha$ -cadinene,  $\alpha$ -amorphene,  $\alpha$ -gurjunene, and  $\beta$ -copaene.

Sullivan et al. (1979) stated that pulegone is found in young peppermint leaves, and is metabolized to menthol as the leaves mature. Similarly, in their review, Bowen and Cubbin (1992) stressed that the pulegone is found only in Peppermint Oil made from young plants and in trace amounts in "inferior" oils; pulegone is absent from "good-quality" Peppermint Oil. However, a supplier of cosmetic Peppermint Oil reported pulegone concentrations of 1% to 4% depending on the origin of the oil (Ungerer and Company 1997). Published studies that investigated the pulegone content of Peppermint Oil also reported a range of <1% to 4% for Oils from a North American origin (Lawrence 1993; Ravid, Putievsky, and Katzir 1994). Several studies cited in this literature review used Peppermint Oil containing pulegone. Because of the extensive study done on this component, pulegone is further examined in the next section of this report.

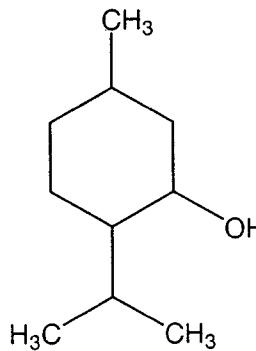
### Components

#### Menthol

Menthol, the primary component of Peppermint Oil, exists as four pairs of optical isomers: (–)- and (+)-menthol, (–)- and (+)-isomenthol, (–)- and (+)-neomenthol, and (–)- and (+)-isoneomenthol. (–)-Menthol is the isomer that is most commonly found in nature (Eccles 1994). Menthol conforms to the structure shown in Figure 1.

### Method of Manufacture

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 (Dooms-Goossens et al. 1977). Fehr (1984) reported that the menthone content decreases while the menthol content increases in peppermint leaves upon storage for 1 to 2 months, at  $22^{\circ}\text{C}$  to  $24^{\circ}\text{C}$ . However, the relative menthone to menthol proportion remained practically constant during the total storage time.



**FIGURE 1**  
Menthol.

A patented technique is available to reduce the pulegone content of a Peppermint Oil preparation by stereospecifically reducing it with  $\text{Na}_2\text{SO}_3$  in the presence of water (as a hydrogen ion source) at neutral pH. The process stabilizes menthofuran against oxidative breakdown and the final product has an increased menthone and menthol content. A sample containing 2.35% pulegone was reduced to 0.34% pulegone (Spencer 1989).

### Analytical Methods

Several components of Peppermint Oil can be estimated by capillary gas chromatography (Sang 1982).

### USE

#### Cosmetic

Peppermint Oil is used in cosmetic formulations as a fragrance component and skin-conditioning agent—miscellaneous (Wenninger, Canterbury, and McEwen 2000) and had previously been used as a denaturant (Wenninger and McEwen 1995). Table 2 presents the 102 reported uses of Peppermint Oil in cosmetics as a function of product type (FDA 1998).

Concentrations of use are no longer reported to the Food and Drug Administration (FDA) (FDA 1992). However, data submitted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) directly to Cosmetic Ingredient Review (CIR) indicated use of Peppermint Oil at the following concentrations: 0.02% in a medicated face mask; 0.1% in a facial cleanser; 0.2% in a lipstick, a body splash, a foot refresher/lotion, and a body refresher; 0.5% in a toothpaste; 0.9% in a fluoride toothpaste; 1.2% in a mouthwash; 2.0% in a lip balm; and 3.0% in a hair lotion (CTFA 1997a).

In addition, two denatured alcohol formulas contained a maximum of 0.4% and 1.5% Peppermint Oil, respectively (CTFA 1997b).

Peppermint Extract is used in cosmetic formulations as a fragrance ingredient, skin-conditioning agent—miscellaneous and skin-conditioning agent—occlusive (Wenninger, Canterbury, and McEwen 2000). As of January 1998, it was reported to be used in 35 formulations (Table 2).

Peppermint Leaves can be used in cosmetic formulations as fragrance ingredients (Wenninger, Canterbury, and McEwen 2000). Peppermint Water can be used as a flavoring agent or fragrance component (Wenninger, Canterbury, and McEwen 2000). While neither was reported in use, the FDA listed two uses of the ingredient "Peppermint" in January 1998 (Table 2).

#### International

All of these ingredients are included in the single name, *Mentha Piperita*, in the European Union (Wenninger, Canterbury, and McEwen 2000).

*Mentha Piperita* (Peppermint) Leaf Extract, as Peppermint Extract, and *Mentha Piperita* (Peppermint) Leaf Water, as Pep-

permint Distillate, are listed in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category (CLS)* with precedent for use without restriction in all *CLS* categories except eyeliner preparations, for which there is no precedent (Santucci 1999). According to Notification 990 of the Pharmaceutical and Medical Safety Bureau of the Japan Ministry of Health and Welfare, issued September 29, 2000, none of these ingredients are prohibited or restricted in its use beyond a basic obligation of manufacturers to use all ingredients in a manner that guarantees safety (Japan Ministry of Health and Welfare 2000).

#### Noncosmetic

Peppermint Oil is a generally recognized as safe (GRAS) ingredient for use in dietary supplements (Rothschild 1990). It is described as a naturally occurring carminative that relaxes gastrointestinal smooth muscle (Gosselin, Smith, and Hodge 1984; Kaffenberger and Doyle 1990). See General Biology for more details.

A final ruling by the FDA labeled Peppermint Oil as safe and effective as an antitussive (topical/inhalant). Final rulings cautioned that 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 (FDA 1991).

#### Exposure Assessment

The FDA calculated an estimated human exposure from cosmetic use based on the concentration of use information supplied by industry. Using a body splash product containing 0.2% Peppermint Oil and assuming 100% absorption over a body surface of  $17,000 \text{ cm}^2$  and a daily application of  $1 \text{ mg/cm}^2$  ( $\sim 17 \text{ ml}$  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 (FDA 1997).

### GENERAL BIOLOGY

#### Absorption, Distribution, Metabolism, Excretion

##### Dermal Administration

Eserine in a Peppermint Oil vehicle was applied to a  $2.2\text{-cm}^2$  shaved area on the abdomen of mice. The absorption rate for Peppermint Oil was measured as the latent period between application and appearance of Eserine-induced signs. Peppermint Oil had a latent period of 58 minutes (Meyer and Meyer 1959).

##### Oral Delivery

The rate of Peppermint Oil absorption and excretion following oral administration was determined by measuring urinary menthol glucuronide. Four male volunteers ingested 180 mg of an enteric-coated Peppermint Oil capsule following a 16-hour fast. The panelists were instructed to increase water intake throughout the day. Total urine output was collected every 2 hours for up to 14 hours post ingestion. Menthol was liberated

**TABLE 2**  
Frequency of use of Peppermint Oil (FDA 1998)

Product category	No. of formulations in category	No. containing Peppermint Oil
<b>Peppermint Oil</b>		
Bath oils, tablets, and salts	124	1
Bubble baths	200	2
Other bath preparations	159	3
Hair conditioners	636	1
Lipstick	790	2
Makeup bases	132	1
Cuticle softeners	19	1
Nail creams and lotions	17	1
Dentrifrices	38	11
Mouthwashes and breath fresheners	49	10
Other oral hygiene products	6	1
Shaving cream	139	2
Cleansing	653	13
Face and neck skin care (excluding shaving)	263	3
Body and hand skin care (excluding shaving)	796	6
Foot powders and sprays	35	4
Moisturizing skin care	769	3
Night skin care	188	1
Paste masks (mud packs)	255	6
Skin fresheners	184	9
Other skin care preparations	692	21
<b>1998 total for Peppermint Oil</b>	<b>102</b>	
<b>Peppermint Extract</b>		
Bubble baths	200	1
Hair conditioners	636	7
Rinses (noncoloring)	40	1
Shampoos (noncoloring)	860	4
Tonics, dressings, and other hair-grooming aids	549	1
Bath soaps and detergents	385	2
Other personal cleanliness products	291	3
Other shaving preparation products	60	1
Cleansing skin care preparations	653	1
Face and neck skin care (excluding shaving)	263	2
Body and hand skin care (excluding shaving)	796	4
Paste masks (mud packs)	255	5
Skin fresheners	184	1
Other skin care preparations	692	2
<b>1998 total for Peppermint Extract</b>	<b>35</b>	
<b>Peppermint (no further description)</b>		
Other bath preparations	159	1
Moisturizing	769	1
<b>1998 total for Peppermint</b>	<b>2</b>	

from its glucuronide metabolite by treating the urine with  $\beta$ -D-glucuronidase and quantitated with capillary gas chromatography. A significant amount of variance was found among individuals. 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 hours (Kaffenberger and Doyle 1990).

### Menthol

In a review, Eccles (1994) noted that some phase 1 metabolism of menthol can occur in the skin and gut following dermal, oral, or inhalation exposure; most of the absorbed compound is transported to the liver. Yamaguchi, Caldwell, and Farmer (1994) administered  $^3\text{H}$ -(-)-menthol (500 mg/kg) to intact and bile duct-cannulated male Fischer 344 rats. In intact rats, ~71% of the dose was recovered within 48 hours, with almost equal amounts in the urine and feces. In bile duct-cannulated rats, 74% of the dose was recovered with 67% in the bile and 7% in the urine. The major biliary metabolite was menthol glucuronide. Madyastha and Srivatsan (1988) reported that oral administration of (-)-menthol to rats (800 mg/kg/day for 20 days) resulted in two major urinary metabolites: *p*-menthane-3,8-diol and 3,8-dihydroxy-*p*-menthane-7-carboxylic acid and two minor metabolites: *p*-menthane-3,9-diol and 3,8-oxy-*p*-menthane-7-carboxylic acid. An in vitro study by these investigators noted that oral administration for up to 7 days induced hepatic microsomal enzymes cytochrome P450 and NADPH-cytochrome *c* (P450) reductase.

### Smooth Muscle-Relaxing Effects

An investigation that used isolated pharmacological preparations from guinea pig large intestine and patch clamp electrophysiology techniques on rabbit jejunum concluded that Peppermint Oil relaxed gastrointestinal smooth muscle by reducing calcium influx (Hills and Aaronson 1991). Similar findings were reported earlier by Hawthorn et al. (1988) and confirmed by Dalvi et al. (1991). Researchers have reported on the use of Peppermint Oil capsules to treat spastic colon and irritable bowel syndrome (Somerville, Richmond, and Bell 1984; Friedman 1991).

Peppermint Oil, in combination with eucalyptus oil and ethanol, increased cognitive performance, and possessed muscle-relaxing properties when applied to large areas of the forehead and temples of 32 healthy human subjects. The mixture did not influence pain sensitivity. A significant reduction in sensitivity to headache was produced by a combination of Peppermint Oil and ethanol (Gobel, Schmidt, and Soyka 1994).

### Effect on Virus

Herrmann and Kucera (1967) reported that Peppermint Extract had protective activity against Newcastle disease and herpes simplex, vaccinia, Semliki forest, and West Nile viruses in embryonated chicken egg and chick embryo fibroblast cell-culture

systems. The effect was noted in eggs only when the Peppermint Oil preparation was injected into the allantoic sac at 3 to 24 hours prior to inoculation with virus; no effect was observed in influenza virus-infected eggs. The protective activity against most of the viruses was attributed to a tannin, consisting of trimers of caffeic acid, that has an affinity for many viruses and is contained in mint plants. A nontannin fraction was considered active against herpes simplex virus.

### Acceptable Daily Intake

In 1976, the Food and Agriculture Organization of the United Nations World Health Organization (FAO/WHO) Joint Expert Committee on Food Additives (JECFA) established an acceptable daily intake (ADI) of 0.2 mg/kg body weight/day for menthol (FAO/WHO 1976, 1994). The JECFA comments were as follows:

Evidence from human studies suggest that menthol is well absorbed from the gut. A large proportion is excreted in urine as glucuronides but the metabolic rate of the remainder has not been elucidated. No long-term studies have been carried out but a 24 week lung adenoma (i.p. dosing) study and extensive mutagenicity studies gave negative results. The results of one study suggested that adverse effects may occur in man ingesting about 2 mg menthol/kg/day. Other evidence from human exposure shows that adverse effects are unlikely to occur when 0.2 mg menthol/kg/day is ingested. The Committee agreed, however, that further information on human menthol intake from food and medicine, and if possible, observations on a group of people with a higher than average intake would need to be carried out if any increase in the ADI is to be contemplated (FAO/WHO 1976).

The evaluation section of the report cited an unpublished oral-dose study in which groups of 80 rats (40 each sex) received 0, 100, or 200 mg/kg of either *l* or *d,l*-menthol for 5½ weeks. No adverse effect was observed in weight gain or excretion of glucuronide, water, and electrolytes; central nervous system reactions to cardiazol or electric shock and intravenous (IV) hexobarbital sleeping time were not affected. Using the 200-mg/kg/body weight level for rats, the Committee estimated an acceptable ADI for humans of 0 to 0.2 mg menthol/kg/body weight.

The Committee listed the following additional studies needed to increase the ADI: long-term toxicity and carcinogenicity in rats, information regarding average and maximum likely intake of menthol, clinical observation following a higher than average intake, and metabolic studies (FAO/WHO 1976).

### ANIMAL TOXICOLOGY

#### Acute Oral Toxicity

Peppermint Oil USP had a 24-hour oral LD<sub>50</sub> of 4441 mg/kg in fasted Wistar rats; the 48-hour LD<sub>50</sub> was 2426 mg/kg (Eickholt and Box 1965). Ohsumi et al. (1984) reported an oral LD<sub>50</sub> of 2410 mg/kg in fasted mice for Peppermint Oil diluted in olive oil.

**Short-Term Oral Toxicity**

Studies using Wistar rats described in this section are summarized in Table 3.

Thorup et al. (1983a) investigated the toxicity of Peppermint Oil administered per os (PO) to groups of 20 Wistar rats at doses of 10, 40, and 100 mg/kg body weight/day for 28 days. The Peppermint Oil sample contained 38.1% menthol, 33.7% menthone, and 1.7% pulegone; the remaining components could not be identified. The sample was diluted in a soybean oil vehicle. Rats were inspected twice daily, and body weight and feed and water consumption were recorded weekly. On day 21, blood samples were taken from 16 animals (8 of each sex) for analysis. Animals were killed at the end of week 4 and necrop-

sied. Organ samples were prepared for light microscopy. Frozen sections of brain were stained with Luxol fast blue. No difference in body weight or feed consumption was observed between groups. A nonsignificant increase (of 10%) in water consumption was noted in dosed groups. All hematological and biochemical parameters were within the normal range. No significant differences were found in absolute and relative organ weights. Cystlike spaces scattered in the white matter of the cerebellum were noted in animals of the 40- and 100-mg/kg/day groups, but no clinical signs of encephalopathy were observed. A non-dose-related dissociation and vacuolization of the hepatocytes, mainly around the central vein, were noted in some rats of the 40- and 100-mg/kg/day groups. The vacuoles did not contain fat.

**TABLE 3**  
Oral dosing studies of Peppermint Oil and components using Wistar rats

Test material	Protocol	Finding (specifically cystlike spaces in the cerebellum)	NOAEL	Reference
Peppermint Oil (38% menthol, 1.7% pulegone)	10, 40, or 100 mg/kg/day for 28 days (20 rats per group, 10 each sex)	Lesions noted in 2/10 males and 2/10 females of 40-mg/kg group and in 7/10 males and 4/10 females in 100-mg/kg group	10 mg/kg/day	Thorup et al. 1983a
Peppermint Oil (content not specified)	20, 150, or 500 mg/kg for 5 weeks (12 rats per group)	No lesions noted		Mengs and Stotzen 1989
Peppermint Oil (content not specified)	10, 40, or 100 mg/kg/day for 28 days (20 rats per group, 10 each sex)	Lesions noted in 4/20 rats of 40-mg/kg group and in 11/20 rats of 100-mg/kg group	10 mg/kg/day	Olsen and Thorup 1984
Peppermint Oil (42% menthol, 1.1% pulegone)	10, 40, or 100 mg/kg/day for 90 days (28 rats per group, 14 each sex)	Lesions noted in all groups, significant in highest dose group	40 mg/kg/day	Spindler and Madsen 1992
Components	Pulegone	Lesions noted in 4/20 rats of 80-mg/kg group and in 13/17 rats of 160-mg/kg group	20 mg/kg/day	Olsen and Thorup 1984
	Pulegone	Lesions observed in 4/20 rats of 80-mg/kg group and in 13/19 rats of 160-mg/kg group	20 mg/kg/day	Thorup et al. 1983b
Menthol	200, 400, or 800 mg/kg/day for 28 days (20 rats per group, 10 each sex)	No lesions noted	<200 mg/kg/day (because of hepatocyte vacuolization observed in all groups)	Thorup et al. 1983b
Menthone	200, 400, or 800 mg/kg/day for 28 days; highest dose reduced to 400 mg/kg/day for females on day 19 (20 rats per group, 10 each sex)	Lesions noted in 1/8 females and 3/9 males of 400-mg/kg group and in 7/10 females and 10 males of the 800-mg/kg group	<200 mg/kg/day	Madsen, Würzten, and Carstensen 1986

The researchers determined the no-effect level for Peppermint Oil was 10 mg/kg body weight/day and noted that consumption of a 28-g box of mint lozenges containing 0.4% Peppermint Oil was an intake close to the observed no effect level.

In a 5-week gavage study by Mengs and Stotzen (1989), 12 male Wistar rats received daily doses of either 20, 150, or 500 mg Peppermint Oil/kg body weight. Mean body weight was between 184 and 214 g. A control group received 4 ml/kg olive oil. The animals were inspected daily and weighed weekly. Blood samples were taken prior to and at the termination of dosing. Rats were killed at the end of dosing and organs were weighed and examined microscopically.

No changes in general condition, behavior, or body weight were observed in treated rats as compared to control rats. All hematological and urine parameters were comparable among treated and control rats. Plasma triglyceride concentrations were lower in rats of the high-dose group at week 5 as compared to the control group; the change was attributed to lower feed consumption by the high-dose group. A non-dose-dependent increase in alkaline phosphatase activity was noted in rats of all treated groups. Relative mean weights of the liver and kidneys were greater in high-dose rats than in controls. These changes were not of "toxicological relevance." No specific lesions of toxicity were noted in the cerebellum, liver, or kidneys. In contrast to the studies of Thorup et al. (1983a), Mengs and Stotzen did not observe cystlike spaces in the white matter of the cerebellum.

Mengs and Stotzen (1989) also conducted a 5-week oral study using dogs. Three dogs received daily oral doses of 25 or 125 mg Peppermint Oil/kg body weight. The doses were contained in enteric-coated gelatin capsules. The animals were inspected daily and weighed weekly. Blood samples were taken prior to and at the termination of dosing.

No effects were noted on body weight or on hematological or urinary parameters. High-dose males had slightly increased plasma alkaline phosphatase activity and urea concentrations during week 5 but the values remained within normal range. No lesions were noted at microscopic examination.

In a study by Olsen and Thorup (1984), groups of 20 rats (10 of each sex) received either 10, 40, or 100 mg/kg/day Peppermint Oil or 20, 80, or 160 mg/kg/day pulegone for 28 days. Encephalopathy developed in rats of the high-dose groups. Cystlike spaces were observed scattered in the white matter of rats treated with either Peppermint Oil or pulegone. The lesions were noted especially in the cerebellum; neither cellular reaction in the surrounding tissue nor demyelination was observed. The changes were dose-related and were not observed in rats that were given the lowest doses of either Peppermint Oil or pulegone.

Thorup et al. (1983b) investigated the toxic effects of pulegone and menthol, two components of Peppermint Oil. Groups of 20 rats (10 of each sex) received either 20, 80, or 160 mg pulegone/kg body weight/day or 200, 400, or 800 mg menthol/kg body weight/day, by gavage for 28 days. The test materials were diluted in soybean oil. Blood and urine samples

were obtained. Animals were killed at the end of week 4 and necropsied. Organ samples were stained for histopathological examination.

Rats treated with pulegone developed dose-dependent atonia shortly after dosing was initiated. Both compounds significantly increased water consumption at the highest dose. Renal function was normal in pulegone-treated rats. Weight gains were significantly reduced in the high-dose (by 20%) and mid-dose (by 10%) pulegone groups. A pulegone dose-dependent decrease in blood creatinine was observed; the value was significant at the highest dose. An increased number of neutrophilic granulocytes was observed in rats of the high-dose group. At necropsy, rats of the high-dose pulegone group had markedly distended and atonic stomachs packed with feed. A significant decrease in terminal body and organ weights was observed in pulegone-dosed rats. Dose-related vacuolization of hepatocytes in the zone around the central vein was observed in 10 of 20 rats of the mid-dose group and in 15 of 19 rats of the high-dose group. Cystlike spaces were observed in the white matter of the cerebellum of pulegone-treated rats from the mid- (4 of 20 rats) and high-dose groups (13 of 19 rats).

In the menthol group, a significant increase in absolute and relative liver weights and vacuolization of hepatocytes were noted in all animals. Neutrophilic granulocytes were increased in animals of the highest dose group. No sign of encephalopathy was observed in rats given menthol. The no effect concentration for pulegone was 20 mg/kg body weight/day and for menthol it was <200 mg/kg body weight/day.

A subsequent study by Madsen, Würtzen, and Carstensen (1986) tested the toxicity of menthone, another component of Peppermint Oil. Groups of 20 rats (10 of each sex) received either 200, 400, or 800 mg/kg body weight/day of menthone by gavage for 28 days. However, after 19 days, females of the highest dose group had pale mucous membranes and signs of pain and their dose was reduced to 400 mg/kg/day. Rats were killed at the end of the study for necropsy.

Dose-dependent decreases in creatinine content and increases in alkaline phosphatase activity and bilirubin were noted in blood samples obtained on the last day of the dosing period. Relative spleen and liver weights were increased. At microscopic examination, cystlike spaces were found in the white matter of the cerebellum in rats of the two highest dose groups. No clinical signs were observed. The no-effect level for menthone was <200 mg/kg body weight/day.

### Subchronic Oral Toxicity

Spindler and Madsen (1992) treated groups of 28 Wistar rats with Peppermint Oil (diluted with soybean oil) at oral doses of 10, 40, and 100 mg/kg body weight/day for 90 days. Gas chromatography analysis determined that the Peppermint Oil sample contained 42% menthol, 25% menthone, 7% iso-menthone, 1.5% limonene, 1.4% cineole, and 1.1% pulegone; the remaining 22% could not be identified. Rats were inspected twice daily,

and body weight and feed and water consumption were recorded weekly. On days 30 and 86, blood samples were taken from 20 animals (10 of each sex) for analysis. Animals were killed on day 90 and necropsied. Organ samples were fixed in formaldehyde, sectioned, and stained for histopathologic examination.

No difference in body weight or feed consumption was observed between groups. All hematological and biochemical parameters were within the normal range. No significant differences were observed in absolute and relative organ weights. Cystlike spaces were scattered in the white matter of the cerebellum of rats from all groups and were significant in high-dose rats. The researchers stated that similar to the results of the 28-day study by Thorup et al. (1983a), the spongiform lesions were unaccompanied by cellular reaction in the adjacent tissues, were not surrounded by a membrane, and did not appear to occur intracellularly. No other lesions of encephalopathy were observed. Nephropathy as evidenced by hyaline droplets was observed in males rats of the highest dose group with no epithelial degeneration. A no-observed-adverse-effect level (NOAEL) of 40 mg/kg body weight/day was determined.

### Acute Parenteral Toxicity

The 24-hour intraperitoneal LD<sub>50</sub> for Peppermint Oil USP was 819 mg/kg in Wistar male rats (Eickholt and Box 1965).

### Immunotoxicity

Basophil cell suspensions, obtained from the blood of factory workers exposed to additive containing penicillin, were incubated with 10<sup>-1</sup> to 10<sup>-3</sup> mg/ml Peppermint (dry aroma). A dose-dependent increase in histamine release was noted. This increase was also noted in control samples obtained from nonfactory employees. The response curve did not change when cells deprived of basophil surface immunoglobins were used, indicating the reaction was not a type I allergy. It was suggested that the histamine release was caused by nonimmunological mechanisms (Moller, Skov, and Norn 1984).

Gaworski et al. (1994) used a rapid screening protocol incorporating elements of the National Toxicology Program's (NTP) immunotoxicity tier testing strategy and FDA testing guidelines to test several GRAS flavoring ingredients for their immunotoxic potential. Groups of 30 female CD-1 mice received either 313, 625, or 1250 mg Peppermint Oil/kg body weight/day in the feed for 5 days. (The high dose was selected to produce minimal toxicity based on early acute toxicity studies; the mid and low dose were one half and one quarter the high dose, respectively.) The Peppermint Oil was diluted in corn oil. Ten animals of each group were used in the plaque-forming cell assay (PFC) and the remaining 20 animals of each group were used in the host resistance assay.

Animals in the PFC assay group were injected with 2 × 10<sup>8</sup> sheep red blood cells (SRBCs) at the end of the 5-day dosing period. Three days after the SRBC injection, a positive-control group (10 mice) was injected (intraperitoneally, IP) with

cyclophosphamide, while an untreated control group (10 mice) received an equivalent amount of saline. Four days after SRBC injection, all mice were killed and single spleen cell suspensions were prepared. The suspensions were mixed with a SRBC-guinea pig complement mixture and incubated. The resulting immunoglobulin M (IgM) anti-SRBC plaques were counted. Peppermint Oil did not significantly alter the PFC response as compared to the nontreated control. The response in the positive-control group was 10% less than that in the nontreated control group, thus validating the test (Gaworski et al. 1994).

Animals of the host-resistance assay group were injected on the third day of Peppermint Oil dosing with *Listeria monocytogenes* isolated from a clinical case of meningitis. Inoculum equivalent to the LD<sub>20</sub> was injected into vehicle control animals. The average survival time for vehicle-control mice was 9.7 days. In contrast, survival times decreased in mice treated with 625 or 1250 mg Peppermint Oil/kg to 7.5 days and 2.8 days, respectively. The decreases were significant ( $p \leq .05$ ) and suggested an increased susceptibility to bacterial-induced deaths and/or immunosuppression (Gaworski et al. 1994).

### Phototoxicity

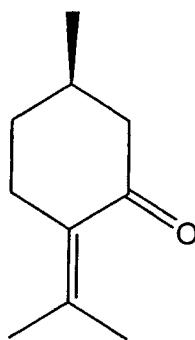
Undiluted Peppermint Oil was applied to the back of six Skh:hairless mice. Thirty minutes later, mice were irradiated for either 1 hour with light from a fluorescent blacklight at an integrated UVA of 3 W/m<sup>2</sup>, or for 40 minutes with light from a Xenon Lamp at a weighted erythema energy of 0.1667 W/m<sup>2</sup>. Mice were examined at 4, 24, 48, 72, and 96 hours following radiation treatment. No effects were noted. In a second experiment using two miniature swine and following the same protocol, no effect was produced by 100% Peppermint Oil (Research Institute for Fragrance Materials 1996).

### Dermal Irritation

Hairless sites on five white rabbits were injected intradermally with 0.05 ml Peppermint Oil. Gross examinations were made at 24 and 48 hours, at 1 and 2 weeks, and in some cases, 1 month following dosing. The dosing was repeated between 5 and 10 times. Microscopic examination of skin samples followed. Moderate reactions characterized by polymorphonuclear leukocytes, lymphocytes, and plasma cells (without necrosis) were noted in three rabbits. Severe reactions, which were marked by the above as well as necrosis, were noted in the other two rabbits (Grossman and Lally 1982).

### Pulegone Hepatotoxicity

As noted earlier, pulegone is found in young peppermint leaves (Sullivan et al. 1979). (R)-(+)-Pulegone (CAS No. 15932-80-6; 89-82-7) is described in the literature as a hepatotoxin that is the main constituent of the abortifacient pennyroyal oil (Sullivan et al. 1979; Gordon et al. 1987; Thomassen, Slattery, and Nelson 1990). It is a monoterpenone that conforms to the structure shown in Figure 2 (McClanahan et al. 1989).



**FIGURE 2**  
Pulegone.

Pulegone is oxidized by cytochrome P450 to reactive metabolites such as menthofuran that are partly responsible for the toxicity observed in mice, rats, and humans (Mizutani et al. 1987; Madyastha and Moorthy 1989; McClanahan et al. 1989; Nelson et al. 1992). Thomassen, Slattery, and Nelson (1990) reported a depletion of both serum and hepatic concentrations of reduced glutathione following intraperitoneal administration of 150 mg/kg pulegone to rats. Oral administration of pulegone (400 mg/kg/day for 5 days) produced significant decreases in activities of hepatic cytochrome P450 and values of heme but did not affect activities of cytochrome b5 or NADPH-cytochrome c reductase (Moorthy, Madyastha, and Madyastha 1989).

### Menthol

Two Tiger Balm formulations containing 8% and 10% menthol were applied for 23 hours under occlusive patches to abraded and intact sites on New Zealand white rabbits. A total of 21 patches were applied. A third group was treated with a control wax (a mixture of hard and soft waxes). Untreated sites on each rabbit served as negative controls. Irritation was scored using the Draize scale. Dermal irritation was noted in all treated animals with the following severity scale: 8% menthol balm < control wax < 10% menthol balm. The 8% menthol balm was almost innocuous in male rabbits. The irritation was not progressive and tolerance developed within 10 days. No severe damage was noted at microscopic examination of the skin (increased hyperkeratosis was noted at treated sites) and no evidence of systemic toxicity was noted. The investigators noted that the balm contained "irritants" such as clove oil, camphor, and menthol and remarked that the irritation was not unexpected (Guppy, Lowes, and Walker 1982).

## REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

### Menthol

Groups of 15 to 23 pregnant animals were dosed by oral intubation with natural Brazilian menthol. Mice were dosed with up to 185 mg/kg body weight on gestation days (GDs) 6 to 15; pregnant rats were given doses up to 218 mg/kg on GDs 6 to

15; pregnant hamsters were dosed up to 405 mg/kg on GDs 6 to 10; and artificially inseminated rabbits were given doses up to 425 mg/kg on GDs 6 to 18. Maternal body weight was recorded regularly. Caesarean sections were performed on all dams. No teratogenic effect was noted (Food and Drug Research Labs, Inc. 1973).

## GENOTOXICITY

### Bacterial Assays

Andersen and Jensen (1984) investigated the mutagenic potential of Peppermint Oil and some of its components in the *Salmonella*/mammalian microsome test. *Salmonella* strains used were 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. Peppermint Oil, menthol, and pulegone, all 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. Addition of S9 appeared to make the compounds less toxic to the bacteria. In contrast, menthone induced a statistically significant number of revertants in TA1537 without S9 activation at doses of 6.4 and 32 µg/plate. Menthone was further tested using the more sensitive TA97 strain. Statistically significant increases in the number of revertants were noted at all doses tested without S9 activation; the results were dose related (though toxicity was observed at 800 µg/plate). The researchers remarked on the unexpected results—menthone was mutagenic, but Peppermint Oil, which contained 33.7% menthone, was not.

### Mammalian Cell Assays

In an in vitro chromosomal aberration test using a Chinese hamster fibroblast cell line, Peppermint Oil, at a maximum concentration of 0.25 mg/ml (in an ethanol solvent), produced polyploidism in 3.0% and structural aberrations in 7.0% of the cells at 48 hours after treatment. The results were considered equivocal as scores of either ≥ 10.0% or ≤ 4.9% were necessary for classification as either positive or negative, respectively (Ishidate et al. 1984).

Peppermint Oil (150 µg/ml) was negative in a mouse lymphoma L5178Y TK +/− cell mutagenesis assay. It was also negative (at 155 µg) in an unscheduled DNA synthesis assay using rat hepatocytes (Heck et al. 1989).

### Menthol

The mutagenic potential of natural Brazilian menthol was tested in the cytogenetic assay (rats), the host-mediated assay (mice), and the dominant lethal assay (rats). The assays were done with menthol doses of 1.45, 14.5, and 145.0 mg/kg and, in some instances, subacute and acute studies were done with doses of 500, 1150, and 3000, or 5000 mg/kg. In the host-mediated assay, a weakly positive but significant response was noted with

the acute high dose against *Salmonella typhimurium* TA 1530, and elevated recombinant frequencies were noted with the subacute doses against *Saccharomyces* D3. All other assays were negative (Litton Bionetics, Inc. 1975).

### CARCINOGENICITY

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 Peppermint Oil/kg/day, 6 days a week for 80 weeks. A 16- to 24-week observation period followed treatment. An untreated group of 52 male mice and a vehicle group of 260 male mice that received the toothpaste base (which did not contain chloroform, eucalyptol, or Peppermint Oil) were maintained as controls.

Body weight gain was reduced initially in animals of the 16-mg/kg/day group. 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. Malignant neoplasms were noted in 39%, 35%, 23%, and 31% of mice of the low-dose, high-dose, untreated-control, and vehicle-control groups, respectively. The incidence of neoplasms of the lungs and kidneys were comparable among mice of the treated and nontreated groups. Hepatic cell tumor incidence for 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 if the difference in the incidence rate was significant (Roe et al. 1979).

A review of the study by the British Industrial Biological Research Association (1992) noted that it was not designed to examine the carcinogenic potential of Peppermint Oil and thus "would have had only a very limited sensitivity to this particular component."

### Menthol

A 2-year oral dosing study by the National Cancer Institute (NCI 1979) found no evidence of carcinogenicity following dosing of Fischer 344 rats with 3750 or 7500 ppm or dosing of B6C3F<sub>1</sub> mice with 2000 or 4000 ppm *d,l*-menthol. A dose-related trend in increased number of deaths was noted in female mice. A negative trend in fibroadenomas of the mammary gland was observed in female rats (20 of 50 control; 10 of 49 low-dose; 7 of 49 high-dose).

Russin et al. (1989) reported a significant inhibition ( $p < .001$ ) of 7,12-dimethylbenz[a]anthracene (DMBA)-induced rat mammary gland carcinogenesis following 20 weeks of oral dosing with 1% (−)-menthol. Dosing with menthol began 2 weeks prior to DMBA tumor induction. A chemopreventive effect was noted when rats were dosed with 0.5% menthol for 2 weeks prior to and 1 week after DMBA induction.

### CLINICAL ASSESSMENT OF SAFETY

#### Dermal Irritation and Sensitization

The International Contact Dermatitis Research Group recommends patch testing with 2% Peppermint Oil in petrolatum. Peppermint Oil is recognized to produce immediate contact reactions (urticaria) (DeGroot 1994).

Clinical studies are cited in the Eccles review (1994) that described the coolant action of 0.2% and 2% menthol following dermal application. However, 5% and 10% menthol produced a strong burning sensation. Menthol also possessed irritant properties. It was suggested that in addition to stimulating cold receptors, menthol also stimulated nociceptors that subsequently released vasodilator peptides. The increased penetration of topically applied drugs in menthol (studies in hairless mice with 1% to 5% menthol) could have resulted from a combination of the vasodilation and the lipophilic nature of menthol.

Following the Kligman maximization protocol, 25 healthy male panelists received five occlusive induction patches containing 8% Peppermint Oil (in petrolatum) for 48 hours. Pre-treatment was for 24 hours with an occlusive patch containing 5% sodium lauryl sulfate (SLS) prior to each exposure. After a 10-day nontreatment period, subjects were challenged on the back with a 48-hour patch (also preceded by SLS treatment). No evidence of sensitization was found (Research Institute for Fragrance Materials 1996).

Positive reactions were noted in 7 of 450 dermatitic patients who were patch tested with 2% Peppermint Oil in yellow soft paraffin (Rudzki and Grzywa 1977). In another study, positive reactions to 2% Peppermint Oil were noted in 6 of 86 dermatitic patients. The 86 patients were selected because they had previously responded to the ICDRG perfume mixture (Rudzki and Grzywa 1986).

An A1 patch containing 1% Peppermint Oil (unknown vehicle) was applied to the back of 56 patients with chronic urticaria. No reactions were noted after a 1- or 48-hour exposure (Warin and Smith 1982).

Positive reactions were noted in 3 of 1200 dermatitis patients patch tested with 2% Peppermint Oil in petrolatum (Santucci et al. 1987).

No reactions were noted in 25 spice factory workers who were patch tested with 2% Peppermint Oil in petrolatum. The workers were selected because they had reported signs and symptoms of dry skin, pruritus, and eczema (Meding 1993).

Saito and Oka (1990) reported that patch testing of individual components of Peppermint Oil using three patients with allergic contact dermatitis established that the allergens were menthol and trace components such as piperitone or pulegone.

Rudzki and Kleniewska (1970) tested 5% menthol in yellow paraffin in 877 people with primary contact, atopic, nummular, and stasis dermatitis and eczema. Reactions were noted in 1% of the panelists within 96 hours.

Others have reported isolated cases of irritation and/or sensitization to Peppermint Oil and/or its components (Smith 1968;

Dooms-Goossens et al. 1977; Andersen 1978; DeGroot 1987; Basto and Azenha 1991; Abifadel et al. 1992; Wilkinson and Beck 1994; Lewis, Shah, and Gawkrodger 1995; Morton et al. 1995).

## SUMMARY

Peppermint Oil, Peppermint Extract, and Peppermint Leaves are obtained from the *Mentha piperita* plant. In 1998, Peppermint Oil was used in 102 cosmetic formulations as a fragrance component. Peppermint Extract was used in 35 formulations as a flavoring agent and fragrance component. Peppermint was used in two formulations.

Peppermint Oil is composed primarily of menthol and menthone. Numerous other possible constituents include pulegone, menthofuran, and limone; some components have yet to be identified.

The 24-hour oral LD<sub>50</sub> for Peppermint Oil in fasted mice and rats was 2410 and 4441 mg/kg, respectively. Several (but not all) short-term and subchronic oral studies noted cystlike lesions in the cerebellum in rats that were given doses of Peppermint Oil containing pulegone, pulegone alone, or large amounts (>200 mg/kg/day) of menthone.

Results of a host-resistance assay suggested immunosuppression and/or increased susceptibility to bacterial-induced mortality. Studies on human basophil suspensions suggested that Peppermint Oil induced histamine release by nonimmunological mechanisms. It was negative in a plaque-forming assay.

Repeated intradermal dosing with Peppermint Oil produced moderate and severe reactions in rabbits. Peppermint Oil did not appear to be phototoxic.

Peppermint Oil was negative in the Ames test and a mouse lymphoma mutagenesis assay but gave equivocal results in a Chinese hamster fibroblast cell chromosome aberration assay. In a carcinogenicity study of toothpaste, mice treated with Peppermint Oil developed neoplasms at the same rate as those treated with the toothpaste base. In some instances, the rates were comparable to those in mice of the untreated control group.

Isolated clinical cases of irritation and/or sensitization to Peppermint Oil and/or its constituents have been reported, but Peppermint Oil (8%) was not a sensitizer when tested using the Kligman maximization protocol.

## DISCUSSION

In assessing the safety of Peppermint (*Mentha Piperita*) Oil, Peppermint (*Mentha Piperita*) Extract, Peppermint (*Mentha Piperita*) Leaves, and Peppermint (*Mentha Piperita*) Water, the CIR Expert Panel was concerned about oral-dosing studies that reported cystlike spaces in the cerebellum of rats. The results of these studies were difficult to interpret. The findings were not consistent among studies (lesions were noted in some studies but not others), and though the lesions appeared to depend on the pulegone content, no definitive conclusion could be made (a greater NOAEL was reported in a 90-day study using a

Peppermint Oil containing 1.1% pulegone versus a 28-day study that tested a Peppermint Oil containing 1.7% pulegone). The Panel also noted that the large differences between doses within each study made it impossible to pinpoint exactly the dose at which changes first appeared.

Noting the lack of dermal exposure studies on Peppermint Oil, the Panel expected its absorption would be rapid, following that of menthol, a major component. Dermal absorption, however, was not expected to be greater than absorption through the gastrointestinal tract. Metabolism from either route of exposure would be similar—phase 1 metabolism followed by transport to the liver. The Panel was of the opinion that the oral-dose data contained in this report were sufficient to address concerns resulting from the expected rapid absorption. However, the Panel noted the evidence that menthol 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.

Clinical dermal testing demonstrated that 8% Peppermint Oil was not a sensitizer, and that 2% Peppermint Oil produced a small number of positive reactions in dermatitic patients.

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

## 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%.

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<sup>2</sup>Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036-4702, USA.

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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
<b>Total</b>	<b>827</b>

**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
<b>Total</b>	<b>198</b>

**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
<b>Total</b>	<b>15</b>

**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
<b>Total</b>	<b>71</b>



## **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:** July 6, 2017

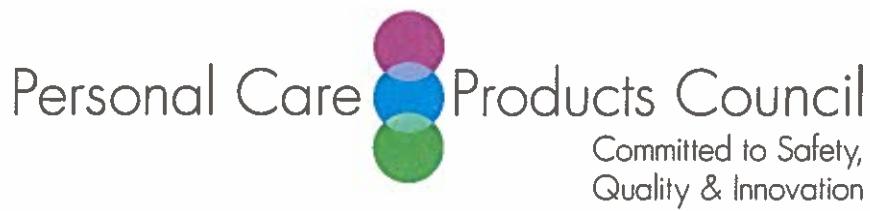
**SUBJECT:** Concentration of Use by FDA Product Category: Additional Peppermint-Derived Ingredients

**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

<b>Ingredient</b>	<b>Product Category</b>	<b>Maximum Concentration of Use</b>
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	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%
Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract	Lipstick (7E)	0.3%

\*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.



**Memorandum**

**TO:** COSMETIC INGREDIENT REVIEW (CIR)

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

**DATE:** June 22, 2017

**SUBJECT:** Mentha Piperita (Peppermint) Leaf Extract and Mentha Piperita (Peppermint)  
Leaf Water

Anonymous. 2017. Summary information Mentha Piperita (Peppermint) Leaf Extract and  
Mentha Piperita (Peppermint) Leaf Water

June 22, 2017

**Summary Information Mentha Piperita (Peppermint) Leaf Extract and Mentha Piperita (Peppermint) Leaf Water**

**1. Method of manufacture**

Ingredient	Method of manufacture
Peppermint Leaf Extract (butylene glycol/water)	Dried raw material→extract with 50vol% 1,3-butylene glycolic solution→filtrate→sedimentation→filtrate→adjustment→packaging
Peppermint Leaf Extract (water/ethanol)	Dried raw material→extract with 30vol% ethanolic solution→filtrate→concentration→adjustment→sedimentation→filtrate→adjustment→packaging
Peppermint Leaf Extract Powder	Dried raw material→extract with 30vol% ethanolic solution→filtrate→concentration→add exsiccated sodium sulfate as vehicle→drying→packaging
Peppermint Leaf Water	Dried raw material→steam distillation→obtainment water soluble fraction→adjustment→filtrate→packaging

**2. Composition**

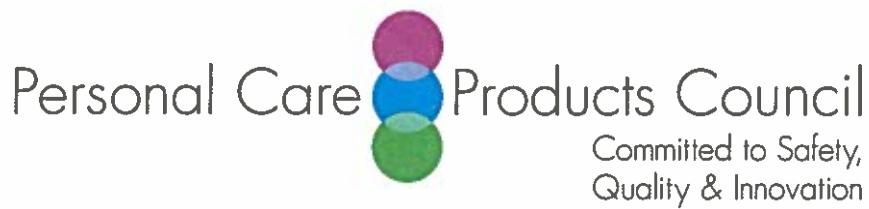
Ingredient	Composition (identification)
Peppermint Leaf Extract (butylene glycol/water)	Tannin and terpenoid (contains 2.8 ppm pulegone)
Peppermint Leaf Extract (water/ethanol)	Essential oil, tannin and terpenoid
Peppermint Leaf Extract Powder	Tannin and terpenoid
Peppermint Leaf Water	Essential oil (menthol)

**3. Impurities**

Ingredient	Impurities
Peppermint Leaf Extract (butylene glycol/water)	Heavy metals: not more than 10ppm Arsenic: not more than 2ppm
Peppermint Leaf Extract (water/ethanol)	Heavy metals: not more than 10ppm Arsenic: not more than 1ppm
Peppermint Leaf Extract Powder	Heavy metals: not more than 10ppm Arsenic: not more than 2ppm
Peppermint Leaf Water	Heavy metals: not more than 10ppm Arsenic: not more than 1ppm

**4. Irritation and sensitization**

Ingredient	Safety data	
	Test	Result
Peppermint Leaf Extract (butylene glycol/water)	No data	No data
Peppermint Leaf Extract (water/ethanol)	In vitro skin irritation:Reconstructed Human Epidermis Test Method (EPSKIN) (100%, 10%)	Negative (MTT> 50%)
	HRIPT (100%)	Negative (52 people)
Peppermint Leaf Extract Powder	No data	No data
Peppermint Leaf Water	No data	No data



## 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, 2<sup>nd</sup> 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."