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

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All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

The 2017 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Ivan Boyer, Ph.D., former Senior Toxicologist.
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 these ingredients and concluded that *Mentha Piperita* (Peppermint) Oil is safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-sensitizing, and that the available data are insufficient to make a determination that the remaining ingredients are safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

The safety of four of the cosmetic ingredients named in this safety assessment has been previously reviewed by the Panel; in 2001, the Panel issued a final report with a conclusion stating that *Mentha Piperita* (Peppermint) Oil, *Mentha Piperita* (Peppermint) Leaf Extract, *Mentha Piperita* (Peppermint) Leaf, and *Mentha Piperita* (Peppermint) Leaf Water are safe as used in cosmetic formulations. The conclusion also stated 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.

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

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

Safety test data that have been found in the published literature or those provided by the Personal Care Products Council (Council) as unpublished data since the final report was issued, are included. Some safety test data on menthol, menthone, and pulegone are also included in the 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) oral carcinogenicity study with positive results on pulegone was published in 2011 and that a 1998 publication on the absence of test substance-related histological cerebellar changes in Wistar rats dosed orally with pulegone is available. These studies are summarized in the report text.

The cosmetic ingredient names, according to the *Dictionary*, are written as listed above, capitalized, without italics, and unabbreviated. When referring to the plant from which these ingredients are derived, the standard scientific practice of using italics 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/preliminary-search-engines-and-websites); [http://www.cir-safety.org/supplementaldoc/cir-report-format-outline](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.

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

CHEMISTRY

Definition and General Characterization

The definitions of *Mentha piperita* (peppermint)-derived ingredients are stated in Table 1.
Chemical and Physical Properties

Properties/specifications relating to Mentha Piperita (Peppermint) Oil are presented in Table 2.\textsuperscript{1}

Method of Manufacture

Mentha Piperita (Peppermint) Oil

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

According to one source, Mentha Piperita (Peppermint) Oil has been extracted (distilled water solvent) from the leaves of *Mentha piperita* harvested (first in July and second harvest in September) in Washington state.\textsuperscript{4}

Mentha Piperita (Peppermint) Leaf Extract

The following method relates to preparation of the butylene glycol/water extract of Mentha piperita (Peppermint) Leaf Extract.\textsuperscript{5} Dried raw material is extracted with 50 vol\% 1,3-butylene glycolic solution. After extraction, the additional steps in the production process include: filtrate $\rightarrow$ sedimentation $\rightarrow$ filtrate $\rightarrow$ adjustment $\rightarrow$ packaging.

In another method, the preparation of a water/ethanol extract is described.\textsuperscript{5} Dried raw material is extracted with 30 vol\% ethanolic solution. After extraction, the additional steps in the production process include: filtrate $\rightarrow$ concentration $\rightarrow$ adjustment $\rightarrow$ sedimentation $\rightarrow$ filtrate $\rightarrow$ adjustment $\rightarrow$ packaging.

The production method described herein relates to preparation of *Mentha piperita* (peppermint) leaf extract powder (another name for Mentha piperita (Peppermint) Leaf Extract).\textsuperscript{5} 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 $\rightarrow$ concentration $\rightarrow$ add exsiccated sodium sulfate as vehicle $\rightarrow$ drying $\rightarrow$ packaging.

Mentha Piperita (Peppermint) Leaf Water

In the preparation of Mentha Piperita (Peppermint) Leaf Water, dried raw material is subjected to steam distillation.\textsuperscript{5} After distillation, the remaining steps in the production process are: water soluble fraction obtained $\rightarrow$ adjustment $\rightarrow$ filtrate $\rightarrow$ 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.*\textsuperscript{1} However, a supplier of Mentha Piperita (Peppermint) Oil reported pulegone concentrations of 1% to 4%, depending on the origin of the oil. *Published studies that have investigated the pulegone content of Mentha Piperita (Peppermint) Oil also reported a range of <1% to 4% for Mentha Piperita (Peppermint) Oils of a North American origin.*

Mentha Piperita (Peppermint) Oil

The major constituents of Mentha Piperita (Peppermint) Oil include: the terpenes (-)-menthol (30-55\%), (-)-menthone (14-32\%), (+)-isomenthone (1.5-10\%), (-)-menthyl acetate (2.8-10\%), (+)-menthofuran (1.0–9.0\%), and 1,8-cineol (3.5-14\%).\textsuperscript{6}

Certain trends were observed between oil extracted from first and second harvest leaves, and oil extracted from fresh leaves versus dried leaves.\textsuperscript{4} 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, and pulegone and lower in \( \beta \)-caryophyllene, germacrene d, and menthol. Menthol 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, pipertone, 1,8-cineole, and pulegone have been identified as major components.\(^7\)

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.\(^8\)

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.\(^9\) Pulegone and menthofuran were among the chemicals detected. A public statement from the European Medicines Agency on the use of herbal medicinal products containing menthofuran indicated that Mentha Piperita (Peppermint) Oil contains a maximum of 4% pulegone and between 1% and 9% menthofuran.\(^10\) 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).\(^11\) The following solvents were used to extract the peppermint leaves: light petroleum, dichloromethane, acetonitrile, ethyl acetate, methanol, n-butanol, and water. Eriocitrin (383.3 ± 2.2 mg/g extract) and rosmarinic acid (381.2 ± 1.9 mg/g extract) were the most abundant components identified within the leaves, while naringenin-7-O-glucoside (0.8 ± 0.01 mg/g extract) was the least abundant component identified. Kynurenic acid (3.82 ± 0.46 µg/g) has also been detected in Mentha Piperita (Peppermint) Leaf Extract.\(^12\) 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.\(^5\) Additionally, *Mentha piperita* (peppermint) leaf extract powder (another name for *Mentha piperita* (peppermint) Leaf Extract) contains tannin and terpenoid.\(^5\)

**Mentha Piperita (Peppermint) Leaf**

The major monoterpene constituents of Mentha Piperita (Peppermint) Leaf are: (-)-limonene; 1,8-cineole; (+)-pulegone; (-)-menthone; (+)-isomenthone; (+)-menthofuran; (-)-menthol; and (+)-neomenthol.\(^13\)

**Mentha Piperita (Peppermint) Leaf Water**

Composition data provided by the Council indicate that Mentha Piperita (Peppermint) Leaf Water contains essential oil (menthol).\(^3\)

**Impurities**

**Mentha Piperita (Peppermint) Leaf Extract**

Data on impurities provided by the Council indicate that Mentha Piperita (Peppermint) Leaf Extract (butylene glycol/water extract) contains not more than 10 ppm heavy metals and not more than 2 ppm arsenic.\(^5\) Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract) contains not more than 10 ppm heavy metals and not more than 1 ppm arsenic.

According to data provided by the Council, *Mentha piperita* (peppermint) leaf extract powder contains not more than 10 ppm heavy metals and not more than 2 ppm arsenic.\(^5\)

**Mentha Piperita (Peppermint) Leaf**
The following elemental contaminants have been detected in *Mentha piperita* herbal tea (tea leaves) samples (n = 3) from Serbia: manganese (111.97 mg/kg dry weight), iron (443.90 mg/kg), copper (17.15 mg/kg), and zinc (26.86 mg/kg), molybdenum (2.695 mg/kg), cobalt (0.161 mg/kg), nickel (1.882 mg/kg), selenium (0.107 mg/kg), aluminum (554 mg/kg), and tin (3.66 mg/kg).14

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.15

**Mentha Piperita (Peppermint) Leaf Water**

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

**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.16 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.17,18

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).16 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.17,18 Current and historical use frequency and concentration of use data are presented in Table 4. These data indicate that the highest maximum use concentration of Mentha Piperita (Peppermint) Oil in cosmetics increased from 3% in 1997 to 5% in 2017. Because 1997 use concentration data on the remaining 3 ingredients that were reviewed in the original safety assessment, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint), were not provided, a comparison of 1997 versus 2017 use concentration data cannot be made.

According to VCRP and Council survey data, the following *Mentha piperita* (peppermint)-derived ingredients are not being used in cosmetic products: Mentha Piperita (Peppermint) Flower/Leaf/Stem Water, Mentha Piperita (Peppermint) 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.19,20,21,22 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.19,20
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.23,24,25

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

*Mentha Piperita* (Peppermint) Oil, *Mentha Piperita* (Peppermint) Extract, *Mentha Piperita* (Peppermint) Flower/Leaf/Stem Extract, and *Mentha Piperita* (Peppermint) Leaf Juice are generally recognized as safe (GRAS) for use in food for human consumption (21CFR182.20). *Mentha Piperita* (Peppermint) Oil is an inactive ingredient in drug products that have been approved by the U.S. FDA.27 A number of active ingredients, *Mentha Piperita* (Peppermint) Oil included, have been present in over-the-counter (OTC) drug products for various uses.28 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.29

**Mentha Piperita**

According to the European Medicines Agency Committee on Herbal Medicinal Products (HMPC) community herbal monograph on *Mentha x piperita* L., aetheroleum (aetheroleum is a term used to describe a preparation made from the above-ground parts of a plant), this herbal medicine is administered orally for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence, and abdominal pain, especially in patients with irritable bowel syndrome.30 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 cm² shaved area on the abdomen of mice. The absorption rate for Mentha Piperita (Peppermint) Oil was measured as the latent period between application and appearance of eserine-induced signs._1 Mentha Piperita (Peppermint) Oil had a latent period of 58 minutes.

**Penetration Enhancement**

**Mentha Piperita (Peppermint) Leaf Extract**

The skin penetration enhancement potential of *Mentha Piperita* (Peppermint) Leaf Extract (aqueous ethanol extract) was evaluated using dorsal porcine skin (dermatomed to thickness of 500 µm).31 A square section of skin was cut to provide a dose area of 1 cm² and placed in a flow-through diffusion cell. ¹³C-Caffeine (hydrophilic) or ¹⁴C-salicylic acid (hydrophobic)
was applied topically with 10% Mentha Piperita (Peppermint) Leaf Extract to porcine skin. Ethanol alone served as the control. When compared to \( ^{14} \text{C-caffeine} \) in the presence of ethanol (control), the dermal absorption of \( ^{14} \text{C-caffeine} \) was significantly greater (p > 0.05; flux and permeability of caffeine increased by over 3-fold) in the presence of Mentha Piperita (Peppermint) Leaf Extract. However, this was not true for \( ^{14} \text{C-salicylic acid} \).

**Penetration Inhibition**

**Mentha Piperita (Peppermint) Oil**

Mentha Piperita (Peppermint) Oil and [ring-UL-\( ^{14} \text{C} \)]benzoic acid were applied to full-thickness human skin (breast or abdominal) samples in a static diffusion cell.\(^{32} \) As the concentration of Mentha Piperita (Peppermint) Oil increased from zero to 5% in the donor phase, the maximal flux of benzoic acid decreased. The differences were significant at 1.0% and 5.0% Mentha Piperita (Peppermint) Oil, where the maximal fluxes were reduced to 81% and 52% of the control, respectively.

**Absorption, Distribution, Metabolism, and Excretion**

**Human**

**Oral**

**Mentha Piperita (Peppermint) Oil**

The rate of Mentha Piperita (Peppermint) Oil absorption and excretion following oral administration was determined by measuring urinary menthol glucuronide.\(^{1} \) Four male volunteers ingested 180 mg of an enteric-coated Mentha Piperita (Peppermint) Oil-coated capsule following a 16-h fast. Menthol was liberated from its glucuronide metabolite by treating the urine with \( \beta \)-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.\(^{9} \) 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 l-menthol in rats indicated approximately equal excretion in the feces and urine. The main metabolite identified was menthol-glucuronide. Additional metabolites are mono- or di-hydroxylated menthol derivatives.

**TOXICOLOGICAL STUDIES**

**Acute Toxicity Studies**

**Oral**

**Mentha Piperita (Peppermint) Oil**

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

**Short-Term Toxicity Studies**

**Oral**

**Mentha Piperita (Peppermint) Oil 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.\(^{1} \) In the remaining study (12 rats per group), these lesions were not observed in rats dosed with Mentha Piperita (Peppermint) Oil at doses of 20, 150, or 500 mg/kg/day for 5 weeks. 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
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.

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

A study was performed to clarify whether the occurrence of cerebellar changes previously observed in pulegone-dosed rats could be influenced by the tissue fixation techniques, using either immersion or perfusion tissue fixation. The authors noted that, in previous studies in which cerebellar changes were observed, the brain was fixed by immersion using 4% neutral buffered formaldehyde and that immersion fixation of nervous tissue might cause artifacts seen as vacuolar reaction spaces around neurons. With this in mind, a perfusion technique was also included in the present study. Groups of 28 female rats (CrL: (WI)BR, SPF strain) were dosed orally (gavage) with pulegone (in soybean oil) at a dose of 0 or 160 mg/kg/day for 28 days. Initially, 12 animals per group were necropsied. The liver and brain were isolated and fixed by immersion in 4% neutral buffered formaldehyde. The remaining animals (14 controls and 15 dosed animals) were also killed and necropsied for the purpose of fixation of the brain using the perfusion technique. After opening the thoracic cavity, each animal was perfused with 4% neutral buffered formaldehyde via a needle lead into the aorta and drainage through the right auricle of the heart. At the end of the perfusion procedure, the brain and liver were preserved in 4% neutral buffered formaldehyde. Any changes of the white matter of the cerebellum observed as cyst-like spaces between unbroken myelin sheaths with no surrounding membrane or reaction in the adjacent tissue were histologically scored blindly 3 times. Two animals from the control group and 1 animal from the dosed group died due to accidental intratracheal application.

The appearance of animals dosed with pulegone was described as depressed, and scattered alopecia was reported. When compared to control rats, a statistically significant decrease in body weight and food consumption (p < 0.001) was observed throughout the study and identified as an adverse effect of pulegone dosing. A statistically significant decrease in the level of plasma glucose was reported, and the authors noted that this finding probably reflects pulegone-induced inactivation of glucose-6-phosphatase, leading to hypoglycemia. Additionally, the reduction in plasma creatinine was described as marked and statistically significant in dosed rats, and a statistically significant increase in plasma alkaline phosphatase and a non-statistically significant increase in alanine aminotransferase (p < 0.1) were also reported for this group. The authors noted that the increased plasma concentrations of alkaline phosphatase and alanine aminotransferase taken together with the increased absolute liver weight was not statistically significant (p < 0.1), but the increased relative liver weight (p < 0.05) is indicative of an adverse effect on the liver. However, it was noted that no significant histopathology of the liver was observed in rats dosed orally with pulegone, and histological examination using light microscopy revealed none or very few of the cyst-like spaces in white matter of the cerebellum. Also, data from blinded scorings, followed by statistical analysis, revealed no difference in the presence of cyst-like spaces in white matter of the cerebellum between animals dosed with pulegone and controls, using either immersion or perfusion tissue fixation. The authors also noted that the results of this study indicate that the presence of cyst-like spaces is not influenced by the fixation technique. Furthermore, they noted that the present study has failed to show that pulegone is neurotoxic in rats using histological techniques, and that the number and severity of cyst-like spaces in this study were considered comparable to observations that are normally present in historical control Wistar rats at the laboratory where the study was performed. The authors noted that a possible explanation for the observed dose-dependent cyst like spaces seen in previous studies could have been due to an interaction between impurities in the test substance and the fixation agent used therein.

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

Chronic Toxicity Studies

Human

Dermal
Exposure Assessment

**Mentha Piperita (Peppermint) Oil**

The FDA calculated an estimated human exposure from cosmetic use based on the concentration of use information supplied by industry.¹ Using a body splash product containing 0.2% Mentha Piperita (Peppermint Oil) and assuming 100% absorption over a body surface of 17,000 cm² and a daily application of 1 mg/cm² (~17 ml of the product), the FDA estimated an exposure of 34 mg/day. For a 60-kg person, this amounted to an estimated daily dose of 0.6 mg/kg/day.

Risk Assessment

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

The authors of a book entitled *Essential Oil Safety* have recommended a maximum dermal use level of 5.4% Mentha Piperita (Peppermint) Oil.³⁴ This dermal restriction is based on 8% menthofuran (pulegone metabolite) and 3% pulegone content, with limits of 0.5% for menthofuran and of 1.2% for pulegone. The authors also recommended that Mentha Piperita (Peppermint) Oil should be avoided altogether in cases of cardiac fibrillation, and in individuals with a glucose-6-phosphate dehydrogenase deficiency.

**Oral Exposure Assessment**

**Mentha Piperita (Peppermint) Oil**

In the European Union, the highest recommended daily dose of Mentha Piperita (Peppermint) Oil is 1.2 ml, i.e., 1080 mg Mentha Piperita (Peppermint) Oil (contains a maximum of 140 mg pulegone + menthofuran).¹⁰ For a 60 kg person, this would correspond to a daily intake of 2.3 mg/kg body weight. This recommended daily dose of Mentha Piperita (Peppermint) Oil in medicinal products results in pulegone/menthofuran that exceeds the tolerated daily intake (TDI) (0.1 mg/kg) that was established for food by the Committee of Experts on Flavoring Substances (CEFS).

**Risk Assessment**

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

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

**Animal**

**Oral**

**Menthol (a component of Mentha Piperita (Peppermint) Oil)**

Developmental toxicity data on menthol, a component of Mentha Piperita (Peppermint) Oil, 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.\textsuperscript{1} 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.\textsuperscript{1} The following Salmonella typhimurium strains were used: TA1535, TA100, TA1537, and TA98. The sample tested contained 38.1% menthol, 33.7% menthone, and 1.7% pulegone; the remaining components were not identified. Mentha Piperita (Peppermint) Oil, 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. Menthol 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.\textsuperscript{1}

The genotoxicity of Mentha Piperita (Peppermint) Oil was evaluated in a chromosome aberration test using human peripheral blood lymphocytes.\textsuperscript{36} 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.\textsuperscript{36} 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 (a component of Mentha Piperita (Peppermint) Oil)**

Genotoxicity data on menthol, a component of Mentha Piperita (Peppermint) Oil, 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).\textsuperscript{1} 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). 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. 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.

Menthol (a component of Mentha Piperita (Peppermint) Oil)

Carcinogenicity data on menthol, a component of Mentha Piperita (Peppermint) Oil, 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 B6C3F1 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).

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

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.\textsuperscript{5,39} 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.\textsuperscript{30} 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.\textsuperscript{38} 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).\textsuperscript{40} 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.\textsuperscript{41} 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.\textsuperscript{42} Statistically
significant (α = 0.05) growth inhibition was observed at a concentration of 31µg/ml. An IC₅₀ (concentration required for 50% inhibition, µg/ml) of 92.3µg/ml was reported for Mentha Piperita (Peppermint) Leaf Extract.

Menthol (a component of Mentha Piperita (Peppermint) Oil)

Anticarcinogenicity data on menthol, a component of Mentha Piperita (Peppermint) Oil, 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.¹ 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.⁴³ Mentha Piperita (Peppermint) Oil from plants that were harvested during the summer and winter was tested. The following IC₅₀ values were reported: MCF-7 cell line (75.2 ± 2.9 [summer]; 80.8 ± 3.2 [winter]) and LNCaP cell line (90.4 ± 3.7 [summer]; 95.7 ± 4.5 [winter]). IC₅₀ values in the 10 to 100 µg/ml range represented a potentially toxic chemical, and IC₅₀ values < 10µg/ml represented a potentially very toxic chemical.

In another study, essential oil was extracted from the leaves of Mentha piperita.⁴⁴ This extract was found to be cytotoxic in the following 4 human cancer cell lines: human lung carcinoma SPC-A1 cells (IC₅₀ = 10.89 µg/ml), human leukemia K562 cells (IC₅₀ = 16.16 µg/ml) and human gastric cancer SGC-7901 cells (IC₅₀ = 38.76 µg/ml). The extract was inactive against human hepatocellular carcinoma BEL-7402 cells.

Mentha Piperita

The inhibitory effect of Mentha piperita on A549 non-small cell lung adenocarcinoma cells was investigated using the MTT assay.⁴⁵ The results indicated that Mentha piperita had a moderate toxic effect on the A549 cell line (IC₅₀ = 879.52 ± 22.55 µg/ml). The growth of A549 cells was inhibited by Mentha piperita in a dose-dependent manner. The inhibitory rate was 54.54% ± 1.38% at the highest concentration tested (1 mg/ml).

Hepatotoxicity

Mentha Piperita (Peppermint)Leaf Extract

Mentha Piperita (Peppermint) Leaf Extract (methanol extract) and other botanical extracts were tested on both human (HepG2/C3A) and rat (MH1C1) hepatoma cells, using a battery of toxicity endpoints.⁴⁶ 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.47

**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.48

**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 10⁻⁴ to 10⁻⁵ mg/ml Peppermint (dry aroma). A dose-dependent increase in histamine release was noted, and it was concluded that this release was due to nonimmunological mechanisms.1

**Immune System Effects**

**Mentha Piperita (Peppermint) Oil**

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

**Effect on Hair Growth**

In a study involving C57BL/6 mice, the data suggest that 3% Mentha Piperita (Peppermint) Oil (diluted in jojoba oil) facilitates hair growth by promoting the conservation of vascularization of hair dermal papilla, which may contribute to the induction of early anagen stage.49

**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.5
Menthol (a component of Mentha Piperita (Peppermint) Oil)

Skin irritation data on menthol, a component of Mentha Piperita (Peppermint) Oil, 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.

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.

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.

Human skin sensitization data are summarized in Table 5.

Human repeated insult patch test (HRIPT) results were negative for sensitization in studies involving 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.

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

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/m², or for 40 minutes with light from a Xenon lamp at a weighted erythema energy of 0.1667 W/m². 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.
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.50 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 5.55

A multicenter study involving 13,398 patients was performed by the US/Canadian North American Contact Dermatitis Group (NACDG), whereby a segment of this population (number of patients not stated) was tested with Piperita (Peppermint) Oil (2% in petrolatum). The prevalence rate for this ingredient was 0.9% (Table 5).56 In another multicenter study, neither irritant nor allergic reactions were observed in 73 patients patch tested with Mentha Piperita (Peppermint) Oil according to International Contact Dermatitis Research Group (ICDRG) patch test procedures.

Case Reports

Case reports are summarized in Table 5.

Mostly positive patch test reactions to Mentha Piperita (Peppermint) Oil and Mentha Piperita were reported in case reports on patients with diseased skin.57,58,59,60,61,62,63 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.64,65

Other Clinical Reports

Mentha Piperita (Peppermint) Oil

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

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

Oral

A triple-blind clinical trial involved 96 randomly selected subjects (47 cases and 49 controls; all pregnant women) with a diagnosis of pruritus gravidarum.66 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).67 Each capsule contained 83 mg of menthol as a constituent of Mentha Piperita (Peppermint) Oil. Each patient drank 125 ml of water after ingestion of the capsule. No adverse events were reported. The delayed appearance
of menthol in the plasma was reported; a substantial lag time (range 1 h to 4 h) was observed in all subjects. Thus, an apparent prolonged absorption time was demonstrated. The authors noted that reasons for the delayed time of peak ($T_{\text{max}}$) likely related to formulation-specific factors (i.e., delayed release) and, potentially, enterohepatic recirculation.

**Menthol (a component of Mentha Piperita (Peppermint) Oil)**

A clinical report on menthol, a component of Mentha Piperita (Peppermint) Oil, 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.*

**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.

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

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

Mentha Piperita (Peppermint) Oil was clastogenic in a chromosome aberration test involving peripheral blood lymphocytes. In a genotoxicity assay involving human lymphocytes, Mentha Piperita (Peppermint) Oil induced sister chromatid exchanges in a dose-dependent manner.
Oral pretreatment with Mentha Piperita (Peppermint) Leaf Extract (aqueous extract) before exposure to gamma radiation was found to be effective in protecting against chromosomal damage in the bone marrow of Swiss albino mice. In another study, the oral administration of Mentha Piperita (Peppermint) Leaf extract had an antigenotoxic (i.e., reduced the frequency of chromosomal aberrations and micronuclei in bone marrow cells) in Swiss albino mice intraperitoneally injected with benzo(a)pyrene.

Carcinogenicity data on pulegone, a constituent of Mentha piperita (peppermint)-derived ingredients, are included in this safety assessment, 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. Another multicenter study involving 13,398 patients was performed by the US/Canadian North American Contact Dermatitis
Mostly positive patch test reactions to Mentha Piperita (Peppermint) Oil (2% in petrolatum) and Mentha Piperita were reported in case reports on patients with diseased skin. In patients without skin disease, but with peppermint sensitivity, positive prick test reactions to Mentha Piperita (Peppermint) Leaf, Mentha Piperita (Peppermint) Leaf Extract, and Mentha Piperita were reported. In other clinical reports, oral dosing with Mentha Piperita (Peppermint) Oil (0.5% in sesame oil, 60 ml) did not cause any side effects in 47 pregnant female patients. A single oral dose of Mentha Piperita (Peppermint) Oil did not cause any adverse events in 6 pediatric patients.

DISCUSSION

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

Because final product formulations may contain multiple botanicals, each possibly containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For Mentha piperita (peppermint)-derived ingredients, the Panel is concerned about the presence of terpenes (e.g., limonene) and terpenoids (e.g. menthol) in cosmetics, which could result in sensitization. In the 2001 published final safety assessment on Mentha piperita (peppermint)-derived ingredients, the Panel was concerned about rat oral-dosing studies on Mentha Piperita (Peppermint) Oil (pulegone content specified) and pulegone in which cyst-like spaces in the cerebellum that appeared to have been caused by this component were observed and established a 1% concentration limit on pulegone in Mentha piperita (peppermint)-derived ingredients due to toxicity concerns. In these studies, brain sections were fixed by immersion using 4% neutral buffered formaldehyde. Because immersion fixation of nervous tissue might cause artifacts observed as vacuolar retraction spaces around neurons, a study involving rats was performed, using both immersion and perfusion tissue fixation methods, to determine whether the cerebellar lesions observed in earlier studies were caused by dosing with pulegone. Study results for rats dosed with pulegone did not reveal the occurrence of test substance-related, cyst-like spaces in the white matter of the cerebellum using either perfusion or immersion tissue fixation techniques. A possible explanation for the observed dose-dependent cyst-like spaces seen in previous studies could have been due to an interaction between impurities in the test substance and the fixation agent used therein. Given this possibility, the Panel agreed that the brain lesions may have been an artifact of the fixation method, and that the 1% limitation on pulegone may not be warranted.

The Panel also considered the positive effects that were observed in female rats, and in male and female mice, dosed with pulegone in the 2011 National Toxicology Program (NTP) oral carcinogenicity study. However, the Panel did not express concern over these findings relative to pulegone as a component of Mentha Piperita (Peppermint) Oil in cosmetic products, based on the understanding that the cytotoxic dose-response relationship (renal and liver toxicity) that was associated with cancer development would not be relevant to pulegone exposure from a cosmetic product containing Mentha piperita (Peppermint) Oil at current use concentrations. Given the toxicity concerns relating to pulegone and other constituents of Mentha piperita (peppermint)-derived ingredients, 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.
The issue of incidental inhalation exposure was discussed by the Panel, as *Mentha piperita* (peppermint)-derived ingredients are being used in products that could possibly be inhaled. For example, *Mentha Piperita* (Peppermint) Oil is being used in both pump hair sprays (maximum use concentrations up to 0.02%) and aerosol hair sprays (maximum use concentrations up to 0.017%) which may result in incidental inhalation exposure. Additionally, the Panel noted that droplets/particles from spray cosmetic products would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel’s approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at [http://www.cir-safety.org/cir-findings](http://www.cir-safety.org/cir-findings).

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

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

**CONCLUSION**

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

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

* Not reported to be in current use.

**TABLES**
<table>
<thead>
<tr>
<th>Ingredient CAS No.</th>
<th>Definition &amp; Idealized Structures</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentha Piperita (Peppermint) Oil</td>
<td>Mentha Piperita (Peppermint) Oil is a volatile oil obtained from the whole plant <em>Mentha piperita</em>. The accepted scientific name for <em>Mentha piperita</em> is <em>Mentha x piperita</em>.</td>
<td>Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Leaf Extract</td>
<td>Mentha Piperita (Peppermint) Leaf Extract is the extract of the leaves of the peppermint, <em>Mentha piperita</em>. The accepted scientific name for <em>Mentha piperita</em> is <em>Mentha x piperita</em>.</td>
<td>Fragrance Ingredients</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Leaf</td>
<td>Mentha Piperita (Peppermint) Leaf is the dried leaves of <em>Mentha piperita</em>. The accepted scientific name for <em>Mentha piperita</em> is <em>Mentha x piperita</em>.</td>
<td>Fragrance Ingredients</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Leaf Water</td>
<td>Mentha Piperita (Peppermint) Leaf Water is an aqueous solution of the steam distillate obtained from the leaves of <em>Mentha piperita</em>. The accepted scientific name for <em>Mentha piperita</em> is <em>Mentha x piperita</em>.</td>
<td>Flavoring Agents; Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Extract</td>
<td>Mentha Piperita (Peppermint) Extract is the extract of the whole plant, <em>Mentha piperita</em>. The accepted scientific name for <em>Mentha piperita</em> is <em>Mentha x piperita</em>.</td>
<td>Skin-Conditioning Agents - Miscellaneous</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract</td>
<td>Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract is the extract of the flowers, leaves and stems of <em>Mentha piperita</em>. The accepted scientific name for <em>Mentha piperita</em> is <em>Mentha x piperita</em>.</td>
<td>Flavoring Agents; Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Flower/Leaf/Stem Water</td>
<td>Mentha Piperita (Peppermint) Flower/Leaf/Stem Water is the aqueous solution of the steam distillates obtained from the flowers, leaves and stems of <em>Mentha piperita</em>. The accepted scientific name for <em>Mentha piperita</em> is <em>Mentha x piperita</em>.</td>
<td>Fragrance Ingredients</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Leaf Cell Extract</td>
<td>Mentha Piperita (Peppermint) Leaf Cell Extract is the extract of a culture of the leaf cells of <em>Mentha piperita</em>. The accepted scientific name for <em>Mentha piperita</em> is <em>Mentha x piperita</em>.</td>
<td>Antioxidants; Skin Protectants</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Leaf Juice</td>
<td>Mentha Piperita (Peppermint) Leaf Juice is the juice expressed from the leaves of <em>Mentha piperita</em>. The accepted scientific name for <em>Mentha piperita</em> is <em>Mentha x piperita</em>.</td>
<td>Skin-Conditioning Agents - Miscellaneous</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Meristem Cell Culture</td>
<td>Mentha Piperita (Peppermint) Meristem Cell Culture is a suspension of the cultured meristem cells of <em>Mentha piperita</em>. The accepted scientific name for <em>Mentha piperita</em> is <em>Mentha x piperita</em>.</td>
<td>Skin-Conditioning Agents - Miscellaneous</td>
</tr>
</tbody>
</table>
Table 2. Physical and Chemical Properties of Mentha Piperita (Peppermint) Oil

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form</td>
<td>Colorless or pale yellow liquid</td>
<td>1</td>
</tr>
<tr>
<td>Angular rotation (°C)</td>
<td>Between -18 and 32</td>
<td>1</td>
</tr>
<tr>
<td>Refractive index (at 20°C)</td>
<td>Between 1.459 and 1.465</td>
<td>1</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>Between 0.896 and 0.908</td>
<td>1</td>
</tr>
<tr>
<td>Assay for total esters</td>
<td>Not less than 5% of esters, calculated as menthyl acetate</td>
<td>1</td>
</tr>
<tr>
<td>Assay for total menthol</td>
<td>Not less than 50% of menthol</td>
<td>1</td>
</tr>
<tr>
<td>Dimethyl sulfide</td>
<td>Passes test (rectified); fails test (natural)</td>
<td>1</td>
</tr>
<tr>
<td>Heavy metals (as Pb)</td>
<td>Passes test (limit of 0.004%)</td>
<td>1</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in alcohol: Passes test (1 volume dissolves in 3 volumes of 70% alcohol); Soluble in most vegetable oils; insoluble in propylene glycol</td>
<td>1, 8</td>
</tr>
</tbody>
</table>

Table 3. Chromatographic Profile for menthe Piperita (Peppermint) Oil.

<table>
<thead>
<tr>
<th>Components</th>
<th>Origins Other Than U.S.</th>
<th>U.S. Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min. (%)</td>
<td>Max. (%)</td>
</tr>
<tr>
<td>3-Octanol</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>1,8-Cineole</td>
<td>3.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Limonene</td>
<td>1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>trans-Sabinene Hydrate</td>
<td>0.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Menthone</td>
<td>13.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Isomenthone</td>
<td>2.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Menthofuran</td>
<td>1.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Neomenthol</td>
<td>2.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Menthol</td>
<td>32.0</td>
<td>49.0</td>
</tr>
<tr>
<td>Pulegone</td>
<td>0.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Menthyl Acetate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.0</td>
<td>8.0</td>
</tr>
<tr>
<td>β-Caryophyllene</td>
<td>1.0</td>
<td>3.5</td>
</tr>
</tbody>
</table>

<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>
<thead>
<tr>
<th>Exposure Type</th>
<th>Ingredient</th>
<th>Rinses</th>
<th>Leave-Off</th>
<th>Duration of Use</th>
<th>Use Type</th>
<th>Frequency and Concentration of Use of Mentha piperita (peppermint)-derived Ingredients According to Duration and Exposure Type</th>
<th># of Uses</th>
<th>Max Conc of Use (%)</th>
<th># of Uses</th>
<th>Max Conc of Use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Table 4. Frequency and Concentration of Use of Mentha piperita (peppermint)-derived Ingredients According to Duration and Exposure Type</td>
<td>4</td>
<td>0.00094</td>
<td>NR</td>
<td>0.0018</td>
</tr>
<tr>
<td>Incidental Inhalation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Table 4. Frequency and Concentration of Use of Mentha piperita (peppermint)-derived Ingredients According to Duration and Exposure Type</td>
<td>214</td>
<td>0.0005-0.5</td>
<td>NR</td>
<td>0.000075-0.5</td>
</tr>
<tr>
<td>Incidental Inhalation-Spray</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Table 4. Frequency and Concentration of Use of Mentha piperita (peppermint)-derived Ingredients According to Duration and Exposure Type</td>
<td>19;120</td>
<td>0.017-1.0002-1.11</td>
<td>NR</td>
<td>0.00041-0.00057</td>
</tr>
<tr>
<td>Incidental Inhalation-Powder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Table 4. Frequency and Concentration of Use of Mentha piperita (peppermint)-derived Ingredients According to Duration and Exposure Type</td>
<td>148</td>
<td>0.0001-0.96</td>
<td>3</td>
<td>0.00018-0.2</td>
</tr>
<tr>
<td>Hair - Non-Coloring</td>
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<td>Table 4. Frequency and Concentration of Use of Mentha piperita (peppermint)-derived Ingredients According to Duration and Exposure Type</td>
<td>148</td>
<td>0.00024</td>
<td>NR</td>
<td>0.032</td>
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<td>Nail</td>
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<td>Table 4. Frequency and Concentration of Use of Mentha piperita (peppermint)-derived Ingredients According to Duration and Exposure Type</td>
<td>7</td>
<td>0.00064-1.5</td>
<td>NR</td>
<td>0.00018</td>
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<td>Mucous Membrane</td>
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<td>Table 4. Frequency and Concentration of Use of Mentha piperita (peppermint)-derived Ingredients According to Duration and Exposure Type</td>
<td>317</td>
<td>0.0022-3.9</td>
<td>8</td>
<td>0.00075-0.5</td>
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<td>Baby Products</td>
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<td>Table 4. Frequency and Concentration of Use of Mentha piperita (peppermint)-derived Ingredients According to Duration and Exposure Type</td>
<td>2</td>
<td>0.023</td>
<td>NR</td>
<td>0.00013-0.00067</td>
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<td></td>
<td>Table 4. Frequency and Concentration of Use of Mentha piperita (peppermint)-derived Ingredients According to Duration and Exposure Type</td>
<td>1</td>
<td>0.0016</td>
<td>NR</td>
<td>0.0018</td>
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<td></td>
<td>Table 4. Frequency and Concentration of Use of Mentha piperita (peppermint)-derived Ingredients According to Duration and Exposure Type</td>
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<td>0.00016</td>
<td>NR</td>
<td>0.0018</td>
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<td></td>
<td>Table 4. Frequency and Concentration of Use of Mentha piperita (peppermint)-derived Ingredients According to Duration and Exposure Type</td>
<td>4</td>
<td>0.00016</td>
<td>NR</td>
<td>0.0018</td>
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<td>0.0018</td>
</tr>
</tbody>
</table>

*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.

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

NR = no reported use
<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Subjects/Cell Type</th>
<th>Protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In Vitro</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract) (10% and 100%)</td>
<td>Reconstructed human epidermis</td>
<td><em>In vitro</em> 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.</td>
<td>Negative (MTT &gt; 50%).3</td>
</tr>
<tr>
<td><strong>Human</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% Mentha Piperita (Peppermint) Leaf Water in a cleansing gel</td>
<td>50 subjects</td>
<td>Subjects applied product twice per day for 4 weeks, and were instructed to record any signs felt or observed during product use.</td>
<td>Slight erythema was observed in one subject.50</td>
</tr>
<tr>
<td>50% Mentha Piperita (Peppermint) Leaf Water in a cleansing gel (10% aqueous dilution [effective concentration = 5%])</td>
<td>52 subjects</td>
<td>Diluted product applied, under occlusive patch, to the skin for 48 h. Reactions scored up to 48 ± 4 h after patch removal (day 4).</td>
<td>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.51</td>
</tr>
<tr>
<td><strong>Sensitization Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% Mentha Piperita (Peppermint) Leaf Extract (water/ethanol extract)</td>
<td>52 subjects</td>
<td>HRIPT (protocol details not included).</td>
<td>Negative results.5</td>
</tr>
<tr>
<td>20% Mentha Piperita (Peppermint) Leaf Water in a face cream</td>
<td>107 subjects (96 women, 11 men) with no history of atopy</td>
<td>In HRIPT, product applied (0.02 ml) to the back using occlusive patch (small Finn chamber), and 9 induction applications made over 3-week period. For 1st, 2nd, 5th, 7th, and 8th applications, duration of exposure was 48 ± 4 h. Duration of exposure was 72 ± 4 h for 3rd, 6th, and 9th applications. Challenge phase consisted of single application to new site and a previously treated site for 48 ± 4 h.</td>
<td>Product did not induce cumulative irritation or sensitization.54</td>
</tr>
<tr>
<td>20% Mentha Piperita (Peppermint) Oil</td>
<td>104 male and female subjects</td>
<td>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.</td>
<td>No evidence of irritation or sensitization.52</td>
</tr>
<tr>
<td>20% Mentha Piperita (Peppermint) Oil</td>
<td>101 male and female subjects</td>
<td>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</td>
<td>No evidence of sensitization.73</td>
</tr>
</tbody>
</table>
### Table 5. Dermal Irritation and Sensitization Data

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Subjects/Cell Type</th>
<th>Protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentha Piperita (Peppermint) Oil (concentration not stated)</td>
<td>73 patients</td>
<td>Patients patch tested according to International Contact Dermatitis Research Group (ICDRG) patch test procedures during 1994 to 1998</td>
<td>Neither irritant nor allergic reactions reported.55</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Oil (2% in petrolatum)</td>
<td>13,398 patients in study (number tested with ingredient not stated)</td>
<td>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.</td>
<td>Prevalence rate for Mentha Piperita (Peppermint) Oil was 0.9%.56</td>
</tr>
</tbody>
</table>

### Multicenter Studies

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Subjects/Cell Type</th>
<th>Protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentha Piperita (Peppermint) Oil (concentration not stated)</td>
<td>Male patient with orofacial granulomatosis mainly affecting lower lip</td>
<td>Patch test</td>
<td>Allergic positive reaction.57</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Oil (concentration not stated)</td>
<td>Female patient with lichenoid eruption on oral mucosa</td>
<td>Patch and prick tests</td>
<td>Positive patch test reaction, i.e., itching, erythema, and swelling, beginning at day 5; ++ reaction by day 7. Prick test results negative.58</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Oil (2% in petrolatum)</td>
<td>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.</td>
<td>Patch test</td>
<td>Strong positive reactions to LAT patch and to Mentha Piperita (Peppermint) Oil (2% in petrolatum).59</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Oil (2% in petrolatum)</td>
<td>Female patient with allergic contact dermatitis after consuming herbal tea containing Mentha Piperita (Peppermint) Oil.</td>
<td>Patch test. Reactions evaluated at 2, 3, and 7 days according to ICDRG procedures.</td>
<td>Positive patch test reaction (+ reaction) observed on days 2 and 3.60</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Oil (concentration not stated)</td>
<td>4 patients with allergic contact cheilitis (lips and perioral skin), secondary to exposure to lip balm that contained Mentha Piperita (Peppermint) Oil.</td>
<td>Patch test. Reactions evaluated at 48 h and 96 h.</td>
<td>Positive patch test reactions to lip balm and to Mentha Piperita (Peppermint) Oil.61</td>
</tr>
<tr>
<td>Ingredient</td>
<td>Subjects/Cell Type</td>
<td>Protocol</td>
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</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Mentha Piperita (Peppermint) Leaf and Peppermint (concentration not stated)</td>
<td>Male patient with IgE-mediated anaphylaxis to peppermint (<em>Mentha piperita</em>) after sucking on peppermint candy, 5 healthy controls</td>
<td>Skin prick and prick-to-prick tests</td>
<td>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.</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) Leaf Extract (concentration not stated)</td>
<td>Female patient became symptomatic with dyspnea when near peppermint (<em>Mentha piperita</em>) scent</td>
<td>Skin prick test</td>
<td>Positive skin prick test reaction to commercial Mentha Piperita (Peppermint) Leaf Extract.</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) (concentration not stated)</td>
<td>Male patient with severe cheilitis</td>
<td>Patch test</td>
<td>Negative reaction.</td>
</tr>
<tr>
<td>Mentha Piperita (Peppermint) fragrance (1:50, 2% in petrolatum)</td>
<td>Female patient with recurrent irritant rash after applying a Mentha Piperita (Peppermint) foot spray</td>
<td>Patch test</td>
<td>+ reaction on days 2 and 4.</td>
</tr>
</tbody>
</table>


58. Fleming, C. J. and Forsyth A. Short communications. D5 patch test reactions to menthol and peppermint oil. Contact Dermatitis. 1998;38:337


62. Guin, J. D. Rosemary cheilitis: one to remember. Contact Dermatitis. 2001;45:63


