EVALUATION OF THE HEALTH ASPECTS OF CORNMINT OIL AS A FOOD INGREDIENT

1981

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health and Human Services
Washington, D.C.

Contract No. FDA 223-78-2100
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20814
NOTICE

This report, one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior-sanctioned food substances as food ingredients, is being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-78-2100 with the Food and Drug Administration (FDA), U.S. Department of Health and Human Services. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshaling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee’s evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available to the public for review in the office of the Dockets Management Branch, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

Kenneth D. Fisher, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

This report concerns the health aspects of using cornmint oil as a food ingredient. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (Rogers, 1978), which summarizes the world's scientific literature from 1920 through 1978. To ensure completeness and currency as of the date of this report, this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, announcement was made in the Federal Register of April 21, 1981 (46 FR 22810) that opportunity would be provided for any interested persons to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the health aspects of using cornmint oil as a food ingredient. The Select Committee held a hearing on September 14, 1981. Those who presented statements at the hearing are identified at the end of this report. The material presented at the hearing has been considered by the Select Committee in reaching its final conclusions.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarketing clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (Office of the Federal Register, 1980) [21 CFR 170.3 and 170.30] that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. These sections of the Code also indicate that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA recognizes further [21 CFR 170.30] that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO reviewed and evaluated the available information on cornmint oil in full recognition of the foregoing provisions. In reaching its conclusions on safety, the Committee, in accordance with FDA's guidelines, relied primarily on the absence of substantive evidence of,
or reasonable grounds to suspect, a significant risk to the public health. While the Committee realized that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognized that there can be instances where, in the judgment of the Committee, there are insufficient data upon which to base a conclusion. This report is intended for the use of FDA in determining the future status of this substance under the Federal Food, Drug, and Cosmetic Act. The Committee anticipates that its conclusions will be reviewed as new information becomes available.
II. BACKGROUND INFORMATION

Cornmint oil is an essential oil obtained by steam distillation of Mentha arvensis L. (Guenther, 1949). It is also known as Japanese mint oil, fieldmint oil, and arvensis oil. According to regulations of the United States Department of Agriculture, cornmint oil, alone or in combination with peppermint oil, may not be labeled as peppermint oil, although this is common practice in other countries (Greenhalgh, 1979).

Crude cornmint oil has a harsh odor and flavor, a dark yellow color, and a menthol content as high as 95%. Its primary use is for the production of menthol. Dementholized cornmint oil is M. arvensis oil from which part of the menthol has been removed by cooling to -5°C. It contains 40-60% menthol, is pale yellow to colorless, and has an odor similar to but harsher than peppermint oil. The oil may be further rectified to produce an oil having a milder odor and flavor (Greenhalgh, 1979; Guenther, 1949; National Research Council, 1981).

M. arvensis grows well in tropical and subtropical climates. It is not cultivated in the United States. Until World War II, Japan was the major supplier of arvensis oil (Guenther, 1949), but Brazil and Paraguay have since become the major suppliers to the United States (Greenhalgh, 1979). In 1979, 208,350 kg of cornmint oil were imported by the United States from the countries shown in Table 1. These figures represent imports of the dementholized oil (Dull, 1980; Patty, 1980). Export of crude cornmint oil is prohibited by the Brazilian government to protect the Brazilian menthol industry. A menthol extraction industry is being developed in Paraguay, the second major supplier of cornmint oil to the United States (Greenhalgh, 1979).

Physical and chemical characteristics

Because cornmint oil is a complex mixture of components, it has neither chemical name nor Chemical Abstracts Service registry number; however, some of its components are listed by this service. Specifications for cornmint oil are included in the Food Chemicals Codex (National Research Council, 1981) which defines "Mentha arvensis oil, dementholized," as "the portion of oil remaining after the partial removal of menthol, by freezing operations only, from the oil of M. arvensis var. piperascens Holmes (forma piperascens Malinvaud)." It is further described as a colorless to yellow liquid having a characteristic minty odor. It is soluble in most fixed (fatty) oils, in mineral oil and in
Table 1. Import of Dementholized Cornmint Oil* by the United States, 1979†

<table>
<thead>
<tr>
<th>Exporting Country</th>
<th>kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>135,000</td>
</tr>
<tr>
<td>Paraguay</td>
<td>55,620</td>
</tr>
<tr>
<td>Singapore</td>
<td>7,200</td>
</tr>
<tr>
<td>Taiwan</td>
<td>4,500</td>
</tr>
<tr>
<td>Chile</td>
<td>3,600</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>2,160</td>
</tr>
<tr>
<td>Argentina</td>
<td>1,280</td>
</tr>
</tbody>
</table>

*Contains 40-60% menthol as compared to about 70% in crude cornmint oil.
†Figures supplied by Horticulture and Tropical Products Division, Foreign Agricultural Service, United States Department of Agriculture.
propylene glycol, but insoluble in glycerin. The specifications of this oil include the following:

Assay: Not less than 40.0% and not more than 60.0% of the total alcohols, calculated as menthol.

Specific gravity: 0.888 to 0.908

Angular rotation at 20°C: -20° to -35°

Refractive index at 20°C: 1.4585 to 1.4650

Total esters as menthy1 acetate: 5% to 20%

Ketone content as menthone: 30% to 50%

Chemical constituents of cornmint oil have been identified and quantified (Table 2). Samples of native and partially dementholized cornmint oils obtained from several geographical areas were analyzed by gas-liquid and a combination of gas-liquid and thin-layer chromatographic techniques (Handa et al., 1964; Nigam and Levi, 1964; Nigam et al., 1963; Smith and Levi, 1961). These investigators identified 15 compounds in cornmint oils (Table 2). The proportions of specific compounds varied with the geographic origin of the samples and proportions of several components increased when the oils were partially dementholized. Similar proportions of several components of steam-distilled crude M. arvensis oil were reported by Haginiwa et al. (1963). However, these investigators identified only six components and reported a large fraction (20%) of unknown compounds. The presence of several compounds not identified by chromatographic techniques was shown when cornmint oil was fractionated and derivatized (Baslas and Baslas, 1969). These components are also listed in Table 2.

GRAS status and uses

The GRAS status of cornmint oil was granted by letters (Buckley, 1970; Cassidy, 1961; Larrick, 1965). A petition asking that the oil of a hybrid of M. arvensis be considered as GRAS was denied (Cassidy, 1962). According to Greenhalgh (1979) dementholized cornmint oil is used primarily for flavoring chewing gum and toothpaste. Lesser amounts are used in confectionery, tobacco, cosmetics, pharmaceuticals, and liqueurs.
Table 2. Components of Native and Dementholized Cornmint Oils

<table>
<thead>
<tr>
<th></th>
<th>Native*</th>
<th>Native†</th>
<th>Dementholized$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Menthol</td>
<td>&gt;53.0</td>
<td>61.5-68.6</td>
<td>50.3</td>
</tr>
<tr>
<td>Neomenthol</td>
<td>-</td>
<td>1.6-2.2</td>
<td>3.4</td>
</tr>
<tr>
<td>Menthone</td>
<td>10.4</td>
<td>9.9-17.1</td>
<td>22.8</td>
</tr>
<tr>
<td>Isomenthone</td>
<td>-</td>
<td>2.7-4.2</td>
<td>7.0</td>
</tr>
<tr>
<td>Menthyl acetate</td>
<td>12.0</td>
<td>4.7-6.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Limonene</td>
<td>1.7</td>
<td>4.3-6.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Piperitone</td>
<td>1.1</td>
<td>1.8-2.7</td>
<td>2.3</td>
</tr>
<tr>
<td>Piperitone oxide</td>
<td>-</td>
<td>0.3</td>
<td>-</td>
</tr>
<tr>
<td>Pulegone</td>
<td>1.1</td>
<td>0.2-1.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Cineole</td>
<td>1.5</td>
<td>0.4-0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>α-Pinene</td>
<td>1.5</td>
<td>0.2-0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>β-Pinene</td>
<td>-</td>
<td>0.9-1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Thujone</td>
<td>1.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>α-Thujone</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>β-Phellandrene</td>
<td>1.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carvone</td>
<td>1.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carvomenthone</td>
<td>1.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Caryophyllene</td>
<td>0.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cadinene</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3-Octanol</td>
<td>-</td>
<td>0.2-0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Linalool</td>
<td>-</td>
<td>0.0-0.8</td>
<td>-</td>
</tr>
<tr>
<td>Menthofuran</td>
<td>-</td>
<td>&lt;0.1</td>
<td>-</td>
</tr>
<tr>
<td>Residue</td>
<td>3.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Unaccounted</td>
<td>6.1</td>
<td>0.0-0.9</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Analysis of cornmint oil from India (Baslas and Baslas, 1969).

†Analyses of cornmint oils from various geographic locations (Handa et al., 1964; Smith and Levi, 1961).

$Analysis of a partially dementholized cornmint oil containing 50.3% menthol (Smith and Levi, 1961).
III. CONSUMER EXPOSURE

Import figures indicate that 208,350 kg of dementholized cornmint oil entered the United States in 1979 (Dull, 1980). The fraction of this oil used in food products is not known. In a 1972 survey (Subcommittee on Review of the GRAS List--Phase II, 1972) 1800 lb/yr (818 kg) of cornmint oil was used in foods, corresponding to a daily per capita usage of 0.01 mg. The 1977 survey of use of food additives (Committee on GRAS List Survey--Phase III, 1979) included cornmint oil in its listing. No industry respondents in the survey reported use of cornmint oil in their products, but some respondents did report use of some compounds found in cornmint oil (menthol, dl-isomenthone, caryophyllene, and carvone). Quantities of these compounds used annually and calculated daily per capita availability were:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Quantity (kg)</th>
<th>Per capita daily availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menthol</td>
<td>54,500</td>
<td>0.7 mg</td>
</tr>
<tr>
<td>Carvone</td>
<td>39,000</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Caryophyllene</td>
<td>0.15</td>
<td>0.02 µg</td>
</tr>
<tr>
<td>dl-Isomenthone</td>
<td>2.7</td>
<td>0.35 µg</td>
</tr>
</tbody>
</table>

In evaluating data on usage of essential oils, it must be remembered that high intake figures represent amounts added for food processing. Losses occurring during processing would decrease the quantity contained in products by an unknown amount.
IV. BIOLOGICAL STUDIES

Absorption, metabolism, and excretion

The Select Committee is not aware of studies on the absorption, metabolism, and excretion of cornmint oil per se. In one experiment 0, 10, 100, or 1000 mg cornmint oil per kg body weight was orally administered to mice weighing 14–20 g (Haginiwa et al., 1963). A dye administered simultaneously with the oil traveled somewhat farther 30 min after gavage in mice given 1000 mg/kg cornmint oil than in control mice or those given the lower levels of this oil. Although considerable overlap in distance traveled by the dye was observed for all groups, the authors considered the results at the highest dosage level evidence of acute toxicity through stimulation of peristalsis.

Limited information is available on metabolism of some components of cornmint oil. Macht (1930) reported that menthol was absorbed through the intact skin of mice. A urinary metabolite of menthol was identified as methyl glucuronide in several species (Atzl et al., 1972; Eisenberg et al., 1955; Quick, 1924, 1928; Südhof, 1952). The proportion of the administered dose excreted in the urine as the glucuronide varied among species and decreased as the dose of menthol was increased (Williams, 1959). Quick (1924, 1928) reported that 5% of a 5 g oral dose to a dog and less than 50% of an unspecified dose given orally to rabbits were excreted as the glucuronide. In one study an adult human male given 1 g menthol (approximately 14 mg/kg body weight) excreted 79% of the dose as methyl glucuronide within 6 h (Quick, 1928). In a second study, one human subject (sex not specified) excreted 77.5% of a 20 g oral dose of menthol in 11 h. Studies of l-menthone orally administered to rabbits (1.5 g/kg) indicated that the ketone was reduced to d-neomenthol which formed a conjugate with glucuronic acid (Williams, 1940).

Other components of cornmint oil—carvone, piperitone, limonene, and β-pinene (tentative)—were identified by gas chromatography/mass spectrometry in urine samples of normal human subjects (Zlatkis and Liebich, 1971; Zlatkis et al., 1973a,b). Urine samples were collected for intervals ranging from several days to 2 mo in 10 subjects. No attempt was made to control dietary intakes.

Earlier studies of carvone metabolism in rabbits (Hildebrandt, 1902) indicated the presence in the urine of a glucuronide containing oxidized carvone, 1,5-dimethyl-1,5-hexadiene-1,6 dicarboxylic acid, and a carbinol in which one ethylenic bond was saturated and the keto group reduced (Fischer and Bielig, 1940). Following oral administration of pulegone to rabbits, Teppati (1937) identified pulegone in urine. The major metabolite of [14C]-d-limonene administered orally to two adult humans was
8-hydroxy-p-menth-1-en-9-yl-β-D-glucopyranosiduronic acid (Kodama et al., 1976). These investigators found different major metabolites of limonene in urine of the five animal species tested.

**Acute toxicity**

The acute oral toxicity (LD₅₀) of steam-distilled cornmint oil in the rat was reported by Wohl (1974) as 1.24 g/kg. The same report indicated the acute dermal LD₅₀ as 5 g/kg in the rabbit. Monographs on fragrance raw materials summarize acute toxicity studies of cornmint oil (Opdyke, 1975), 1-menthol (Opdyke, 1976a), racemic menthone (Opdyke, 1976b), 1-menthyl acetate (Opdyke, 1976c), 1-carvone (Opdyke, 1973a), and caryophyllene (Opdyke, 1973b). Acute toxicity values for cornmint oil and for several of its major components are shown in Table 3.

**Short-term studies**

No short-term feeding studies on the effects of cornmint oil have come to the attention of the Select Committee. Short-term feeding studies of only three of its components, 1-menthol, carvone, and d-limonene were found.

Diets containing 1-menthol (0, 100, and 200 mg/kg body weight) were fed to groups of 40 male and 40 female rats for 5½ wk (Herken, 1961). No adverse effects were reported on weight gain, or excretion of glucuronide, water, and electrolytes. Menthol did not affect central nervous system reactions to cardagrol or electric shock or hexobarbital sleeping time (Herken, 1961). Oral administration of 1.2, 2.0 or 9.3 g/kg 1-menthol to mice caused an increase in β-glucuronidase activity in liver at the two lower doses but not at the highest dose (Levvy et al., 1948). Enzyme activity was measured 1 or 3 d after administration of the lower doses of menthol and 5 d after the higher dose. Unspecified numbers of adult mice, 30-40 g, given a single intraperitoneal injection of 1-menthol (0.333 mg/kg in olive oil) had increased β-glucuronidase activity in liver which peaked at 24 h and persisted for 7 d. Liver damage, without signs of repair, was observed after 24 h. Repair was almost complete by day 14 and the enzyme level returned to its pretreatment level. In the kidney, swelling and necrosis in the distal convoluted tubules and some glomeruli was observed after 3 d, and β-glucuronidase activity was elevated after 7 d. Spleen glucuronidase activity was not affected (Levvy et al., 1948). The effects of menthols administered by varying routes on functions of heart, kidney, liver, smooth muscle, and central nervous system of cats and rabbits were reported by Macht (1939).
Table 3. Acute Toxicity (LD$_{50}$) of Cornmint Oil and Some of its Components

<table>
<thead>
<tr>
<th>Substance</th>
<th>Species</th>
<th>Route</th>
<th>Dosage g/kg</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornmint oil</td>
<td>rat</td>
<td>oral</td>
<td>1.24</td>
<td>Wohl (1974)</td>
</tr>
<tr>
<td>Cornmint oil</td>
<td>rabbit</td>
<td>dermal</td>
<td>5.0</td>
<td>Wohl (1974)</td>
</tr>
<tr>
<td>1-Menthol</td>
<td>rat</td>
<td>oral</td>
<td>3.3</td>
<td>Herken (1961)</td>
</tr>
<tr>
<td>1-Menthol</td>
<td>cat</td>
<td>oral</td>
<td>0.8-1.0</td>
<td>Flury and Seel (1926)</td>
</tr>
<tr>
<td>1-Menthol</td>
<td>mouse</td>
<td>i.p.</td>
<td>2.0</td>
<td>Macht (1939)</td>
</tr>
<tr>
<td>1-Menthol</td>
<td>rat</td>
<td>i.p.</td>
<td>1.5</td>
<td>Macht (1939)</td>
</tr>
<tr>
<td>1-Menthol</td>
<td>rat</td>
<td>i.p.</td>
<td>0.71</td>
<td>Herken (1961)</td>
</tr>
<tr>
<td>1-Menthol</td>
<td>rat</td>
<td>i.p.</td>
<td>0.79</td>
<td>Hazard and Lechat (1952)</td>
</tr>
<tr>
<td>1-Menthol</td>
<td>cat</td>
<td>i.p.</td>
<td>0.8-1.0</td>
<td>Flury and Seel (1926)</td>
</tr>
<tr>
<td>1-Menthol</td>
<td>rabbit</td>
<td>i.p.</td>
<td>2.0</td>
<td>Herken (1961)</td>
</tr>
<tr>
<td>1-Menthol</td>
<td>guinea pig</td>
<td>i.p.</td>
<td>0.86</td>
<td>Hazard and Lechat (1952)</td>
</tr>
<tr>
<td>1-Menthol</td>
<td>guinea pig</td>
<td>i.p.</td>
<td>4.0</td>
<td>Macht (1939)</td>
</tr>
<tr>
<td>Menthone (racemic)</td>
<td>mouse</td>
<td>oral</td>
<td>1.95</td>
<td>Levenstein (1973)</td>
</tr>
<tr>
<td>1-Menthyl acetate</td>
<td>rat</td>
<td>oral</td>
<td>&gt;5.0</td>
<td>Shélanski (1972)</td>
</tr>
<tr>
<td>dl-Menthyl acetate</td>
<td>rat</td>
<td>oral</td>
<td>6.8</td>
<td>Levenstein (1973)</td>
</tr>
<tr>
<td>Carvone</td>
<td>rat</td>
<td>oral</td>
<td>1.64</td>
<td>Jenner et al. (1964)</td>
</tr>
<tr>
<td>Carvone</td>
<td>guinea pig</td>
<td>oral</td>
<td>0.77</td>
<td>Jenner et al. (1964)</td>
</tr>
<tr>
<td>Caryophyllene</td>
<td>rat</td>
<td>oral</td>
<td>&gt;5.0</td>
<td>Hart (1971)</td>
</tr>
<tr>
<td>Limonene</td>
<td>mouse</td>
<td>oral</td>
<td>5.6-6.6</td>
<td>Tsuji et al. (1975a)</td>
</tr>
<tr>
<td>Limonene</td>
<td>rat</td>
<td>oral</td>
<td>4.4-5.1</td>
<td>Tsuji et al. (1975a)</td>
</tr>
<tr>
<td>$\alpha$-Pinene</td>
<td>rat</td>
<td>oral</td>
<td>3.7</td>
<td>Research Institute for Fragrance Materials (undated)</td>
</tr>
<tr>
<td>Piperitone</td>
<td>mouse</td>
<td>s.c.</td>
<td>1.42</td>
<td>Wenzel and Ross (1957)</td>
</tr>
<tr>
<td>Pulegone</td>
<td>mouse</td>
<td>i.p.</td>
<td>0.15</td>
<td>Plzak and Doull (1969)</td>
</tr>
<tr>
<td>Pulegone</td>
<td>mouse</td>
<td>s.c.</td>
<td>1.71</td>
<td>Wenzel and Ross (1957)</td>
</tr>
<tr>
<td>Thujone</td>
<td>mouse</td>
<td>oral</td>
<td>0.25</td>
<td>Le Bourhis and Soenen (1973)</td>
</tr>
</tbody>
</table>
Groups of five male and five female weanling Osborne-Mendel rats were fed diets containing 1000 ppm (50 mg/kg body weight) carvone for 27 or 28 wk and 10,000 ppm carvone (500 mg/kg body weight) for 16 wk (Hagan et al., 1967). The lower levels caused no adverse effects on growth or hematologic and histologic parameters, whereas the highest level produced growth retardation and testicular atrophy. Administration of carvone (100 mg/kg) to albino rats for 10 d caused increased urinary excretion of glucuronic acid and ascorbic acid (Tamura et al., 1962). Ascorbic acid content of liver, brain, and plasma following oral administration of carvone (300 mg/kg) was determined in groups of 3-5 male and female rats 3 mo of age (Ritz et al., 1940). Livers of animals given two doses 9 h apart and sacrificed 22 h after the first dose showed a slight increase in ascorbic acid content, but brain and plasma levels were unchanged. A similar dose administered twice daily for 3 d caused increases only in liver and plasma ascorbic acid and in liver weight (Ritz et al., 1940).

General pharmacological effects of d-limonene on mice, rats, rabbits and dogs were investigated by Tsuji et al. (1974). d-Limonene (277, 554, 1385, or 2770 mg/kg in 1% Tween 80® solution) administered orally to Sprague-Dawley male and female rats (9 or 10 rats/group) for 1 mo caused decreased food consumption and body weight (Tsuji et al., 1975a). Urinary pH decreased with increasing levels of limonene. Total white blood cell counts and numbers of lymphocytes were lower in rats fed 2770 mg/kg d-limonene while numbers of neutrophils and monocytes were increased in this group. Total cholesterol, glucose, and urea nitrogen in blood decreased as intakes of limonene increased. Histopathologic examination showed granular casts in the kidneys of male rats but no significant changes in other tissues (Tsuji et al., 1975a). Rats given 1385 mg/kg d-limonene orally for 6 mo, demonstrated changes similar to those of rats given 2770 mg/kg for 1 mo, whereas findings in rats given 277 or 554 mg/kg d-limonene were similar to those in controls treated only with Tween 80® (Tsuji et al, 1975b).

In Japanese beagles, oral administration of 0.3, 1.0, or 3.0 mg/kg of d-limonene for 6 mo was associated with increased body weight in males at all levels of intake and in females at the 0.3 mg/kg level. Food consumption was not changed (Tsuji et al., 1975c). Serum concentrations of total cholesterol and blood glucose concentrations were lowered at 3.0 mg/kg and granular casts were noted in kidneys of males at the two higher levels and of females at all levels.

Long-term studies

No long-term studies of effects of cornmint oil were available to the Select Committee. Only one long-term study of the effects of carvone was identified. Hagan et al. (1967) fed
2500 ppm carvone in the diet (125 mg/kg body weight) to rats for 1 yr. No adverse effects on growth, hematology, or histology were noted.

Special studies

Effects of cornmim oil such as skin irritation, phototoxicity and sensitization, and inhibition of microbial growth have been evaluated. Urbach and Forbes (1974) found that cornmint oil did not cause irritation or phototoxicity when applied to the backs of hairless mice or swine. Similarly, it did not irritate intact or abraded rabbit skin after 24-h exposure (Wohl, 1974). When applied to human skin at the 8% level in petrolatum, cornmint oil caused no irritation after 48 h and no sensitization reactions (Epstein, 1974). In contrast, menthol in toothpaste, peppermint candy, and mentholated cigarettes has been reported to cause urticaria (McGowan, 1966). In vitro growth of 8 of 10 bacteria and fungi tested was inhibited by cornmint oil (Sanyal and Varma, 1969).

Thujone had convulsive properties; menthol, carvone, and limonene demonstrated weak psycholeptic activity when administered orally to mice (Le Bourhis and Soenen, 1973). The authors stated that the psychotropic effects were transient and thought that such effects were unlikely to occur in man after consumption of foods containing these substances. It may be noted that the limitation "finished food, thujone free" has been placed on three natural flavorings listed in [21 CFR 172.510] (Office of the Federal Register, 1980).

Carcinogenicity, teratogenicity, and mutagenicity

No information on carcinogenicity, teratogenicity, or mutagenicity of cornmint oil was available to the Select Committee.

Carcinogenicity of dl-menthol was recently evaluated in groups of 50 Fischer 344 rats of each sex and 50 B6C3F1 mice of each sex (Carcinogenesis Testing Program, 1978). dl-Menthol was incorporated into the diet at 3750 or 7500 ppm for rats (about 170 or 340 mg/kg/d for males and 200 or 400 mg/kg/d for females) and 2000 or 4000 ppm for mice (about 250 or 500 mg/kg/d for males and 270 or 530 mg/kg/d for females). Animals consumed these diets for 103 wk. Incidence of tumors in treated male or female rats and mice was no greater than in controls.

Driedger and Blumberg (1978) reported that limonene caused increased deoxyglucose transport in chicken embryo fibroblasts, a reaction associated with tumor promotion by phorbol 12-myristate 13-acetate in mouse skin. However, limonene did not cause a second tumor-associated reaction, loss of large external
transformation-sensitive (LETS) protein from the surface of these cells. d-Limonene reduced incidence and growth of tumors in mice (Homburger et al., 1971; Van Duuren and Goldschmidt, 1976). Watabe et al. (1980) found the d-limonene was metabolized by rat liver microsomes to epoxides that were nonmutagenic toward Salmonella typhimurium. Offspring of mice orally administered 2363 mg/kg of limonene on d 7-12 of gestation showed abnormalities in rib development; incidence of cleft palate was increased in offspring of dams given 591 mg/kg of d-limonene daily (Kodama et al., 1977).
V. OPINION

Cornmint oil, also known as Japanese mint oil, fieldmint oil, or arvensis oil, is a complex mixture of components whose proportions vary somewhat with geographic origin of the plant source. Its odor and flavor are similar to but harsher than that of peppermint oil. It is used as a flavoring agent for such products as chewing gum, toothpaste, confectionery, and liqueurs. The major component of native and demethylated cornmint oils is menthol. Other compounds, present in smaller proportions, are found in a variety of essential oils. Demethylized cornmint oil, which still contains 40-60% menthol, is the form of the oil imported into the United States.

Estimates of consumer exposure to cornmint oil indicate that the amount added for food processing is on the order of 0.01 mg/d. Losses during processing may reduce the quantity of cornmint oil retained in a product by an unknown amount.

Studies of the biological effects of cornmint oil itself are limited, as are studies on the biological effects of some of its components. The oral LD$_{50}$ in rats of cornmint oil is 1.24 g/kg. There are no short-term feeding tests, no long-term feeding tests, no carcinogenicity, mutagenicity, and teratogenicity tests on cornmint oil that have come to the attention of the Select Committee. Although short- and long-term feeding studies have been reported for menthol which makes up about 50% of cornmint oil, there remain at least 10 components amounting to about 45% of the oil for which no reports of short- or long-term feeding studies, teratogenicity or mutagenicity tests were available to the Select Committee.

In light of the above considerations, the Select Committee concludes that:

In view of the deficiency of relevant biological studies, the Select Committee has insufficient data upon which to base an evaluation of cornmint oil when it is used as a food ingredient.
VI. REFERENCES CITED


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December 16, 1981  George W. Irving, Jr., Chairman
Date Select Committee on GRAS Substances
PUBLIC HEARING ON CORNMINT OIL*
September 14, 1981

The following individuals made a presentation:

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*A transcript of the hearing is available from Ace-Federal Reporters, Inc. 444 North Capitol Street, Washington, DC. 20001.