EVALUATION OF THE HEALTH ASPECTS OF NUTMEG, MACE AND THEIR ESSENTIAL OILS AS FOOD INGREDIENTS

FEBRUARY 1973

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D. C.

THIS DOCUMENT HAS NOT BEEN APPROVED FOR PUBLIC RELEASE

Contract No. FDA 72-85
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Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
NOTICE

This report is one of a series of evaluations of the health aspects of the Generally Recognized as Safe (GRAS) food substances that are being made by the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) under contract with the Food and Drug Administration (FDA) of the U. S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office, established in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to make a continuing review, analysis, and evaluation of 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. Members of the Select Committee on GRAS Substances who have contributed to this report are named in Section VII. The Select Committee's evaluations are being made independently of FDA or any other governmental or nongovernmental group.

These reports are approved by the Select Committee prior to submission to FDA. Although most LSRO consultants are members of FASEB constituent societies, the reports do not necessarily reflect the views of the Federation as a corporate body or carry the endorsement of the members of its constituent societies.

C. Jeffery Carr, Ph. D., Director
Life Sciences Research Office
FASEB
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>II. Background information</td>
<td>2</td>
</tr>
<tr>
<td>III. Consumer exposure data</td>
<td>5</td>
</tr>
<tr>
<td>IV. Biological studies</td>
<td>8</td>
</tr>
<tr>
<td>V. Opinion</td>
<td>12</td>
</tr>
<tr>
<td>VI. References cited</td>
<td>14</td>
</tr>
<tr>
<td>VII. Scientists contributing to this report</td>
<td>17</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

Under terms of FDA Contract 72-85, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using nutmeg, mace, and their essential oils as food ingredients, primarily on the basis of information contained in a monograph furnished by FDA (1), summarizing the world's scientific literature from 1920 through 1970, and in certain supplemental documents, including current literature citations obtained through Toxline* and Medline, * available as of February, 1973. Nutmeg, mace, and their essential oils are food substances that have been generally recognized as safe (GRAS) under the provisions of Section 121.101 of the Code of Federal Regulations (21 CFR 121.101, revised April 1, 1973).

As indicated in the Food, Drug, and Cosmetic Act[21 USC 321 (s)], GRAS substances are exempt from the requirement of premarketing clearance for food additives. It is stated in 21 CFR 121.1 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. This section of the Code also indicates 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. It is recognized further (21 CFR 121.3) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety the Select Committee in accord with FDA's guidelines, is relying primarily on the absence of substantive evidence of or reasonable grounds to suspect a significant risk to the public health, and realizes that a conclusion based on such reasoned judgment, is expected even in instances where the available

*Nationwide online bibliographic retrieval systems initiated by the National Library of Medicine, Bethesda, Maryland.
information is qualitatively or quantitatively limited. The Committee is also aware that biological testing, like all of science, is dynamic. Accordingly, the Committee’s conclusions, based as they are on the information now available, cannot anticipate and be guided by experiments not yet done or by the results of tests that may be reconducted, using new technologies that are continually being evolved. These conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on nutmeg, mace and their essential oils and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of these substances under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Nutmeg is the dried, ripe seed and mace is the dried aril which envelopes the shell containing the seed of trees of Myristica species, principally Myristica fragans Houtt. The ground seed is the spice nutmeg; the ground aril is the spice mace. Oil of nutmeg and oil of mace are the essential oils obtained by steam distillation of nutmeg and mace, respectively. Nutmeg and mace owe their characteristic aroma to these essential oils. Mace oleoresin, a butter-like product obtained by pressing, consists chiefly (73 percent) of the fat trimyristin, about 12 percent of rather firmly bound essential oil, and smaller amounts of other fats, fatty acids, and unsaponifiable lipids (1, 2). A similar product, nutmeg butter, can be expressed from nutmeg.

Nutmeg trees bear fruit nearly all year in the two major production areas, the East Indies (principally the islands of Indonesia, but with some production in Ceylon, New Guinea, Malaya, and Africa) and the West Indies (principally Grenada). In the East Indies the mature, partially dried and opened fruit is picked by hand from the trees; in the West Indies the partially dried fruit is allowed to drop and is harvested from the ground. The collected fruit is separated into mace (the arils) and the nutmeg seed still in the shell, and both products are carefully dried. In the East Indies lime is sometimes added as protection against insects. The dried mace and nutmeg seed (without the shell) are sorted, graded, and marketed (2). East Indian nutmeg and mace are produced in five grades in the following
order of decreasing quality: Banda Nutmeg, Java Estate Nutmeg, Siauw Nutmeg, Penang Nutmeg and Papua Nutmeg. The last-named is not derived from *M. fragrans* but from *M. argentina* Warb.

Nutmeg and mace differ widely in essential oil content, certain oil properties, and composition, depending on the geographical source and age, and probably on harvesting and subsequent processing procedures. For example, the essential oil content of East Indian nutmeg of good quality may vary from 4 to 10 percent; the specific gravity of the essential oil from about 0.86 to 0.92, the optical rotation from about +7 to +30 degrees, and the acid number from about 2.5 to 8.8. In comparison, West Indian nutmeg of good quality tends to be somewhat higher (usually about 9 percent) in essential oil which, on the average, has a lower specific gravity, lower acid number and higher optical rotation (2).

Oils of nutmeg and mace from the same source are reported to have grossly similar composition, about 80 percent terpenes and 6 percent terpene alcohols (3). However, qualitative and quantitative differences between the East and West Indian essential oils of nutmeg have been revealed in relatively recent chromatographic analyses for a large number of constituents (4), as follows:

<table>
<thead>
<tr>
<th></th>
<th>East Indian (three samples)</th>
<th>West Indian</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A Percent</td>
<td>B Percent</td>
</tr>
<tr>
<td><strong>α-Pinene</strong></td>
<td>13.9</td>
<td>12.9</td>
</tr>
<tr>
<td><strong>β-Pinene</strong></td>
<td>12.3</td>
<td>12.6</td>
</tr>
<tr>
<td>Terpinolene</td>
<td>none</td>
<td>1.4</td>
</tr>
<tr>
<td>Limonene</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>β-Cymene</strong></td>
<td>1.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Linalool</td>
<td>10.6</td>
<td>8.1</td>
</tr>
<tr>
<td>Camphor</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Terpinen-4-ol</td>
<td>14.5</td>
<td>14.2</td>
</tr>
<tr>
<td><strong>α-Terpineol</strong></td>
<td>7.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Geraniol</td>
<td>0.3</td>
<td>11.9</td>
</tr>
<tr>
<td>Safrole</td>
<td>6.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Eugenol</td>
<td>1.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Eight unknown consti-</td>
<td>27.1</td>
<td>19.3</td>
</tr>
</tbody>
</table>

- 3 -
Certain other constituents have been reported to occur in oil of nutmeg (whether East or West Indian not indicated): myristicin (5.3 percent), elemicin (2.1 percent), isoeugenol (0.2 percent), methoxeyugenol (0.25 percent) and trans-isoelemicin (0.1 percent) (5).

The Food Chemicals Codex (6) recognizes in its specifications that the essential oils (myristica oils) of East and West Indian nutmegs differ and that for this reason marketed products must indicate the source on the label. The specifications are as follows:

<table>
<thead>
<tr>
<th></th>
<th>East Indian nutmeg oil</th>
<th>West Indian nutmeg oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optical rotation</td>
<td>+8 to +30°</td>
<td>+25 to +45°</td>
</tr>
<tr>
<td>Refractive index at 20°</td>
<td>1.474 to 1.488</td>
<td>1.469 to 1.476</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>0.880 to 0.910</td>
<td>0.854 to 0.880</td>
</tr>
<tr>
<td>Residue on evaporation</td>
<td>Not more than 60 mg per 3 ml</td>
<td>Not more than 50 mg per 3 ml</td>
</tr>
</tbody>
</table>

Neither oil may contain more than 3 ppm of arsenic, 40 ppm heavy metals as lead, or 10 ppm of lead.

Nutmeg and mace have been used to flavor foods since at least the twelfth century in Europe and presumably well before that in the Far East where these spices originated. They have been used in the United States since Colonial days (2).

These spices and their essential oils are used in the following categories of foods, arranged approximately in each case in decreasing order of content (7):

**Nutmeg** (3,000 to less than 1 ppm, equivalent to 0.30 to less than 0.0001 percent): Sweet sauces, toppings and syrups; baked goods; frozen dairy desserts and mixes; milk products (1,100 to 900 ppm); condiments and relishes; breakfast cereals; meat products; gelatins and puddings; nonalcoholic beverages (380 ppm); processed vegetables; processed fruit products; fats and oils (200 to 100 ppm); soups and mixes; gravies; alcoholic beverages.
Nutmeg oil (600 to 1 ppm): Gravies; meat products; baked goods (100 to 70 ppm); chewing gum; soft candy (40 to 30 ppm); gelatins and puddings; condiments and relishes; frozen dairy desserts and mixes (25 to 20 ppm); alcoholic beverages; non-alcoholic beverages; hard candy.

Mace (1450 to 20 ppm): Baked goods; processed vegetables; condiments and relishes (600 to 100 ppm); nonalcoholic beverages; snack foods; meat products; soups and soup mixes (200 to 50 ppm); gravies.

Mace oil (550 to 2 ppm): Alcoholic beverages; soft candy; gelatins and puddings (90 to 70 ppm); meat products; frozen dairy desserts and mixes; condiments and relishes (70 to 60 ppm); baked goods; nonalcoholic beverages; chewing gum (40 to 30 ppm); gravies; processed vegetables.

Mace oleoresin (775 to 3 ppm): Alcoholic beverages; soft candy, frozen dairy desserts and mixes; condiments and relishes; gelatins and puddings (150 to 125 ppm); baked goods; nonalcoholic beverages; chewing gum; gravies.

The amounts of nutmeg, mace, and nutmeg oil imported annually have been relatively constant for a number of years, averaging about 4 million pounds of nutmeg, 568,000 pounds of mace, and 139,000 pounds of nutmeg oil between 1965 and 1971 (8). No import statistics for mace oil or mace oleoresin have been found. Moreover, there is no information available to the Select Committee that permits it to determine the extent to which there has been significant change in the nutmeg or mace content of the foregoing food categories over the past decade.

III. CONSUMER EXPOSURE DATA

A National Research Council subcommittee (7) has supplied the information given in the following table on the possible daily human intake of nutmeg, mace, and their products in the total diet, by individuals in various age groups. The Select Committee has converted these figures to possible intakes per kilogram of body weight.

It is recognized that the figures calculated for the daily intake of nutmeg, mace, and their products per kg body weight in the age
# Nutmeg Related Substances

## Possible daily intake

<table>
<thead>
<tr>
<th>AGE</th>
<th>Total</th>
<th>Per kilogram of body weight*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-5 mos.</td>
<td>6-11 mos.</td>
</tr>
<tr>
<td>Av.</td>
<td>mg</td>
<td>mg</td>
</tr>
<tr>
<td>Max.</td>
<td>mg</td>
<td>mg</td>
</tr>
<tr>
<td></td>
<td>13.0</td>
<td>29.0</td>
</tr>
<tr>
<td>Nutmeg</td>
<td>2.6</td>
<td>5.8</td>
</tr>
<tr>
<td>0.5</td>
<td>0.9</td>
<td>5</td>
</tr>
<tr>
<td>Nutmeg oil</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>3.0</td>
<td>8.0</td>
<td>5</td>
</tr>
<tr>
<td>Mace</td>
<td>0.6</td>
<td>1.6</td>
</tr>
<tr>
<td>0.6</td>
<td>1.5</td>
<td>6</td>
</tr>
<tr>
<td>Mace oil</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>1.0</td>
<td>3.0</td>
<td>10</td>
</tr>
<tr>
<td>Mace oleoresin</td>
<td>0.6</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*Calculations based on an average weight of 60 kg for an adult (9) and the following estimated weights of infants by age groups: 0-5 mos., 5 kg; 6-11 mos., 8 kg; 12-23 mos., 11 kg (10).
group 2-65+ yrs. could be low for some, since many individuals from age 2 to maturity will obviously weigh less than 60 kg; thus the daily intake per kg for a 20 kg child, for example, could be higher by a factor of three than the figures indicated in the table.

However, such deviations from the figures in the table must also be considered in respect to total annual use of nutmeg, mace, and their products. The NRC subcommittee has pointed out that its calculations of intakes in most cases are overstated, often by considerable margins. * That this is undoubtedly true in the case of these spice products is borne out by the following calculations: Other NRC data (7) show that the use of nutmeg, mace, and their essential oils for food purposes in the United States in 1970 was 1,785, 970 pounds (811, 805 kg) of nutmeg, 480, 102 pounds (218, 228 kg) of mace, 172, 375 pounds (78, 352 kg) of nutmeg oil, 44, 396 pounds (20, 181 kg) of mace oil, and 12, 067 pounds (5, 485 kg) of mace oleoresin. On the basis of a U. S. population of 200 million, the per capita per day average intake of nutmeg and mace, for example, would be 11 and 3 mg instead of the 336 and 133 mg, respectively, indicated in the foregoing table. Even if all of the nutmeg (4 million pounds) and mace (568, 000 pounds) reported as imported annually into the U. S. (8) were to be used in food, the per capita per day average intake would be only 25 mg of nutmeg and 3. 5 mg of mace. This means that there is not enough of these spices available annually in the U. S. to permit daily human intakes as high as are indicated in the table. In the light of these considerations, therefore, the Select Committee regards the figures given in the table as levels that are highly unlikely to be achieved by any of the age groups.

Another estimate can be made with the data available of the actual essential oil intake in the daily diet. Using the NRC subcommittee survey figures of the poundage of the several products used annually, and assuming that the essential oils of nutmeg and mace

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (7). The Select Committee finds this explanation reasonable, and concurs in the first recommendation in Section XII of the same report, that "In order to conduct a more accurate survey on the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."
are equivalent chemically, and that nutmeg, mace, and mace oleoresin contain about 12 percent of the essential oil, it can be calculated that 225,068 kg of nutmeg oil or equivalent is the total used in the U. S. food supply annually, which amounts to a per capita intake of 3.1 mg per day or 0.05 mg per kg per day for adults.

IV. BIOLOGICAL STUDIES

No information is available concerning the absorption of orally administered nutmeg, mace, or the essential oils derived from them. However, since the major constituents of the essential oils are relatively simple substances, significant absorption from the gastrointestinal tract can be assumed. It is to be noted that several of the reported constituents of nutmeg oil, namely, limonene, linalool, geraniol, and eugenol (4, 5), are included in the Food and Drug Administration's Generally Recognized as Safe list (11) and that all of the reported constituents except safrole, myristicin, methoxy-eugenol, and trans-isoelemicin are included in the GRAS list of the Flavor Extract Manufacturers Association (12).

Some information is available concerning the metabolism of two constituents of these essential oils, myristicin and safrole. Myristicin, of which about 5 percent is present in the essential oil (5), has been considered the psychoactive constituent of nutmeg (13). Safrole, reported to be present to the extent of 4 to 6 percent in East Indian nutmeg oil, but apparently absent from West Indian nutmeg oil (4), is reported to be a weak hepatocarcinogen (14, 15).

The close structural similarity and possible metabolic interrelationship of these two compounds, and several of the others reported to be present in the essential oil of nutmeg, should be noted.

\[ \text{Safrole: } 4\text{-allyl-1,2(methylenedioxy) benzene} \]

\[ \text{CH}_2=\text{CH}-\text{CH}_2\text{CH}=(\text{O})\text{CH}=\text{CH}_2 \]
Myristicin: 4-allyl-1, 2(methylenedioxy)-6-methoxybenzene

\[ \text{CH}_2 = \text{CH}-\text{CH}_2 - \text{OCH}_3 \]

Eugenol: 4-allyl-2-methoxyphenol

\[ \text{CH}_2 = \text{CH}-\text{CH}_2 - \text{OCH}_3 \]

Methoxy eugenol: 4-allyl-2, 6-methoxyphenol

\[ \text{CH}_2 = \text{CH}-\text{CH}_2 - \text{OCH}_3 \]

Trans-isoeleminic: 4-allyl-1, 2, 6-methoxybenzene

\[ \text{CH}_2 = \text{CH}-\text{CH}_2 - \text{OCH}_3 \]

Myristicin labeled with \(^{14}\text{C}\) in the methylenedioxy group, has been administered orally to mice at a dosage of 5 \(\mu\)moles per kg (16). The distribution of radioactivity in the animals was 73 percent as respiratory \(\text{CO}_2\), 15 percent in urinary products, 3 percent in feces, 3 percent in intestine, 1.5 percent in liver, and 6.1 percent in carcass. This work establishes that demethylation occurs to yield a one-carbon fragment and a catechol derivative as the principal metabolic pathway. The relative amounts of minor fractions which are found in the urine probably increase with dosage.

Two nitrogen-containing metabolites of myristicin were obtained after administration of 5 to 20 mg per kg orally or intraperitoneally (17). Of these, 3-piperidyl-1-(3-methoxy-4, 5-methylene-
Dioxyphenyl)-propanone was the principal metabolite found in rat urine while 3-pyrrolidinyl-1-(3-methoxy-4,5-methylenedioxyphenyl)-propanone was the principal metabolite in guinea pig urine. In contrast to safrole, no N,N-dimethylaminoketone derivative was found (17).

The metabolism of methylenedioxy compounds occurs, at least in part, in the liver microsomes mediated by an NADPH-dependent mixed function oxidase. The products are suspected of being competitive inhibitors of the enzymic reaction (16).

Nutmeg exhibits a mild degree of monoamine oxidase inhibitory effect in vivo and in vitro (18). Doses of 0.2 and 1.0 g per kg of nutmeg given to rats and mice produced demonstrable inhibitory effects on monoamine oxidase activity 17 to 24 hours after feeding, as measured by a lowering of the convulsive threshold to intravenous tryptamine. In rats, after tryptamine injection, the monoamine oxidase inhibition caused an increase in the concentration of 5-hydroxytryptamine in the brain (18).

Some investigators have speculated that myristicin can be converted in vivo to the known psychotomimetic agent, 3-methoxy-4,5-methylenedioxyamphetamine, thus accounting for the reported psychoactivity of myristicin (19).

There are no long-term animal feeding studies available to the Committee concerning nutmeg, mace, and their products. Relevant short-term animal studies and studies on man are summarized below.

The following LD₅₀ values for orally administered oil of nutmeg have been reported: rat, 2600 ± 220 mg per kg; mouse, 5620 ± 520 mg per kg; hamster, 6000 ± 230 mg per kg (1). In another report, an oral LD₅₀ value of 3640 mg per kg was indicated for mace oil and 2620 mg per kg for nutmeg oil in the rat (20). There appears to be a difference in toxicity between the East Indian and the West Indian nutmegs. For example, the LD₅₀ for orally administered ground East Indian nutmeg in the rat was found to be 500 mg per kg; for the West Indian nutmeg it was 700 mg per kg. This difference was apparently due to the essential oil fraction since East Indian nutmeg, freed of volatile constituents by steam distillation, had an oral LD₅₀ in the rat of 1720 mg per kg and West Indian nutmeg, 1730 mg per kg (13).

Oral LD₅₀ values in mg per kg for several of the constituents of oil of nutmeg have been reported (21) as follows: safrole 1950 (rat); myristicin 570 (cat); eugenol 500 (rat); isoeugenol 1560 (rat). In another report (20) oral LD₅₀ values found in mg per kg were as
follows: p-cymene 4750 (rat); eugenol 2680 (rat), 3000 (mouse); 2130 (guinea pig); geraniol 3600 (rat); isoeugenol 1410 (guinea pig); isosafrole 1340 (rat); 2470 (mouse); linalool 2790 (rat).

The cat has been found to be particularly susceptible to nutmeg; a 1900 mg per kg oral dose was fatal. Myristicin was lethal to cats at a dosage of 50 mg per kg intraperitoneally (13). The major pathological finding was fatty degeneration and necrosis of the liver. However, the same investigators found that rats survived 10 mg per kg daily doses of myristicin orally for 26 days with no ill effects. Intraperitoneal administration up to 1500 mg per kg produced no liver or kidney damage. Myristicin, 50 to 75 mg per kg by intubation, evoked ataxia and disorientation in monkeys lasting for two or three hours (13).

Historically, nutmeg has been considered as part of folklore, to be useful as a sedative, carminative, antispasmodic, rubefacient, dentifrice, emmenagogue, and abortifacient (22). Single oral doses of 10 to 15 g of ground nutmeg are required to produce acute intoxication in man, while single oral doses of 400 mg of myristicin have not shown toxicity in human volunteers (13). In doses of 5 gm or more, nutmeg produces a characteristic syndrome in man involving stimulation and a feeling of euphoria. However, from one to seven hours after ingestion, symptoms of a burning, midabdominal pain, with nausea accompanied by restlessness, giddiness, and excitement may occur (22-26). During the next ten hours, drowsiness progressing to a stupor may develop. If aroused, the patient is delirious. The reported physical findings include hypotension, cyanosis, and shock. Tachycardia, rapid respiration, dilatation of the pupils, evidence of transient toxic effects on the kidney, loss of peripheral reflexes and fever may occur. These symptoms subside quickly and, as a rule, recovery is complete within 24 to 48 hours. Only one fatal outcome is recorded in which an eight-year old boy ate two whole nutmegs, became comatose, and died less than 24 hours later (19).

The psychological consequences of ingestion of nutmeg vary from heightened awareness of color and sound to full hallucinogenic experiences (27). Nutmeg which had been freed of volatile oils still produced abdominal discomfort but no psychological effects (13). Although the psychopharmacological activity of the oil has been attributed to its myristicin content (13), it was demonstrated in 1963 that the so-called myristicin fraction is actually a mixture of myristicin with perhaps 25 percent of similar compounds, principally elemicin and methyl eugenol (28). Comparative tests in animals and humans suggest that pure myristicin is not as effective as whole
nutmeg in producing psychotropic effects. In spite of claims for mild cerebral stimulation produced by nutmeg, other studies involving 6 g doses of nutmeg were interpreted as showing that nutmeg has no psychological effect (29). It is possible that some individuals are more susceptible than others.

Teratologic studies of oil of nutmeg in mice, rats, and hamsters have been reported (30). Oral administration of up to 560 mg per kg in mice (day 6 through 15 of gestation), up to 260 mg per kg in rats (day 6 through 15) and up to 600 mg per kg in hamsters (day 6 through 10), had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

No mutagenic investigations of nutmeg and related products have been reported. However, there are reports indicating that one constituent of nutmeg oil, safrole, is a weak hepatocarcinogen (14, 15).

V. OPINION

The toxic and alleged psychogenic effects of nutmeg and some of its pharmacologically active constituents such as myristicin, elemicine, and safrole are clearly manifested only at doses vastly greater than the usual levels of intake in the human diet. Historically the toxic effects of massive doses (10 or more grams) of nutmeg when taken as an emmenagogue, abortifacient, or hallucinogen, although distressing, are transient and rarely fatal. However, it is to be recognized that as much as 6 percent of safrole, a weak hepatocarcinogen, is reported to be present in the essential oil of East Indian nutmeg, the major U. S. source. In 1960 FDA prohibited the use of safrole in food. Moreover, the closely related methoxy derivative of safrole, myristicin, is also present in some nutmeg oils in amounts approximating 5 percent.

Our calculations (see Section III of this report) indicate that the intake level of nutmeg oil and its equivalent in the form of nutmeg and mace, based on the total imports available annually for use in food in the U. S., is of the order of 0.05 mg per kg per day for adults. Assuming a maximum content of 6 percent safrole in the oil, possible daily intake of safrole would be about 4 μg per kg per day.
for an adult and about 5 times this amount for a child 6-11 months of age, who, according to the NRC survey, consumes the largest amounts of nutmeg products per kg of body weight. If myristicin is capable of conversion to safrole in vivo, intakes could be about double these amounts. All of these intake estimates would be low, of course, for any in the population who are particularly heavy consumers of food products containing nutmeg.

While there is no evidence that such levels of consumption are capable of eliciting adverse effects, it is the opinion of the Select Committee that the safrole and myristicin content of nutmeg products, and perhaps the content of such related constituents as elemicin, eugenol, and methoxyeugenol, should be further investigated to determine the range of content in both the East and West Indian products and to investigate or reinvestigate their possible mutagenic, teratogenic, and carcinogenic effects.

The Select Committee has weighed the foregoing and concludes that:

While no evidence in the available information on nutmeg, mace, or their essential oils demonstrates a hazard to the public when they are used in the manner now practiced, uncertainties exist requiring that additional studies should be conducted.
VII. REFERENCES CITED


VII. SCIENTISTS CONTRIBUTING TO THIS REPORT

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