EVALUATION OF THE HEALTH ASPECTS OF OIL OF RUE

AS A FOOD INGREDIENT

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.)

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Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
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 competence 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. Jelleff Carr, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

Under terms of FDA Contract 72-85, FASEB'S Life Sciences Research Office was requested to evaluate the health aspects of using oil of rue as a food ingredient, 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 available as of February 1973. Oil of rue is one of the food substances that has been generally recognized as safe (GRAS) under the provisions of the Code of Federal Regulations (21 CFR 121.101, revised January 1, 1972).

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 a significant risk to the public health, and realizes that a decision, based on reasoned judgment, is expected even in instances where the available information is qualitatively or quantitatively limited. The Committee is also aware that biological testing, like all of science, is dynamic. Accordingly, the Committee's decisions, 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 constantly being evolved. These decisions 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 oil of rue and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of oil of rue under the Federal Food, Drug and Cosmetic Act.

II. BACKGROUND INFORMATION

Oil of rue is obtained by steam distillation of fresh blossoming plants of several species of Ruta. The yellow to yellow-amber oil contains primarily (80 to 90 percent or more) methyl nonyl ketone and methyl heptyl ketone. It also contains cineole, limonene, methyl salicylate, pinene, and other compounds less well identified. Spain is the most important commercial source (1, 2).

The Food Chemicals Codex specifies that food grade oil of rue should contain not less than 90 percent ketones, calculated as methyl nonyl ketone, but no other organic chemical specifications are given (3).

Oil of rue is used as a flavoring agent in amounts ranging from 8.6 ppm to 0.5 ppm in the following categories of foods arranged in decreasing order of content: baked goods, soft candy, frozen dairy desserts and mixes, non-alcoholic beverages, alcoholic beverages, gelatins, condiments, and hard candy (4).

It is reported that in 1970, 3 pounds of rue which according to Guenther (2) would not contain more than 0.03 pounds of the oil, and 90 pounds of oil of rue were used in foods in the United States (4). The Select Committee has no information to indicate the year of first use in the U. S. or whether the total poundage used in food or the content of the above food categories has changed significantly in recent years, or is likely to change in the future.

III. CONSUMER EXPOSURE

A comprehensive survey by a National Research Council subcommittee has provided information on the possible daily human intake of oil of rue in the total diet, as shown in the following table for individuals in various age groups (4). The Select Committee has converted these figures to possible intakes per kilogram of body weight.
<table>
<thead>
<tr>
<th>Age group</th>
<th>Possible daily intake</th>
<th></th>
<th>Per kilogram of body weight*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Average</td>
<td>Maximum</td>
</tr>
<tr>
<td></td>
<td>mg</td>
<td>mg</td>
<td>micrograms</td>
</tr>
<tr>
<td>0-5 mos.</td>
<td>0.03</td>
<td>0.06</td>
<td>6</td>
</tr>
<tr>
<td>6-11 mos.</td>
<td>0.25</td>
<td>0.62</td>
<td>31</td>
</tr>
<tr>
<td>12-23 mos.</td>
<td>0.51</td>
<td>1.06</td>
<td>46</td>
</tr>
<tr>
<td>2-65+ yrs.</td>
<td>1.20</td>
<td>2.28</td>
<td>20</td>
</tr>
</tbody>
</table>

*Calculations based on an average weight of 60 kg for an adult (5) and the following estimated weights of infants by age groups: 0-5 mos., 5 kg; 6-11 mos., 8 kg; and 12-23 mos., 11 kg (6).

It is recognized that the figures calculated for the daily intake of rue per kg of body weight in the age group 2-65+ years could be underestimated, since the majority of individuals from age 2 to maturity will probably weigh less than 60 kg. Thus the daily intake of oil of rue for a 20 kg child could be threefold the figures indicated in the foregoing table.

However, such deviations from the figures in the table must also be considered in respect to total quantity of oil of rue used in foods. The NRC subcommittee has pointed out that its calculations of intakes in most cases are overstated, often by considerable margins.* That human intakes are undoubtedly overstated in the case of oil of rue is

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*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (4). 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."
borne out by the following calculation: The NRC subcommittee has
provided data to indicate that 90 pounds (40.9 kg) of oil of rue and
insignificant amounts of rue itself, were used in foods in the United
States in 1970. This figure is reported to comprise between 60 and
70 percent of the total poundage used in food. On the basis of 60 percent
adjusted to 100 percent (150 lbs. or 68.2 kg), and a U. S. population
of 200 million, the average intake would be less than 1 microgram per
person per day rather than the 1.2 mg indicated in the foregoing table.
No data on annual imports of rue or oil of rue are available but Spain,
the major commercial source, was reported to produce 3 metric tons in
1948 (2). Even if all of this were imported and used in food in the U. S.
the average intake would be of the order of only 0.04 mg per person per
day.

On the basis of these considerations, therefore, the Select Commit-
tee regards the figures in the table as levels that are not likely to be
achieved by any of the age groups.

IV. BIOLOGICAL STUDIES

Data on the biological effects of oil of rue administered orally to
either animals or man are extremely limited.

The oral LD₅₀ for mice of samples of oil of rue prepared by steam
distillation of plants collected by the investigator has been reported
to be 2,070 mg per kg; the LD₅₀ of methyl-n-nonyl ketone was reported
to be 3,880 mg per kg (7). No studies have been found on the absorption,
disposition, biotransformation, and excretion of oil of rue, nor are
there any data on the possible teratogenic, mutagenic, or carcinogenic
properties of the oil when administered orally.

Guinea pigs and rabbits have been administered relatively large
doses of oil of rue by oral intubation. The doses varied from "250
to 300 drops for guinea pigs weighing 250 to 300 g and from 500 to 600
drops for rabbits weighing 2,000 to 2,500 g" (8). Of ten animals, three
died within seven to nine days, four were alive after twenty days and
were sacrificed, and three (all pregnant) did not seem to "suffer further
from their intoxication." The animals, variously, showed evidence of
dyspnea, diarrhea, body weight loss, fatty livers, and nephritis, with
more pronounced pathological changes reported to occur in fetal than in
maternal tissues. The investigators observed that "the experimental
and histological results do not match the quantities ingested."

When two pregnant guinea pigs were fed a relatively large dose but unknown quantity, i.e. 12 drops of oil of rue, both animals aborted and direct analysis of fetal tissues indicated that oil of rue penetrated the placenta and was toxic to fetal tissues (9). Infusions of the rue plant were also reported to cause sharp contractions of the isolated guinea pig uterus (9).

The oil rapidly penetrates the abdominal skin of male mice (10). Direct application of the oil to the skin persistently or rubbing leaves of the plant on the skin can produce redness, burning, and vesication (11). Large oral doses are reported to cause violent gastric pain, confusion, convulsive twitching, and in pregnant women, abortion (11). There are two reports in the literature indicating oil of rue, together with other plant products, can be used to produce abortion (9, 11); neither report provides supportive data.

In most of the work referred to above it is not possible to quantify the doses used but it would appear that the toxic manifestations reported were elicited by amounts of oil of rue that are orders of magnitude greater than those now consumed in food in the U. S.

V. OPINION

The data available indicate that the quantity of oil of rue in the diet is minute, probably as little as one microgram per person per day. Adverse effects due to oil of rue from long-term exposure at such a low level in the human diet are not evident in the meager data now available.

It is to be noted, however, that oil of rue is a complex of organic substances only a few of which have been identified. Chemical identification of all the substances in the oil could be accomplished with present analytical techniques and would provide positive assurance that oil of rue does not contain components known to be toxic. Moreover, the evidence that oil of rue is absorbed, can pass the placenta and is toxic to fetal tissues at relatively high doses, suggests the desirability, in due course, of conducting teratological and fetal toxicity tests at oral dosages equivalent to the present very low levels of consumption. The Select Committee recognizes that there is little incentive to develop this kind of information for a substance that is used in the U. S. to the extent of less than 100 pounds per year.
The Select Committee has weighed the foregoing and concludes that:

There is no evidence in the available information on oil of rue that demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced.
VI. REFERENCES CITED


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Report submitted by:

May 31, 1973
Date

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