SOON AFTER the enactment of the Food Additives Amendment of 1958 the Flavor and Extract Manufacturers’ Association (FEMA) initiated a program of gathering all available data on the identity, production, and usage of natural and flavoring substances for safety evaluation by a panel of “experts qualified by scientific training and experience” as specified in the statute. This year marks the 25th anniversary of the organization by the senior author of an expert panel commissioned to review and evaluate the vast amount of data assembled by experienced technologists in the food and flavor industries. In 1965, the first comprehensive paper was published listing over 1,100 GRAS substances and their use levels in at least 10 major categories of food.

With the passage of years, there have resulted changes in the composition of the expert panel, as described below, as a result of the “normal processes of attrition.” However, the panel’s efforts have kept pace both with the increasing demands of safety evaluation and with the increasing number of flavoring substances developed by industrial scientists. These advances have resulted in large part from replication of newly identified flavor compounds in natural foods through the application of more sophisticated analytical technology and instrumentation.

The panel’s conclusions must always be unanimous and are based on the judgement that they could reasonably be expected to be shared by other qualified scientists equally informed of the underlying scientific and technical data. The policy of publishing its conclusions was adopted from the beginning, as recommended by the Food and Drug Administration (FDA).

The growth in the number of substances the panel has declared to be GRAS, up to the present, is illustrated in Figure 1, based on the series of 14 GRAS lists published in this journal from 1960 to date under the title “Recent Progress in the Consideration of Flavoring Substances under the Food Additives Amendment” and listed in the References section.

Criteria for GRAS Consideration

As previously described (Oser and Hall, 1977) the criteria for the GRAS decisions of the expert panel included, inter alia, “experience in common use in food” taking into account naturally occurring as well as added substances and, where indicated, “scientific procedures,” i.e. chemical structure and analogies, metabolic fate, and toxicological tests when necessary.

Among the latter, acute oral toxicity in rats as measured in terms of oral LD_{50} values were frequently considered. FEMA and the expert panel have never attached much probative value to these crude, but widely used estimates of acute toxicity. However, such tests did serve to (1) support structural analogy among closely related compounds, and, in other cases, (2) provide range-finding data for longer-term screening tests. Because of its limitations, the conventional LD_{50} has gradually been abandoned by many scientists, including those of the FDA, in favor of more informative screening tests for oral toxicity. The expert panel has therefore been studying an abbreviated version of a screening test based on dietary inclusion of the test substance for a short period, but including more observations than simply mortality.

Studies are underway based principally on the published experience of Weil et al. (1963, 1969), in which estimates of toxicity are predicted from dosage periods as short as 7 or 14 days. They will be reported later when sufficient data are accumulated to justify the added time and expense of these routine tests. It is the present opinion of the panel that short-term tests, which include body weight, food efficiency, and limited behavioral and pathological observations, will provide substantially more significant data than the simplistic LD_{50} type of tests.

It should be mentioned in this connection that the classification for priority-setting, based on natural occurrence, chemical structure, and estimated maximum levels of exposure as proposed by Cramer, Ford, and Hall (1978), has played a useful role in predicting...
potential degrees of risk in the use of the majority of flavoring substances.

**Basic Research**

FEMA continues to sponsor research on the safety of individual and structurally related classes of flavoring substances. Recently such work has resulted in publications on cinnamyl anthranilate (Anthony et al., 1983) as well as trans-anethole (Caldwell et al., 1983; Sangster et al., 1984b; Sangster et al., 1984a) p-propylanisole (Sangster et al., 1983), eugenol (Caldwell et al., 1985; Sutton et al., 1985) and benzyl acetate (Caldwell and Chidgey, 1985). Work continues on the metabolism of substituted propyl benzene substances, cinnamyl compounds, and benzyl acetate. The interaction of \( \alpha, \beta \)-unsaturated ketones with DNA model systems is currently being investigated.

**Panel Membership**

Previous issues of the FEMA series of GRAS lists have indicated the membership of the expert panels that participated in the decisions reported therein. The panel regretfully reports the retirement, since the publication of GRAS 13 in 1984, of Dr. David W. Fassett, who was a member of the original panel established in 1960. The panelists who participated in the present GRAS 14 determinations and their affiliations are: Lauren A. Woods, Ph.D., M.D., Professor Emeritus, Medical College of Virginia, Virginia Commonwealth University; John Doull, M.D., Ph.D., Professor, University of Kansas Medical School; Paul M. Newberne, D.V.M., Ph.D., Professor Emeritus, Massachusetts Institute of Technology. Carrol S. Weil, M.A., Carrol S. Weil, Inc.; Robert L. Smith, Ph.D., D.Sc., Professor, St. Mary's Hospital, University of London; Bernard M. Wagner, M.D., Professor, Columbia University and Director of Laboratories, Overlook Hospital; Philip S. Portoghese, Ph.D., Professor, University of Minnesota.

Drs. Oser and Woods served as co-chairmen, Dr. Richard A. Ford as liaison with The Research Institute for Fragrance Materials, and Dr. Bruce K. Bernard as executive secretary during the proceedings that led to the current additions to the lists of GRAS substances.

**Notes to the Reader**

Readers should be aware of a typographical error occurring in GRAS 13 (Oser et al., 1984, p. 72 and 89). The correct chemical name for the substance identified by FEMA number 3735 is 2,2,6-trimethyl-6-vinyltetrahydropyran, not 2,6,6-trimethyl-6-vinyltetrahydropyran as reported therein: Scientific Literature Reviews (SLRs) containing the revisions associated with the additions found in GRAS 13 are available through the
National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161. The location of the individual GRAS substances, including those found in GRAS 13, in the 69 SLS can be found in "Flavor and Fragrance Materials 1985" (Bernard, 1985).

Table I of this report is an alphabetical cross reference list. Substances with cis-trans stereochemical designations have also been named according to the more recent and less ambiguous IUPAC (E)-(Z) nomenclature system.

References


Oser, B.L. and Ford, R.A. 1984. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 8. GRAS substances. Food Technol. 28(9): 76.


— "Primary Names and Synonyms Alphabetical Cross Reference List" is on page 114
— "GRAS Flavoring Ingredients and Usage Levels" are on pp. 116-117
### GRAS 14—Primary Names and Synonyms

**Alphabetical Cross Reference List**

<table>
<thead>
<tr>
<th>FEMA No.</th>
<th>Substance</th>
<th>FEMA No.</th>
<th>Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>m-Anisaldehyde, 4-hydroxy, isobutyrate  (see Vanillin isobutyrate, no. 3754)</td>
<td>m-Anisaldehyde, 4-hydroxy, 2-methylpropionate  (see Vanillin isobutyrate, no. 3754)</td>
<td>(R)-(−) Massoilactone  (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)</td>
<td>(−)-p-Menth-3-yl lactate  (see p-Menth-3-yl lactate, no. 3748)</td>
</tr>
<tr>
<td>3740 ANISYL PHENYLACETATE  Anisyl α-toluic acid  (see Anisyl phenylacetate, no. 3740)</td>
<td>3,4-Methoxy-4-isobutyrylbenzaldehyde  (see Vanillin isobutyrate, no. 3754)</td>
<td>3-Methylphenyl 2-methylpropanoate  (see α-Tolyl isobutyrate, no. 3753)</td>
<td>cis &amp; trans-2-Methyl-2-vinyl-5[2-hydroxy-2-propyl]tetrahydrofuran  (see Linalool oxide, no. 3746)</td>
</tr>
<tr>
<td>3741 α-CAMPHOLENIC ALCOHOL  α-Campholenol  (see α-Campholenic alcohol, no. 3741)</td>
<td>1-Ethoxyethyl ether of potassium lactate  (see Potassium 2-(1'-ethoxy)ethoxypropanoate, no. 3752)</td>
<td>3749 cis-5-OCTENAL  (2E)-5-Octenal  (see cis-5-Octenal, no. 3749)</td>
<td>3750 OSMANTHUS ABSOLUTE  Osmanthus fragrans lour.  (see Osmanthus absolute, no. 3750)</td>
</tr>
<tr>
<td>(−)-2-Decenoic acid, 5-hydroxy, δ-lactone  (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)</td>
<td>1-Ethoxyethyl ether of potassium lactate  (see Potassium 2-(1'-ethoxy)ethoxypropanoate, no. 3752)</td>
<td>Osmanthus fragrans  (see Osmanthus absolute, no. 3750)</td>
<td>cis-5-[2-Pentenyl]pentanolide  (see 5-Hydroxy-7-decenoic acid δ-lactone, no. 3745)</td>
</tr>
<tr>
<td>3742 5- and 6-DECENOIC ACID</td>
<td>1-Ethoxyethyl ether of potassium lactate  (see Potassium 2-(1'-ethoxy)ethoxypropanoate, no. 3752)</td>
<td>Phenylicetic acid, p-methoxybenzyl ester  (see Anisyl phenylacetate, no. 3740)</td>
<td>5-Hydroxy-7-decenoic acid δ-lactone  (see 5-Hydroxy-7-decenoic acid δ-lactone, no. 3745)</td>
</tr>
<tr>
<td>5,6-Dihydro-6-pentyl-2H-pyran-2-one  (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)</td>
<td>5-Hydroxy-2-decenoic acid δ-lactone  (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)</td>
<td>3751 2-(3-PHENYLPROPYL)PYRIDINE</td>
<td>3752 POTASSIUM 2-(1'-ETHOXY)ETHOXYPROPA NOATE  Potassium α-(1'-ethoxyethyl)lactate  (see Potassium 2-(1'-ethoxyethoxypropanoate, no. 3752)</td>
</tr>
<tr>
<td>(R)-5,6-Dihydro-6-pentyl-2H-pyran-2-one  (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)</td>
<td>4-Formyl-2-methoxyphenyl 2-methylpropanoate  (see Vanillin isobutyrate, no. 3754)</td>
<td>Propanoic acid, 2-hydroxy, 5-methyl-2(1-methylethyl)cyclohexyl ester [1R-{1R(R*)}, 2β, 5α]  (see α-Campholenic alcohol, no. 3748)</td>
<td>Propanoic acid, 2-methyl, 4-formyl-2-methoxyphenyl ester  (see Vanillin isobutyrate, no. 3754)</td>
</tr>
<tr>
<td>(±)-5,6-Dihydro-6-pentyl-2H-pyran-2-one  (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)</td>
<td>1-Ethoxyethyl ether of potassium lactate  (see Potassium 2-(1'-ethoxy)ethoxypropanoate, no. 3752)</td>
<td>Propanoic acid, 2-hydroxy, 5-methyl-2(1-methylethyl)cyclohexyl ester  (see α-Campholenic alcohol, no. 3748)</td>
<td>3753 α-TOLYL ISOBUTYRATE  α-Tolyl 2-methylpropanoate  (see α-Tolyl isobutyrate, no. 3753)</td>
</tr>
<tr>
<td>1-Ethoxyethyl ether of potassium lactate  (see Potassium 2-(1'-ethoxy)ethoxypropanoate, no. 3752)</td>
<td>4-Formyl-2-methoxyphenyl 2-methylpropanoate  (see Vanillin isobutyrate, no. 3754)</td>
<td>cis-5-[2-Pentenyl]pentanolide  (see 5-Hydroxy-7-decenoic acid δ-lactone, no. 3745)</td>
<td>3,2,3-Trimethyl-3-cyclopentene-1-ethanol  (see α-Campholenic alcohol, no. 3741)</td>
</tr>
<tr>
<td>3744 5-HYDROXY-2-DECENOIC ACID δ-LACTONE</td>
<td>4-Formyl-2-methoxyphenyl 2-methylpropanoate  (see Vanillin isobutyrate, no. 3754)</td>
<td>cis-5-[2-Pentenyl]pentanolide  (see 5-Hydroxy-7-decenoic acid δ-lactone, no. 3745)</td>
<td>3754 VANILLIN ISOBUTYRATE  Vanillyl isobutyrate  (see Vanillin isobutyrate, no. 3754)</td>
</tr>
<tr>
<td>3745 5-HYDROXY-7-DECENOIC ACID δ-LACTONE  α-Hydroxypropanoic acid, 5-methyl-2(1-methylethyl)cyclohexyl ester  (see α-Methyl lactate, no. 3748)</td>
<td>2-(2,3,4-Trimethylcyclohex-2-en-1-yl)ethanol  (see α-Campholenic alcohol, no. 3741)</td>
<td>cis &amp; trans-2-Vinyl-2-methyl-5-(1'-hydroxy-1'-methyl)tetrahydrofuran  (see Linalool oxide, no. 3746)</td>
<td>cis &amp; trans-2-Vinyl-2-methyl-5-(1'-hydroxy-1'-methyl)tetrahydrofuran  (see Linalool oxide, no. 3746)</td>
</tr>
<tr>
<td>4-Formyl-2-methoxyphenyl 2-methylpropanoate  (see Vanillin isobutyrate, no. 3754)</td>
<td>2-(2,3,4-Trimethylcyclohex-2-en-1-yl)ethanol  (see α-Campholenic alcohol, no. 3741)</td>
<td>cis &amp; trans-2-Vinyl-2-methyl-5-(1'-hydroxy-1'-methyl)tetrahydrofuran  (see Linalool oxide, no. 3746)</td>
<td>cis &amp; trans-2-Vinyl-2-methyl-5-(1'-hydroxy-1'-methyl)tetrahydrofuran  (see Linalool oxide, no. 3746)</td>
</tr>
</tbody>
</table>

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*aPrimary names, in capital letters, and synonyms, in lower case, are listed alphabetically. Synonyms are followed by reference to the primary name and FEMA number.*
<table>
<thead>
<tr>
<th>Substance</th>
<th>Baked Goods</th>
<th>Frozen Dairy</th>
<th>Meat Products</th>
<th>Soft Candy</th>
<th>Gelatins &amp; Puddings</th>
<th>Soups</th>
<th>Snack Foods</th>
<th>Nonalcoholic Beverages</th>
<th>Alcoholic Beverages</th>
<th>Gravies</th>
<th>Other Uses</th>
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<tr>
<td>3740</td>
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<td>6.16</td>
<td>—</td>
<td>10.8</td>
<td>6.16</td>
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<td>3741</td>
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<td>2.0</td>
<td>—</td>
<td></td>
<td>2.0</td>
<td>1.5</td>
<td></td>
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</table>

**3742**

5- and 6-Decenoic acid

**3743**

5-Hydroxy-2-decenoic acid 6-lactone

**3744**

2,5-Diethyltetrahydrofuran

**3745**

5-Hydroxy-7-decenoic acid 6-lactone

**3746**

Linalool oxide

**3747**

Massola bark oil

**3748**

α-Menthyl lactate

**3749**

cis-5-Octenal

14. GRAS Substances (continued)
<table>
<thead>
<tr>
<th>Substance</th>
<th>Baked Goods</th>
<th>Frozen Dairy</th>
<th>Meat Products</th>
<th>Soft Candy</th>
<th>Gelatins &amp; Puddings</th>
<th>Soups</th>
<th>Snack Foods</th>
<th>Nonalcoholic Beverages</th>
<th>Alcoholic Beverages</th>
<th>Gravies</th>
<th>Other Uses</th>
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<tr>
<td>3479 cis-5-Octenal (continued)</td>
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<td></td>
<td></td>
<td></td>
<td>Confectionary and frosting—5.0; Jams and jellies—5.0; Sweet sauce—5.0; Nut products—0.5; Reconstituted vegetables—1.0; Hard candy—10.0; Chewing gum—25.0</td>
</tr>
<tr>
<td>3750 Osmanthus absolute</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Milk products—0.2; Fruit ices—0.15; Jams and jellies—0.3; Hard candy—0.4; Chewing gum—2.0</td>
</tr>
<tr>
<td>2-(3-Phenylpropyl) pyridine</td>
<td>2.0</td>
<td>0.3</td>
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<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
<td>1.0</td>
<td></td>
<td>2.0</td>
<td>Breakfast cereals—2.0; Processed vegetables—1.0; Condiments and relishes—2.0; Reconstituted vegetables—1.0; Household seasonings and flavors—2.0</td>
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<tr>
<td>3752 Potassium 2-(1'-ethoxy) ethoxypropanoate</td>
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<td>100</td>
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<td></td>
<td>150</td>
<td>400</td>
<td></td>
<td></td>
<td>100</td>
<td>150</td>
<td>Milk products—100; Processed fruit—100; Fruit ices—100; Condiments and relishes—400; Confectionary and frosting—150; Jams and jellies—400; Sweet sauce—400; Nut products—100; Imitation dairy products—150; Hard Candy—150; Chewing gum—1,500; Household seasonings and flavors—400</td>
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<tr>
<td>3753 o-Tolyl isobutyrate</td>
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<td>Breakfast cereals—10.0; Confectionary and frosting—15.0; Imitation dairy products—15.0; Chewing gum—20.0</td>
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<td>3754 Vanillin isobutyrate</td>
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<td>Breakfast cereals—10.0; Confectionary and frosting—15.0; Imitation dairy products—15.0; Chewing gum—20.0</td>
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