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The 18th publication by the Flavor and Extract Manufacturers' Association's Expert Panel on recent progress in the consideration of flavoring ingredients generally recognized as safe under the Food Additives Amendment

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For more than 35 years, the Flavor and Extract Manufacturers' Association of the United States (FEMA) has sponsored the activities of the FEMA Expert Panel. The Expert Panel has conducted an independent program to review the safety of flavor ingredients under the authority of Section 201(s) of the Federal Food, Drug, and Cosmetic Act, a provision commonly known as the GRAS ("generally recognized as safe") provision (Hallagan and Hall, 1995).

The GRAS provision exempts, from the food additive provisions of the Act, a substance that can be "generally recognized, by experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures . . . to be safe under the conditions of intended use." In 1960, the FEMA Expert Panel was established as an independent panel of toxicologists, biochemists, and other scientists to evaluate flavor ingredients for potential GRAS status (Oser and Ford, 1991).

The majority of flavoring substances that are recognized as FEMA GRAS were first reviewed by the Expert Panel prior to 1965. The first compilation of FEMA GRAS flavoring substances was published in 1965 and included 1,124 substances (Hall and Oser, 1965). Twenty years later, the "FEMA GRAS list" had grown to 1,740 flavoring substances (Hall and Oser, 1970; Oser and Ford, 1973a, 1973b, 1974, 1975, 1977, 1978, 1979; Oser and Hall, 1972; Oser et al., 1984, 1985). During this time, the first comprehensive and systematic scientific literature reviews (SLRs) of flavoring substances were completed by FEMA under a contract with the Food and Drug Administration. These SLRs served as the basis for a comprehensive reassessment by the Expert Panel of the GRAS status of all existing FEMA GRAS flavoring substances. The first comprehensive reassessment and affirmation of GRAS status, known as "GRAS affirmation" or "GRASa" was completed in 1985.

During the ten years between 1985 and 1995, 75 flavoring substances were determined to be GRAS by the FEMA Expert Panel and described in a series of publications in *Food Technology* (Burdock et al., 1990; Smith and Ford, 1993; Smith et al., 1996a, b). The modest number of new GRAS flavoring substances during this period suggested that there might be a limit to the number of substances serving as useful, economically viable flavoring substances.

In 1994, the Expert Panel initiated a second comprehensive reassessment

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program to review and evaluate scientific data related to the FEMA GRAS status of flavoring substances. This program is known as "GRAS reaffirmation" or "GRASr" and should be completed by 2005. As part of the GRASr program, the Expert Panel is publishing the key scientific data on which GRAS decisions are based. GRAS assessments of groups of structurally related flavoring substances (Adams et al., 1996, 1998a) and important individual substances (Adams et al., 1997, 1998b) are scheduled to appear in the peer-reviewed literature at regular intervals.

Beginning in 1996, a significant increase occurred in the number of applications for new flavoring substances to be considered for GRAS status. This is the 18th GRAS publication by the FEMA Expert Panel; it includes the results of the Expert Panel's review of 90 new flavoring substances (Tables 1 and 2 on pages 79–91) during 1997 and 1998. In addition, the Expert Panel determined that new use levels and food categories for eight flavoring substances previously considered GRAS are consistent with their GRAS status (Table 3 on page 92). In this publication, the Expert Panel also corrects synonyms for two flavoring substances currently recognized as GRAS by the Expert Panel (FEMA Nos. 2806 and 3141), and clarifies the official name of one other FEMA GRAS flavoring substance (FEMA No. 3104). As with previous reports, this publication also describes the results of other recent FEMA Expert Panel activities.

Recent Developments in the Flavor Industry

This publication includes 90 new GRAS flavoring substances, the most to be included in a FEMA GRAS publication since 1970 (GRAS 4). This increase suggests that the flavor industry continues to evolve to meet consumer demands, and to address the dynamic nature of business in the global marketplace. The past five years have seen the rapidly increasing globalization of the American flavor industry as its customers have quickly moved to capitalize on business opportunities around the world.

One consequence of increasing globalization is the corresponding increase in global regulation. The predominant trend in global regulation is the development of open positive lists of substances, including flavoring substances. An open positive list contains substances that have been thoroughly evaluated and regarded as safe under conditions of intended use in food. The long-standing GRAS program established and maintained by the FEMA Expert Panel remains the primary avenue for the creation of a global, open positive list of flavoring substances. It is not surprising that members of FEMA may identify substances in use outside of the United States and seek to obtain FEMA GRAS status for those substances through an evaluation by the FEMA Expert Panel.

Therefore, it is likely that the recent increase in GRAS applications is the result of a rapidly changing global regulatory environment. For example, the European Union is moving toward the creation of an open positive list of flavoring substances. Not unexpectedly, it is encountering similar problems to those encountered by FDA after the enactment of the Food Additives Amendments in 1958, i.e., how to evaluate the safety of a very large number of flavoring substances, the vast majority of which are used at very low levels in food and have less than a full complement of toxicology and metabolism data. By obtaining FEMA GRAS status, members of the global flavor industry can be assured that substances in use in Europe have been evaluated and recognized as GRAS for their intended use as flavoring substances in the U.S.

An added benefit is that scientific data relevant to the safety evaluations are maintained and periodically updated in the extensive FEMA database on flavoring substances. Once a substance is granted FEMA GRAS status, the data supporting the safety of the substance become available for use by other groups performing safety assessments in a global regulatory environment.

Safety Evaluation of Natural Complexes

The FEMA Expert Panel is using a new paradigm for the safety evaluation of natural flavoring complexes. This novel approach, called the naturals paradigm, will be used in the safety evaluation of new natural complexes and the more than 300 natural complexes currently recognized as GRAS for use as flavoring substances. Many of the 300 natural complexes have often been assumed to be safe by virtue of their long history of safe use in food. However, the naturals paradigm is a flexible procedure to aid in the safety evaluation of novel and recognized natural complexes under different conditions of use as flavoring substances. The procedure was initially developed by a subcommittee chaired by Nancy Higley and composed of Expert Panel members Richard Hall, Richard Ford, and Timothy Adams.

The naturals paradigm is a procedure that prioritizes constituents according to their relative intake from use of the natural complex as a flavoring substance. Additionally, it prioritizes constituents according to chemical structure (Cramer et al., 1978; Munro et al., 1996). The procedure ultimately focuses on those constituents that, because of their structure and intake, may pose some significant risk from consumption of the natural complex. A detailed analysis of scientific data relevant to the safety of those constituents is then performed as part of the overall safety evaluation of the natural complex. Key elements used by the Expert Panel to evaluate chemically defined flavoring substances include exposure, structural analogy, metabolism, pharmacokinetics, and toxicology (Adams et al., 1996, 1997; Woods and Doull, 1991; Oser and Ford, 1991; Oser and Hall, 1977). It is at this point in the evaluation process that the professional judgment and scientific expertise of the Expert Panel play a key role in the safety evaluation of a natural complex.

The paradigm begins with a review of available data on the history of dietary use of the natural complex. If there is adequate evidence of safe, long-term use of

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the natural complex in the diet, the safety evaluation is straightforward. If no information is available on the history of use or dietary use has changed significantly, the paradigm is used to evaluate the natural complex. The constituents of the natural complexes are identified and prioritized according to decreasing level of intake resulting from consumption of the natural complex. Intake is determined from the highest concentrations of each constituent from different commercial sources of the natural complex and intake of that natural complex based on reported annual volumes of use as a flavoring substance (NAS, 1987).

For instance, commercially available distilled lemon oil of different geographical origins has been analyzed for 17 common constituents (Srinivas, 1986). The lowest reported concentration of the major constituent limonene was reported to be 65% in Italian lemon oil, while the highest concentration was 71% in lemon oil from Florida. Based on the highest reported concentration (71%) and the reported annual volume of 1.5 million kg of lemon oil (NAS, 1987), the daily *per capita* intake of limonene from lemon oil is estimated to be 18,500–20,200 mg/person/day. The intake was calculated as follows:

$$\frac{(\text{annual volume in kg})(1 \times 10^9\ \mu\text{g/kg})}{(\text{population})(0.6)(365\ \text{days})}\ (\%\ \text{limonene})$$

where population was 240×10^6 for the U.S. in 1987 and 0.6 represents the assumption that only 60% of the flavor volume was reported in the survey (NAS, 1987).

Studies on the concentration of 33 constituents of lemon oil isolated at different harvesting times from different locations within the same province in Sicily illustrate the sheer volume of analytical data available for lemon oil and other important natural complexes (Licandro et al., 1987). Recent analyses performed with advanced separation technologies have identified more constituents—51 constituents of lemon oil from California have been identified and quantified in the range from 0.01 to 200 ppm (Chamblee et al., 1991). The quantification of extremely low concentrations of constituents such as the terpenoid ether 1,8-cineole (1.9 ppm, 0.00019%) in lemon oil provides assurance that essentially all constituents of widely used natural complexes have been identified.

In the next step, constituents are assigned to one of three structural classes based on toxic potential (Cramer et al., 1978). Class I substances have structures and related data suggesting a low order of oral toxicity. Class II substances have structures that are clearly less innocuous than those of Class I, but do not offer the basis of a positive indication of toxicity. Class III substances have structures that permit no strong initial presumption of safety or that may even suggest significant toxicity (e.g., epoxide functional group or unsubstituted heteroaromatic substance). For instance, the simple aliphatic terpene hydrocarbon limonene is assigned to structural class I, while the terpenoid cyclic ether 1,8-cineole is assigned to class III.

The toxic potential of each of the three structural classes has been quantified (Munro et al., 1996). An extensive toxicity database has been compiled for substances in each structural class, and conservative "no observable effect" levels (5th-percentile NOELs) have been determined for each class. The 5th-percentile NOELs in each structural class are then converted to thresholds of concern for each class (1,800 µg/person/day for Class I, 544 for Class II, and 90 for Class III) by applying a 100-fold safety factor and correcting for mean body weight (60 kg)—i.e., NOEL × 60/100).

In the next two steps, the estimated daily intake of each identified constituent of the natural complex is compared to the "threshold of regulation" of 1.5 µg/person/day (Rulis et al., 1986), then to the human exposure thresholds for the respective structural class (Munro et al., 1996). If the intake of a constituent is greater than the 1.5 µg/person/day level and greater than the human exposure threshold for its respective structural class (Munro et al., 1996), it will be retained for further evaluation, if exposure to the constituent from that natural complex is a significant (i.e., >5%) part of the total diet. This latter provision takes into account exposure to that constituent relative to total exposure in the diet. When exposure to a constituent is trivial compared to its exposure in the total diet (Stofberg and Kirschman, 1985; Stofberg and Grundschober, 1987), a conclusion of safety is, again, straightforward.

Following this prioritization sequence, the Expert Panel continues the safety evaluation by considering scientific data on the natural complex and on constituents that exceed their threshold and have an intake from that natural source that exceeds 5% of total dietary intake. For instance, the intake of limonene from lemon oil is greater than the human exposure threshold for structural class I (20,200 µg/person/day vs 1,800 for class I) (Munro et al., 1996) and greater than 5% of the intake from all food sources. Therefore, because of its relatively high intake from lemon oil, limonene would be reviewed during the GRAS evaluation of lemon oil. However, intake of 1,8-cineole (1.9 ppm; 0.00019%) is less (0.055 µg/person/day) than the exposure threshold for structural class III (90 µg/person/day). Because of its extremely low estimated intake, 1,8-cineole would be deleted from further consideration in the evaluation of lemon oil.

Other aspects of the naturals paradigm involve the evaluation of constituents of unknown structure. As a conservative default assumption, the total intake of all constituents of unknown structure are considered together and placed in the structural class of greatest toxic potential (i.e., class III). Therefore, total intake of unidentified constituents is compared to the most conservative exposure threshold (90 µg/person/day). Different sources of the natural complex are reviewed to identify a recently analyzed source with the highest fraction of unknown constituents. For example, the unknown component of bitter orange oil has recently been reported to be in the range from 0.08% (Lin et al., 1986) to 3% (Haubruge, 1989). If the intake of the total unknown constituents is greater than the threshold value for structural class III (90 µg/person/day) and the major constituents (i.e., unidentified constituents that account for >25% of the total unknown constituents by weight), the natural complex is placed on hold until analytical data can be obtained to identify the structures of additional constituents. In this manner, any natural complex with sufficient intake of an unknown fraction would be set aside until further analytical work is performed. In the above example using bitter orange oil, the total intake of the unknown con-

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stituents (1.05 μg/person/day) from bitter orange oil is less than the human exposure threshold (90 μg/person/day) for class III. Therefore, bitter orange oil would be of no safety concern based on the extremely low intake of unknown constituents.

It is apparent that the quality of the analytical data will determine the percentage of unknown constituents in the natural complex. Data obtained from older studies used less sophisticated analytical methodology and must be carefully screened against results of more exhaustive analyses. For instance, an older Cuban study reported 11.7% unknown constituents in bitter orange oil (Soulari and Fanghaenel, 1971). However, that study was limited to the identification of the terpene hydrocarbon constituents and therefore did not provide level of analyses as is found in more recent studies on bitter orange oil (Boelens and Jimenez, 1989; Lin et al., 1986).

The paradigm also addresses the concept of "additivity of effect" among structurally related constituents. For the purpose of evaluating constituents of flavoring complexes, a conservative default assumption will be used. If a common pathway of intoxication has been identified (e.g., the pulegone–menthofuran pathway for hepatotoxicity) or can be reasonably predicted on the basis of known structure–activity relationships (e.g., reactivity of the epoxide functional group) for a group of structurally related constituents, the combined intake of those substances will be compared to the appropriate human exposure threshold. Therefore, in the evaluation of dill herb seed oil, the combined intake of *p*-alkoxyallylbenzene derivatives apiole, dill apiole, and myristicin would be compared to the human exposure threshold for structural class III (90 μg/person/day).

Since the vast majority of constituents of natural complexes are simple terpenoid substances which are readily detoxicated by established metabolic pathways (Hawkins, 1988–96), use of the additivity default assumption is expected to be limited to a few natural complexes. Additionally, major constituents of natural complexes have been tested individually and pose no toxicological threat even at dose levels that are orders of magnitude greater than those experienced through normal levels of intake as flavoring substances. However, in a very few cases, high dose levels of more than one constituent of a natural complex have been shown to participate in a common intoxication pathway. For instance, high dose levels of pulegone, 1,2-dehydropulegone (piperitenone), and menthofuran, all constituents of peppermint oil, have been shown to participate in an intoxication pathway leading to a hepatotoxic intermediate (Gordon et al., 1987, 1982; McClanahan et al., 1989; Madyastha and Raj, 1992, 1993; Nelson et al., 1992a, b; Thomassen et al., 1988). Even though an intoxication pathway such as the one above is not the primary metabolic pathway at normal levels of intake of the natural complex, it will, nevertheless, be considered in the evaluation of the natural complex.

In summary, the paradigm is an exposure and structure-based sequence in which chemically identified constituents, the fraction of unidentified constituents, and any additive effects among constituents are prioritized for further evaluation. The outcome of this prioritization sequence is that some minor constituents of significant toxicological concern (i.e., higher structural class) will be elevated to a level that will force consideration along with the major constituents as defined above. If unknown constituents account for a significant amount of the natural complex and intake is significant, the natural complex will require further chemical characterization. If constituents of a natural complex are known or can reasonably be presumed to participate in the same intoxication pathway, their intakes are combined and further evaluated, provided that the combined intake is greater than the human exposure threshold for the appropriate structural class.

Based on these three strategies, the overall objective of the paradigm can be attained: that no reasonably significant risk associated with the intake of natural complexes will go unevaluated. A publication on the naturals paradigm is forthcoming.

GRASr Activities

The most recent comprehensive and systematic reevaluation of FEMA GRAS flavoring substances (the GRASr program) began in 1994. As of May 1998, the Expert Panel has reaffirmed as GRAS approximately 800 substances. As part of the GRAS reaffirmation (GRASr) process, the Expert Panel has initiated a program to publish in the peer-reviewed literature individual summaries for important flavoring substances and group summaries for structurally related substances. These summaries integrate the relevant scientific information on metabolism, pharmacology, toxicology, and exposure, which is the basis for the Expert Panel's GRAS and GRASr decisions. Publications on the FEMA GRAS assessment of furfural (FEMA No. 2489) by Adams et al. (1997) and *trans*-anethole (FEMA No. 2086) by Adams et al. (1998b) are recent examples of individual GRAS assessments. Group GRAS assessments for 119 structurally related alicyclic substances (Adams et al., 1996) and 45 aliphatic and aromatic lactones (Adams et al., 1998a) are examples of the Expert Panel's safety evaluation of groups of structurally related substances.

In these GRAS assessments, new sources of scientific information from disciplines such as toxicokinetics, biochemistry, metabolism, toxicologic pathology, and genetics have strongly influenced the field of safety evaluation. Classical safety evaluation of food constituents has been based on the results of animal feeding studies that provided quantitative limits on toxicity. Safe use of substances is concluded if adequate margins are established between estimated levels of human intake and levels of intake producing no adverse effects in test animals.

Advances in toxicokinetics, biochemistry, metabolism, and toxicologic pathology have yielded information on the mechanism by which a substance may exert a toxic effect. When appropriate data are available, the Expert Panel has used its multidisciplinary composition and the unique expertise of its members to perform mechanism-based safety evaluations for flavoring substances. The following is a summary of the Expert Panel's mechanism-based safety evaluation of *trans*-anethole.

Safety of *trans*-Anethole

trans-Anethole (FEMA No. 2086) is 4-methoxypropenylbenzene. It has important use as a flavoring substance in baked goods, candy, ice cream, chewing gum, and alcoholic beverages (Hall and Oser, 1965). It is the major volatile com-

ponent in sweet and bitter fennel, and anise. Based on the reported annual volume of 17,100 kg (NAS, 1987), the estimated daily per capita intake ("eaters only") is 0.054 mg/kg of body weight/day from use of anethole as a flavoring substance. The intake was calculated as follows:

$$\frac{(\text{annual volume in kg})(1 \times 10^6 \text{ mg/kg})}{(\text{population})(0.6)(60)(365 \text{ days})}$$

where "eaters only" population is 24×10^6 for the U.S. in 1987; 0.6 represents the assumption that only 60% of the flavor volume was reported in the survey; and the average adult body weight in the U.S. is 60 kg (NAS, 1987).

In 1989, it was reported that chronic intake of high dose levels of *trans*-anethole in the female rat was associated with hepatotoxicity and a low incidence of liver tumors (Truhaut et al., 1989; Newberne et al., 1989). Subsequent studies on the genotoxicity, toxicity, pharmacokinetics, and metabolism of *trans*-anethole in laboratory animals and humans have been performed and are used here in a mechanism-based safety evaluation to interpret the observed hepatotoxicity and related tumorigenic effects (Adams et al., 1998b).

Changes reported in the liver of laboratory rodents exposed to *trans*-anethole in the diet for periods up to 833 days (i.e., 2+ years) may be further understood in terms of the hepatic intoxication pathway in which *trans*-anethole is metabolized to the ultimate hepatotoxic agent, anethole epoxide.

In a 2+-year study, Sprague-Dawley rats exhibited evidence of hepatotoxicity at dietary levels of 200 and 400 mg/kg of body weight/day for males and 250 and 550 mg/kg bw/d for females based on a statistically significant increased incidence of focal and nodular hyperplasia, sinusoidal dilatation, and distended bile ducts (Truhaut et al., 1989). An independent histopathological evaluation confirmed the presence of hepatic injury at these dose levels (Newberne et al., 1989). Additionally, a statistically significant increase in hepatocellular carcinoma was reported in female rats at the highest dose level (i.e., 550 mg/kg bw/d) (Truhaut et al., 1989; Newberne et al., 1989). The neoplasms occurred primarily in livers with significant non-neoplastic lesions indicative of hepatotoxicity and necrosis (Newberne et al., 1989). They were found to be of late onset, after week 98, and had no effect on the longevity of the animals. Based on the evidence of hepatotoxicity in males at ≥200 mg/kg bw and females at ≥250 mg/kg bw, the no observable adverse effect level (NOAEL) for the study was concluded to be 100 mg/kg bw/d for males and 120 mg/kg bw/d for females (Truhaut et al., 1989; Newberne et al., 1989).

The extensive biochemical and metabolic data on *trans*-anethole demonstrate that the hepatotoxicity observed in rats exposed to *trans*-anethole is associated with the dose-dependent metabolic formation of anethole epoxide, AE (Sangster et al., 1984a, b; Bounds and Caldwell, 1996). At high dose levels (≥100 mg *trans*-anethole/kg bw), a metabolic shift to greater epoxidation in rats leads to increased hepatocellular concentrations of AE. Epoxidation is more pronounced in rats than mice (Sangster et al., 1984a, b; Bounds and Caldwell, 1996) and significantly greater than in humans (Sangster et al., 1987; Caldwell and Sutton, 1988) at low dose levels (i.e., <12 mg *trans*-anethole/kg bw/d). Therefore, the rat is considered to be the more sensitive rodent species for evaluating the potential for AE-related hepatotoxicity in humans exposed to *trans*-anethole from use as a flavoring substance.

At low doses of *trans*-anethole in rats, AE is readily detoxicated by enzymes such as the fast-acting enzyme epoxide hydrolase, EH, and the slower-detoxication enzyme glutathione-*S*-transferase, GST (Marshall and Caldwell, 1992). With increasing dose levels of *trans*-anethole, hepatic levels of AE increase and these enzymes (especially EH) approach saturation leading to cytotoxicity. The female rat is probably more sensitive than the male, since it exhibits lower EH activity which would result in higher hepatocellular levels of AE (Meijer et al., 1987). Inhibition of these detoxication enzymes (i.e., EH and GST) is directly related to an increase in the cytotoxic effects of *trans*-anethole. AE is approximately 10 times more cytotoxic than *trans*-anethole in the hepatocytes of rats (Marshall and Caldwell, 1992, 1996; Caldwell, 1991; Caldwell et al., 1991, 1992). This difference corresponds approximately to the proportion (12–18%) of *trans*-anethole that is metabolized to AE in rats at dose levels (≥200 mg *trans*-anethole/kg bw/d) required to observe hepatotoxicity. Taken together, these data indicate that cytotoxicity and hepatotoxicity are linked metabolically to the formation of AE from *trans*-anethole in the liver.

Based on repeated-dose metabolic studies, daily production of AE is higher in female rats than in male rats. At higher dose levels, more *trans*-anethole is converted to AE, which saturates the "fast-acting" EH detoxication pathway in the liver. This leads to increased hepatocellular AE concentrations that may react with glutathione or cellular components. At the highest dose level of anethole (i.e., 400 mg/kg/d in males and 550 mg/kg bw/d in females), daily hepatic production of AE in females (120 mg/kg bw) was at least twice that of males (≈50 mg/kg bw). The NOAEL of 120 mg *trans*-anethole/kg bw/d for female rats in the 2+-year study corresponds to production of approximately 22 mg of AE/kg bw/d, which is more than 10,000 times the level of 0.002 mg of AE/kg bw/d produced by humans from intake of *trans*-anethole as a flavoring substance.

Since no significant hepatotoxicity was observed in male or female rats at dose levels up to 300 mg *trans*-anethole/kg bw/d (≈55–60 mg of AE/kg bw/d) for 90 days (Minnema, 1997), it may be concluded that daily exposure to significant levels of AE must continue over a long duration in order to observe the onset of hepatotoxicity in rats. Cumulative exposure to AE may be directly related to the incidence and severity of the observed dose-dependent hepatotoxicity. Hepatotoxicity reported in female rats at dose levels ≥250 mg *trans*-anethole/kg bw/d in the 2+-year study corresponds to cumulative AE production of at least 20,000 mg of AE/kg bw. It is postulated that continuous exposure to high-dose levels of *trans*-anethole leads to a continuum of biochemical and toxicological events: (1) hepatic metabolism to form AE, (2) saturation of rapid (EH) detoxication pathways, (3) concomitant increase in hepatocellular concentrations of AE, (4) cytotoxicity, (5) cell death (necrosis), (6) hepatocyte proliferation, and ultimately (7) liver tumors in a few female rats, as reported in the 2+-year study (Truhaut et al., 1989).

The low incidence (6/52) of carcino-

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mas observed in the severely compromised livers of female rats given 550 mg of *trans*-anethole/kg bw/d in the 2+-year study occurred following an estimated total lifetime exposure to AE exceeding 100,000 mg/kg bw. The fact that hepatocellular carcinomas occurred only in the female rat is a reflection of a higher daily dose of *trans*-anethole for the females, increased conversion to AE compared to the male, and decreased detoxication of AE by the female, which exhibits a lower activity of the AE-detoxication enzyme EH compared to that of the male (Meijer et al., 1987).

Genotoxicity data, considered together, demonstrate that neither anethole nor AE is genotoxic (Adams et al., 1998b). The pattern of significant induction of Phase II conjugation enzymes (GGT and GST) and the weak induction of Phase I CYP450 monooxygenase enzymes by *trans*-anethole, along with the incidence of hepatocyte hypertrophy and increased relative liver weights in mice and rats (Rompelburg et al., 1993; Reed and Caldwell, 1992) are phenomena associated with an increased requirement for metabolism of *trans*-anethole and are widely observed with other non-genotoxic hepatotoxic substances (Grasso and Hinton, 1991). Therefore, the weight of evidence indicates that the neoplasms observed in the liver of female rats at a dose level of 550 mg of *trans*-anethole/kg bw/d are secondary to dose-dependent hepatotoxicity resulting from continuous exposure to high hepatocellular concentrations of anethole epoxide (Adams et al., 1998b).

The conclusion that *trans*-anethole–induced carcinogenicity in female rats is secondary to hepatotoxicity is significant to the overall safety evaluation of *trans*-anethole from use as a flavoring substance because hepatotoxicity is a threshold phenomenon. It has recently been proposed that a default assumption of nonlinearity is appropriate when carcinogenicity results from a secondary effect of toxicity (EPA, 1996). In the 2+-year study in female rats, hepatotoxicity was reported only when dietary levels of *trans*-anethole were ≥250 mg/kg bw/d and hepatic production of AE was >40 mg/kg bw/d. Furthermore, hepatocellular neoplasms were only reported in severely compromised livers of female rats when dietary levels increased to 550 mg of *trans*-anethole/kg bw/d and hepatic production of AE was >120 mg/kg bw/d. These observations strongly suggest that *trans*-anethole–induced carcinogenicity in female rats is a threshold effect.

trans-Anethole was reaffirmed as GRAS (GRASr) by the Expert Panel, based on its low level of flavor use (0.054 mg/kg bw/d); its metabolic detoxication in humans, which has been demonstrated at levels up to 12 mg/kg bw; the lack of mutagenic or genotoxic potential; the NOAEL of 120 mg of *trans*-anethole/kg bw/d in the female rat reported in a 2+-yr study which produces a level of AE (i.e., 22 mg of AE/kg bw/d) at least 10,000 times the level (0.002 mg of AE/kg bw/d) produced from the intake of *trans*-anethole from use as a flavoring substance; and the conclusion that a slight increase in the incidence of hepatocellular tumors in the damaged, metabolically compromised livers of the high-dose group (550 mg of *trans*-anethole/kg bw/d) of female rats was the only significant neoplastic finding in a 2+-yr dietary study.

Clarifications

The following corrections and clarifications are being made:

Octyl acetate (FEMA No. 2806). The Expert Panel's conclusion that octyl acetate is considered GRAS for use as a flavoring substance was published in GRAS 3 (Hall and Oser, 1965). However, GRAS 3 incorrectly listed 2-ethylhexyl acetate as a synonym for octyl acetate. 2-Ethylhexyl acetate has not been evaluated by the Expert Panel for consideration as GRAS. The correct synonyms for octyl acetate are "acetate C-8" and "octyl ethanoate."

2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal (FEMA No. 3141). The Expert Panel's conclusion that this compound is considered GRAS for use as a flavoring substance was published in GRAS 4 (Hall and Oser, 1970), and α-sinensal was listed as a synonym. However, the name α-sinensal was replaced with β-sinensal to correspond with the nomenclature assigned to α- and β-farnesene (Büchi and Wüst, 1967; Bertele and Schudel, 1967; Teranishi et al., 1968). Therefore, α-sinensal is now 2,6,10-trimethyl-2,6,9,11-dodecatrienal and is no longer a synonym for the FEMA GRAS substance 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal. α-Sinensal (i.e., 2,6,10-trimethyl-2,6,9,11-dodecatrienal) has not been evaluated by the FEMA Expert Panel for consideration as GRAS. The correct synonym for 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal (FEMA No. 3141) is β-sinensal.

Vanilla. The name "vanilla" listed in GRAS 3 as FEMA No. 3104 has been officially changed to "vanilla beans."

Expert Panel Membership Changes

In January 1997, Jay I. Goodman, Professor of Pharmacology and Toxicology, Michigan State University, joined the Expert Panel. At the January 1997 meeting, Paul Newborn, D.V.M., was elected to a three-year term as chair of the Expert Panel, and Robert Smith was elected to vice chair for the same term. In January 1998, Lauren A. Woods, M.D., who was an original member of the FEMA Expert Panel since 1960, retired from the Expert Panel.

REFERENCES

Adams, T.B., Hallagan, J.B., Putnam, J.M., Gierke, T.L., Doull, J., Munro, I.C., Newberne, P., Portoghese, P.S., Smith, R.L., Wagner, B.M., Weil, C.S., Woods, L.A., and Ford, R.A. 1996. The FEMA GRAS assessment of alicylic substances used as flavor ingredients. Food Chem. Toxicol. 34(9): 763-828.

Adams, T.B., Doull, J., Goodman, J.I., Munro, I.C., Newberne, P., Portoghese, P.S., Smith, R.L., Wagner, B.M., Weil, C.S., Woods, L.A., and Ford, R.A. 1997. The FEMA GRAS assessment of furfural used as a flavor ingredient. Food Chem. Toxicol. 35(8): 739-751.

Adams, T.B., Greer, D.B., Doull, J., Munro, I.C., Newberne, P., Portoghese, P.S., Smith, R.L., Wagner, B.M., Weil, C.S., Woods, L.A., and Ford, R.A. 1998a. The FEMA GRAS assessment of lactones used as flavor ingredients. Food Chem. Toxicol. In press.

Adams, T.B., Lucas, C.D., Putnam, J.M., Doull, J., Goodman, J.I., Munro, I.C., Newberne, P., Portoghese, P.S., Smith, R.L., Wagner, B.M., Weil, C.S., Woods, L.A., and Ford, R.A. 1998b. The FEMA GRAS assessment of trans-anethole used as a flavor ingredient. Food Chem. Toxicol. In press.

Bertele, E. and Schudel, P. 1967. Synthesis of alpha- and beta-sinensals. Helv. Chim. Acta 50(8): 2445-2456.

Boelens, M.H. and Jimenez, R. 1989. The chemical composition of the peel oils from unripe and ripe fruits of bitter orange. *Citrus aurantium* L. ssp. *amara* Eng. Flav. Fragr. J. (4): 139-142.

Bounds, S.V. and Caldwell, J. 1996. Pathways of metabolism of [1'-^{14}C] trans-anethole in the rat and mouse. Drug Metab. Dispos. 24: 717-724.

Büchi, G. and Wüst, H. 1967. Synthesis of beta-sinensal. Helv. Chim. Acta 50(8): 2440-2445.

Burdock, G.A., Wagner, B.M., Smith, R.L., Munro, I.C., and Newberne, P.M. 1990. Recent progress in the consideration of flavor ingredients under the food additives amendment. 15. GRAS substances. Food Technol. 44: 78-86.

Caldwell, J. 1991. Trans-anethole-another nongenotoxic rodent carcinogen? Presented at Toxicology Forum, July 15-19, Aspen, Colo., pp. 616-639.

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CONTINUED

Caldwell, J. and Sutton, J.D. 1988. Influence of dose size on the disposition of trans-[methoxy-^{14}C] anethole in human volunteers. Food Chem. Toxicol. 26: 87-91.

Caldwell, J., Marshall, A.D., Reed, P., and Bounds, S.V.J. 1991. Metabolic and mechanistic studies to underpin the safety assessment of trans-anethole. Unpublished interim report of the Anethole Task Force of FEMA, Washington, D.C.

Caldwell J., Chan, V.S.W., Marshall, A.D., Hasheminejad, G., and Bounds, S.V.J. 1992. 1'-Hydroxylation is the only metabolic pathway of simple alkenylbenzenes involved in their genotoxicity. Toxicologist 12: 56.

Chamblee, T.S., Clark, B.C., Brewster, G.B., Radford, T., and Iacobucci, G.A. 1991. Quantitative analysis of the volatile constituents of lemon peel oil. Effects of silica gel chromatography on the composition of its hydrocarbon and oxygenated fractions. J. Agric. Food Chem. 39: 162-169.

Cramer, G.M., Ford, R.A., and Hall, R.L. 1978. Estimation of toxic hazard—A decision tree approach. Food Chem. Toxicol. 16: 255-276.

EPA. 1996. Proposed guidelines for carcinogen risk assessment; Notice. Environmental Protection Agency, Fed. Reg. 61: 17981, April 23.

Gordon, W.P., Forte, A.J., McMurtry, R.J., Gal, H., and Nelson, S.D. 1982. Hepatotoxicity and pulmonary toxicity of pennyroyal oil and its constituent terpenes in the mouse. Toxicol. Appl. Pharmacol. 65: 413-424.

Gordon, W.P., Huitric, A.C., Seth, C.L., McClanahan, R.H., and Nelson, S.D. 1987. The metabolism of the abortifacient terpene, (R)-(+)-pulegone, to a proximate toxin, menthofuran. Drug Metab. Dispos. 15: 589-594.

Grasso, P. and Hinton, R.H. 1991. Evidence for and possible mechanisms of non-genotoxic carcinogenesis in rodent liver. Mutation Res. 248: 271-290.

Hall, R.L. and Oser, B.L. 1965. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 3. GRAS substances. Food Technol. 19(2, Part 2): 151-197.

Hall, R.L. and Oser, B.L. 1970. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment 4. GRAS substances. Food Technol. 24(5): 25-34.

Hallagan, J. B. and Hall, R.L. 1995. FEMA GRAS—A GRAS assessment program for flavor ingredients. Regulatory Toxicol. Pharmacol. 21: 422-430.

Haubruge, E. 1989. Etude de la toxicity de cinq huiles essentielles extraites de citrus etc. Med. Fac. Landbouww. Rijksuniv. Gent. 54(3b): 1083-1093.

Hawkins, D.R. 1988-96. "Biotransformations: A Survey of the Biotransformations of Drugs and Chemicals in Animals," ed. D. R. Hawkins, Vols. 1-7. Royal Soc. of Chemistry, Cambridge, U.K.

Licandro, G., Cotroneo, A., and Trozzi, A. 1987. Sulla genuinita' Delle Essenze Agrumarie. Nota XX. Particolarita' Riscontrate nelle composizione di Essenze di Limone prodotte durante il periodo estivo da frutti provenienti da une zona della provincia di Siracusa. Essenze Deriv. Agrum. 57: 620-627.

Lin, Z.K., Hua, Y.F., and Gu, Y.H. 1986. The chemical constituents of the essential oil from the flowers, leaves and peels of *Citrus aurantium*. Zhiwa Xuebao 28: 635-640.

Madyastha, K.M. and Raj, C.P. 1992. Metabolic fate of menthofuran in rats: Novel oxidative pathways. Drug Metab. Dispos. 20: 295-301.

Madyastha, K.M. and Raj, C.P. 1993. Studies on the metabolism of a monoterpene ketone, R-(+)-pulegone—A hepatotoxin in rat: Isolation and characterization of new metabolites. Xenobiotica 23: 509-518.

Marshall, A.D. and Caldwell, J. 1992. Influence of modulators of epoxide metabolism on the cytotoxicity of trans-anethole in freshly isolated rat hepatocytes. Food Chem. Toxicol. 30: 467-473.

Marshall, A.D. and Caldwell, J. 1996. Lack of influence of modulators of epoxide metabolism on the genotoxicity of trans-anethole in freshly isolated rat hepatocytes assessed with the unscheduled DNA synthesis assay. Food Chem. Toxicol. 34: 337-345.

McClanahan, R.H., Thomassen, D., Slattery, J.T., and Nelson, S.D. 1989. Metabolic activation of (R)-(+)-pulegone to a reactive enonal that covalently binds to mouse liver proteins. Chem. Res. Toxicol. 2: 349-355.

Meijer, J., Lundqvist, G., and Williams, G.M. 1987. Comparison of the sex and subcellular distributions, catalytic and immunochemical reactivities of hepatic epoxide hydrolases in seven mammalian species. Eur. J. Biochem. 167: 269-279.

Minnema, D.J. 1997. 90-Day subchronic dietary toxicity study of trans-anethole in mice and rats. Unpublished draft final report to FEMA. Covance Laboratories, Vienna, Va.

Munro, I.C., Ford, R.A., Kennepohl, E., and Sprenger, J.G. 1996. Correlation of structural class with no-observed-effect levels: A proposal for establishing a threshold of concern. Food Chem. Toxicol. 34: 829-867.

NAS. 1987. "Evaluating the Safety of Food Chemicals." Natl. Acad. of Sciences, Washington, D.C.

Nelson, S.D., McClanahan, R.H., Thomassen, D., Gordon, W.P., and Knebel, N. 1992a. Investigations of mechanisms of reactive metabolite formation from (R)-(+)-pulegone. Xenobiotica 22: 1157-1164.

Nelson, S.D., McClanahan, R.H., Knebel, N., Thomassen, D., Gordon, W.P., and Oishi, S. 1992b. The metabolism of (R)-(+)-pulegone, a toxic monoterpene. Environ. Sci. Res. 44: 287-296.

Newberne, P.M., Carlton, W.W., and Brown, W.R. 1989. Histopathological evaluation of proliferative liver lesions in rats fed trans-anethole in chronic studies. Food Chem. Toxicol. 27: 21-26.

Oser, B.L. and Ford, R.A. 1973a. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 6. GRAS substances. Food Technol. 27(1): 64-67.

Oser, B.L. and Ford, R.A. 1973b. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 7. GRAS substances. Food Technol. 27(11): 56-57.

Oser, B.L. and Ford, R.A. 1974. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 8. GRAS substances. Food Technol. 28(9): 76-80.

Oser, B.L. and Ford, R.A. 1975. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 9. GRAS substances. Food Technol. 29(8): 70-72.

Oser, B.L. and Ford, R.A. 1977. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 10. GRAS substances. Food Technol. 31(1): 65-74.

Oser, B.L. and Ford, R.A. 1978. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 11. GRAS substances. Food Technol. 32(2): 60-70.

Oser, B.L. and Ford, R.A. 1979. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 12. GRAS substances. Food Technol. 33(7): 65-73.

Oser, B.L. and Ford, R.A. 1991. FEMA Expert Panel: 30 years of safety evaluation for the flavor industry. Food Technol. 45(11): 84-97.

Oser, B.L. and Hall, R.L. 1972. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 5. GRAS substances. Food Technol. 26(5): 35-42.

Oser, B.L. and Hall, R.L. 1977. Criteria employed by the expert panel of FEMA for the GRAS evaluation of flavoring substances. Food Technol. 15: 457-466.

Oser, B.L., Ford, R.A., and Bernard, B.K. 1984. Recent progress in consideration of flavoring ingredients under the Food Additives Amendment. 13. GRAS substances. Food Technol. 38(10): 66-89.

Oser, B.L., Weil, C.L., Woods, L.A., and Bernard, B.K. 1985. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 14. GRAS substances. Food Technol. 39(11): 108-117.

Reed, P.M. and Caldwell, J. 1992. Effects of dietary administration of trans-anethole on the liver of the Sprague-Dawley CD rat. Toxicol. Lett., Suppl. 1: 283.

Rompelburg, C.J., Verhagen, H., and Bladeren, P.J. 1993. Effects of the naturally occurring alkenylbenzenes eugenol and trans-anethole on drug metabolizing enzymes in the rat liver. Food Chem. Toxicol. 31: 637-645.

Rulis, A.M. 1986. De minimis and the threshold of regulation. In "Food Protection Technology," ed. Felix, C.W., pp. 29-37. Lewis Publishers Inc., Chelsea, Mich.

Sangster, S.A., Caldwell, J., Smith, R.L., and Farmer, P.B. 1984a. Metabolism of anethole. I. Pathways of metabolism in the rat and mouse. Food Chem. Toxicol. 22: 695-706.

Sangster, S.A., Caldwell, J., and Smith, R.L. 1984b. Metabolism of anethole. II. Influence of dose size on the route of metabolism of trans-anethole in the rat and mouse. Food Chem. Toxicol. 22: 707-713.

Sangster, S.A., Caldwell, J., Hutt, A.J., Anthony, A., and Smith, R.L. 1987. The metabolic disposition of [methoxy-^{14}C]-labelled trans-anethole, estragole and p-propylanisole in human volunteers. Xenobiotica 17: 1223-1232.

Smith, R.L. and Ford, R.A. 1993. Recent progress in consideration of flavoring ingredients under the Food Additives Amendment. 16. GRAS substances. Food Technol. 47(6): 104-117.

Smith, R.L., Newberne, P., Adams, T.B., Ford, R.A., Hallagan, J.B., and the FEMA Expert Panel. 1996a. GRAS flavoring substances 17. Food Technol. 50(10): 72-78, 80-81.

Smith, R.L., Newberne, P., Adams, T.B., Ford, R.A., Hallagan, J.B., and the FEMA Expert Panel. 1996b. Correction to GRAS flavoring substances 17. Food Technol. 51(2): 32.

Soulari, M. and Fanghaenel, E. 1971. Analisis parcial de aceite escencial de naranja agria (*Citrus aurantium* L.) producido en Cuba. Rivista Clinic 3(1): 125-128.

Srinivas, S.R. 1986. In "Atlas of Essential Oils," published by author, Bronx, N.Y.

Stofberg, J. and Grundschober, F. 1987. Consumption ratio and food predominance of flavoring materials. Perfumer Flavorist 12: 27.

Stofberg, J. and Kirschman, J.C. 1985. The consumption ratio of flavoring materials: A mechanism for setting priorities for safety evaluation. Food Chem. Toxicol. 23: 857-860.

Teranishi, R., Thomas, A.F., Schudel, P., and Büchi, G. 1968. The nomenclature of the sinensals. Chem. Commun. 15: 928.

Thomassen, D., Slattery, J.T., and Nelson, S.D. 1988. Contribution of menthofuran to the hepatotoxicity of pulegone: Assessment based on matched area under the curve and on matched time course. J. Pharmacol. Exp. Therapeutics 244: 825-829.

Truhaut, R., Le Bourhis, B., Attia, M., Glomot, R., Newman, J., and Caldwell, J. 1989. Chronic toxicity/carcinogenicity study of trans-anethole in rats. Food Chem. Toxicol. 27: 11-20.

Woods, L. and Doull, J. 1991. GRAS evaluation of flavoring substances by the Expert Panel of FEMA. Regulatory Toxicol. Pharmacol. 14: 48.

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Tables 1–3 on pages 79–92 →

Table 1 Primary names (in boldfaced capital letters) and synonyms (in lower case) of flavoring substances are listed alphabetically

FEMA No.	Substance primary name and synonyms
3816	**3-ACETYLMERCAPTOHEXYL ACETATE** 3-Acetylthiohexyl acetate 3-Acetylthiohexyl ethanoate
3817	**2-ACETYL-2-THIAZOLINE** Acetyl thiazoline-2 2-Acetyl-4,5-dihydrothiazole
3818	**L- AND DL-ALANINE** L-α-Alanine L-α-Aminopropionic acid (S)-2-Aminopropanoic acid DL-Alanine DL-2-Aminopropanoic acid
3819	**L-ARGININE** (S)-2-Amino-5-guanidinovaleric acid Arginine 2-Amino-5-guanidinovaleric acid
3820	**1-BUTEN-1-YL METHYL SULFIDE** 1-Butene, 1-(methylthio)-
3821	**3-CARENE** *d*-3-Carene Car-3-ene Isodiprene 4,7,7-Trimethyl-3-norcarene 3,7,7-Trimethylbicyclo[4.1.0]hept-3-ene 3,7,7-Trimethylbicyclo[4.1.0]-3-heptene 3,7,7-Trimethylbicyclo[4.1.0]heptene-3
3822	**CYCLOIONONE** 5H-1-Benzopyran, 6,6,7,8,8a-tetrahydro-2,5,5,8a-tetramethyl 6,6,7,8,8a-Tetrahydro-2,5,5,8a-tetramethyl-5H-1-benzopyran
3823	**DAIDAI PEEL OIL** *Citrus aurantium* L. subspecies *cyathifera* Y.
3824	**1-DECEN-3-OL**
3825	**DIETHYL SULFIDE** Ethane, 1,1-thiobis- Ethyl sulfide 1,1-Thiobisethane 3-Thiopentane Diethylthioether Ethyl monosulfide Ethyl thioether Ethyl thioethane Thioethyl ether Sulfodor
3826	**2,5-DIHYDROXY-1,4-DITHIANE** 1,4-Dithiane-2,5-diol Mercaptoacetaldehyde dimer *p*-Dithiane-2,5-diol
3827	**DIISOPROPYL DISULFIDE** Disulfide, bis(1-methylethyl) Isopropyl disulfide 2,5-Dimethyl-3,4-dithiohexane *Bis*(1-methylethyl)disulfide
3828	**2,4-DIMETHYLANISOLE** 1-Methoxy-2, 4-dimethylbenzene 4-Methoxy-m-xylene
3829	**(E)-2-(3,7-DIMETHYL-2,6-OCTADIENYL)CYCLOPENTANONE** 2-(3,7-dimethyl-2,6-octadienyl) cyclopentanone Cyclopentanone, 2-(3,7-dimethyl-2,6-octadienyl) Decenyl cyclopentanone
3830	**(E)-3,7-DIMETHYL-1,5,7-OCTATRIEN-3-OL** Hotrienol Dehydrolinalool
3831	**1,4-DITHIANE** *p*-Dithiane 1,4-Dithiocyclohexane 1,4-Dithiin, tetrahydro- Diethylene disulfide
3832	**ETHYL 2,4,7-DECATRIENOATE** Ethyl deca-2,4,7-trienoate 2,4,7-Decatrienoic acid, ethyl ester
3833	**2-ETHYLHEXANETHIOL** 1-Hexanethiol, 2-ethyl- 2-Ethylhexylmercaptan
3834	**ETHYL 2-(METHYLDITHIO)PROPIONATE** Propionic acid, 2-(methyldithio), ethyl ester
3835	**ETHYL 2-(METHYLTHIO)ACETATE** Acetic acid, (methylthio), ethyl ester Ethyl 2-methylthioacetate
3836	**ETHYL 3-(METHYLTHIO)BUTYRATE**
3837	**ETHYL VANILLIN ISOBUTYRATE** Propanoic acid, 2-methyl-, 2-ethoxy-4-formylphenyl ester
3838	**ETHYL VANILLIN PROPYLENE GLYCOL ACETAL** Phenol, 2-ethoxy-4-(4-methyl-1,3-dioxalan-2-yl)-
3839	**FARNESENE** 1,3,6,10-Dodecatetraene, 3,7,11-trimethyl (α-isomer) 1,6,10-Dodecatriene, 7, 11-dimethyl-3-methylene (ß-isomer)
3840	**4-[(2-FURANMETHYL)THIO]-2-PENTANONE** 4-Furfurylthio-2-pentanone 4-(Furan-2-ylmethylsulfanyl)pentane-2-one 2-Pentanone, 4-[(2-furanylmethyl)thio]
3841	**(Z)-4-HEPTEN-1-OL** 4-(Z)-Heptenol cis-4-Heptenol
3842	**1-HEXANETHIOL** Hexyl mercaptan
3843	**3-HYDROXY-2-OXOPROPIONIC ACID** Propanoic acid, 3-hydroxy-2-oxo- 3-Hydroxy-2-oxopropanoic acid 3-Hydroxy-2-oxopropionic acid
3844	**ß-IONYL ACETATE** 3-Buten-2-ol, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-, acetate
3845	**α-ISOMETHYLIONYL ACETATE** 3-Buten-2-ol, 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, acetate 3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)- 3-buten-2-yl acetate
3846	**LITSEA CUBEBA BERRY OIL** May chang *Litsea cubeba* berry oil *Litsea cubeba* Pers.
3847	**L-LYSINE** Lysine (S)-2,6-Diaminohexanoic acid Lysine hydrochloride α, ϵ-Diaminocaproic acid

Table 1 **Primary names and synonyms of flavoring substances are listed alphabetically *CONTINUED***

FEMA No	Substance primary name and synonyms
3848	***CIS*- AND *TRANS*-P-1(7),8-MENTHADIEN-2-YL ACETATE** Menthadienyl acetate Acetic acid, p-1(7),8-menthadien-2-yl ester
3849	**3-(*l*-MENTHOXY)-2-METHYLPROPANE-1,2-DIOL** 3-*l*-Menthoxy-2-methylpropan-1,2-diol TPG-1
3850	**3-MERCAPTOHEXANOL** 3-Thiohexanol 3-Thiohexan-1-ol
3851	**3-MERCAPTOHEXYL ACETATE** 3-Thiohexyl acetate 3-Thiohexyl ethanoate
3852	**3-MERCAPTOHEXYL BUTYRATE** 3-Thiohexyl butyrate 3-Thiohexyl butanoate
3853	**3-MERCAPTOHEXYL HEXANOATE** 3-Thiohexyl caproate 3-Thio-1-hexyl hexanoate 3-Thio-1-hexyl caproate 3-Mercaptohexyl caproate
3854	**3-MERCAPTO-3-METHYL-1-BUTANOL** 1-Butanol, 3-mercapto-3-methyl- 3-Methyl-3-mercaptobutyl alcohol 3-Mercapto-3-methylbutyl alcohol
3855	**3-MERCAPTO-3-METHYLBUTYL FORMATE** 3-Methyl-3-thiobutyl formate 1-Butanol, 3-mercapto-3-methyl, formate ester 3-Methyl-3-mercaptobutyl formate
3856	**1-MERCAPTO-2-PROPANONE** Mercaptoacetone
3857	**S-METHYL BENZOTHIOATE** S-Methyl thiobenzoate Methanethiol, benzoate
3858	**3-METHYLBUTANETHIOL** 1-Butanethiol, 3-methyl Isoamyl mercaptan
3859	**METHYL (E)-2-(Z)-4-DECADIENOATE** Methyl decadienoate, 2-(E), 4-(Z), natural (E)-2-(Z)-4-Decadienoic acid, methyl ester natural
3860	**METHYL ETHYL SULFIDE** Ethane, (methylthio)- (Methylthio)ethane Sulfide, ethyl methyl 1-(Methylthio)ethane 2-Thiobutane Ethyl methyl sulfide Ethyl methyl thioether Methyl ethyl sulfide
3861	**METHYL ETHYL TRISULFIDE** Trisulfide, ethyl methyl 2,3,4-Trithiohexane Ethyl methyl trisulfide
3862	**S-METHYL HEXANETHIOATE**
3863	**2-(4-METHYL-2-HYDROXYPHENYL)PROPIONIC ACID-γ-LACTONE** Furaminton Dimethyl-3,6-benzo-2(3H)-furanone
3864	**S-METHYL 3-METHYLBUTANETHIOATE** Methanethiol isovalerate S-Methyl 3-methylbutyrate Butanethioic acid, 3-methyl-, S-methyl ester
3865	**METHYL 3-METHYL-1-BUTENYL DISULFIDE**
3866	**2-METHYL-2-(METHYLDITHIO)PROPANAL** Propanal, 2-methyl-2-(methyldithio)- 2-(Methyldithio)isobutyraldehyde
3867	**S-METHYL 4-METHYLPENTANETHIOATE** Pentanethioic acid, 4-methyl, S-methyl ester
3868	**(E)-7-METHYL-3-OCTEN-2-ONE** *trans*-7-Methyl-3-octen-2-one 3-Octen-2-one, 7-methyl-
3869	**3-METHYL-2-OXOBUTANOIC ACID** Butanoic acid, 3-methyl-2-oxo- 2-Oxoisovaleric acid Dimethylpyruvic acid Sodium α-ketoisovalerate Butanoic acid, 3-methyl-2-oxo-, sodium salt Sodium 3-methyl-2-oxobutanoate
3870	**3-METHYL-2-OXOPENTANOIC ACID** 3-Methyl-2-oxovaleric acid Methyl ethyl pyruvic acid Valeric acid, 3-methyl-2-oxo-, sodium salt Sodium 3-methyl-2-oxopentanoic acid
3871	**4-METHYL-2-OXOPENTANOIC ACID** 4-Methyl-2-oxovaleric acid Isopropyl pyruvic acid Valeric acid, 4-methyl-2-oxo-, sodium salt 4-Methyl-2-oxopentanoic acid Sodium 4-methyl-2-oxopentanoate
3872	**METHYL PHENYL DISULFIDE** Disulfide, methyl phenyl Phenyl methyl disulfide
3873	**METHYL PHENYL SULFIDE** Benzene, (methylthio)- Sulfide, methyl phenyl- (Methylthio) benzene 1-Phenyl-1-thioethane Anisole, thio- Methyl phenyl thioether Phenyl methyl sulfide Phenylthiomethane Thioanisole
3874	**2-METHYL-1-PROPANETHIOL** 1-Propanethiol, 2-methyl Isobutyl mercaptan
3875	**METHYLSULFINYLMETHANE** Methane, sulfinylbis- Methyl sulfoxide Dimethyl sulfoxide DMSO

Table 1 **Primary names and synonyms of flavoring substances are listed alphabetically *CONTINUED***

FEMA No.	Substance primary name and synonyms
3876	**S-METHYL THIOACETATE** Methanethiol acetate
3877	**3-METHYLTHIOHEXANAL**
3878	***BIS*-(METHYLTHIO)METHANE** Methane, *bis*(methylthio)- 2,4-Dithiopentane *Bis*[methylmercapto]methane Formaldehyde dimethyl dithioacetal Formaldehyde dimethyl mercaptal Methylene *bis*[methyl sulfide] Thioformaldehyde dimethyl acetal
3879	**METHYLTHIOMETHYL BUTYRATE** Butanoic acid, (methylthio)methyl ester
3880	**METHYLTHIOMETHYL HEXANOATE** Hexanoic acid, (methylthio)methyl ester
3881	**4-(METHYLTHIO)-2-OXOBUTANOIC ACID** Butanoic acid, 4-(methylthio)-2-oxo-, sodium salt 4-(Methylthio)-2-oxobutanoic acid, sodium salt Sodium 4-(methylthio)-2-oxobutanoate
3882	**1-METHYLTHIO-2-PROPANONE** 2-Propanone, 1-(methylthio)- 2-Propanone, (methylthio)- (Methylthio)acetone α-(Methylthio)acetone α-(Methylthio)propanone 2-Thio-4-pentanone
3883	**3-(METHYLTHIO)PROPYL ACETATE** 1-Propanol, 3-(methylthio)-, acetate 3-Acetoxypropyl methyl sulfide Acetic acid, 3-(methylthio)propyl ester Methionyl acetate
3884	**(E)-3-(Z)-6-NONADIEN-1-OL** 3,6-Nonadien-1-ol, (E,Z)
3885	**(Z)(Z)-3,6-NONADIEN-1-OL** 3,6-Nonadien-1-ol, (Z,Z)
3886	**8-OCIMENYL ACETATE** 2,6-Dimethyl-2,5,7-octatriene-1-yl acetate Piperitanate
3887	**(E)-2-OCTEN-1-OL** 2-(E)-Octenol 2-Octen-1-ol, (E)- *trans*-2-Octen-1-ol
3888	**(E)-2-OCTEN-4-OL** *trans*-2-Octen-4-ol Butyl propenyl carbinol
3889	**(E)-2-(2-OCTENYL)CYCLOPENTANONE** Cyclopentanone, 2-(2-octenyl)- 2-(2-octenyl)cyclopentanone
3890	**(Z)-5-OCTENYL PROPIONATE** *cis*-5-Octen-1-yl propionate (Z)-5-Octen-1-yl propionate (Z)-5-Octen-1-yl propanoate 5-Octen-1-ol, propanoate, (Z)-
3891	**2-OXOPENTANEDIOIC ACID** Pentanedioic acid, 2-oxo- 2-Oxopentanedioic acid 2-Oxoglutaric acid 2-Ketoglutaric acid
3892	**2-OXO-3-PHENYLPROPIONIC ACID** 3-Phenylpyruvic acid 3-Phenyl-2-oxopropanoic acid
3893	**2-PENTYL BUTYRATE** Butanoic acid, 1-methylbutyl ester 2-Pentyl butanoate
3894	**PHENYLETHYL MERCAPTAN** 2-Phenylethanethiol 2-Phenethylthiol 2-Phenethyl mercaptan
3895	**PRENYL THIOACETATE** Ethanethioic acid, S-(3-methyl-2-buten-1-yl) ester Thioacetic acid, S-(3-methyl-but-2-en-1-yl) ester
3896	**PRENYLTHIOL** Prenyl mercaptan 2-Butene-1-thiol, 3-methyl- 3-Methyl-2-buten-1-thiol 3-Methyl-2-butenyl mercaptan 3-Methyl-2-butenthiol-1
3897	**2-PROPANETHIOL** Isopropyl mercaptan
3898	**1-PYRROLINE** 3,4-Dihydro-(2H)-pyrroline
3899	**SARCODACTYLIS OIL** *Citrus medica* L. var. *Sarcodactylis swingle* Fingered citron
3900	**SODIUM DIACETATE** Acetic acid, sodium salt Sodium ethanoate Ethanoic acid, sodium salt
3901	**SODIUM 3-MERCAPTOOXOPROPIONATE** Sodium 3-mercapto-2-oxopropanoate Sodium mercaptopyruvate Pyruvic acid, 3-mercapto-, sodium salt 3-Mercapto-2-oxopropionic acid, sodium salt
3902	**TEA TREE OIL** *Melaleuca alternifolia*
3903	**2,3,4-TRIMETHYL-3-PENTANOL** Diisopropyl methyl carbinol 3-Pentanol, 2,3,4-trimethyl-
3904	**VANILLIN 3-(*l*-MENTHOXY)PROPANE-1,2-DIOL ACETAL** 4-(*l*-Menthoxymethyl)-2-phenyl-1,3-dioxolane 4-[2-(methylethyl)-5-methylcyclohexyloxy)]-2,5-dioxolanyl-2 methoxyphenol
3905	**VANILLIN PROPYLENE GLYCOL ACETAL** Phenol, 2-methoxy-4-(4-methyl-1,3-dioxalan-2-yl)-

Tables 2 & 3 on pages 82–92 →

Table 2 **Use levels for new FEMA GRAS flavoring substances on which the FEMA Expert Panel based its judgments that the substances are generally recognized as safe (GRAS)**

	Average usual ppm/Average maximum ppm								
	1	2	3	4	5	6	7	8	9
	3-Acetyl-mercapto-hexyl acetate	2-Acetyl-2-thiazoline	L- and DL-Alanine	L-Arginine	1-Buten-1-yl methyl sulfide	3-Carene	Cycloionone	Daidai peel oil	1-Decen-3-ol
Category	FEMA No. 3816	3817	3818	3819	3820	3821	3822	3823	3824
Baked goods	0.01/0.1	0.02/0.2	75/375	20/100	0.06/1	10/50	10/30	424/848	2.01/10
Beverages (nonalcoholic)	0.005/0.05		50/250	3/30	0.2/2	15/50	0.1/1	260/520	0.001/0.005
Beverages (alcoholic)	0.01/0.1		50/150	3/30		20/60	0.5/5	105/210	0.001/0.005
Breakfast cereal		0.01/0.1	50/150	20/100		10/50			0.6/2.0
Cheese			10/20	15/100		1/5			0.01/0.05
Chewing gum	0.05/0.3	0.05/0.5	5/10	3/15		60/100	10/50		0.001/0.003
Condiments/ relishes			20/100	2/25		10/50		45/90	0.001/0.005
Confectionery frostings	0.01/0.1	0.01/0.1	25/100	3/15		20/60	0.5/5		0.001/0.003
Egg products			50/250	5/10					0.01/0.05
Fats/oils		0.01/0.1	10/30	5/15	0.01/0.04	5/30			0.01/0.05
Fish products		0.02/0.2	50/250	15/30		1/5			0.02/0.10
Frozen dairy	0.01/0.1		60/200	5/15		20/50	0.5/5	90/180	0.001/0.005
Fruit ices	0.01/0.1		10/20	5/15		20/50	0.2/2		0.001/0.005
Fruit juices									
Gelatins/ puddings	0.01/0.1		50/150	3/15	0.1/1	5/40	0.2/5	138/276	0.001/0.003
Gravies		0.02/0.2	200/1,000	15/100	0.1/1	5/20			0.05/0.25
Hard candy	0.01/0.1	0.01/0.1	50/200	1/20		40/80	1/10		0.001/0.003
Imitation dairy			50/150	5/10		1/5			0.001/0.005
Instant coffee/tea	0.0001/0.001		100/500	10/100		5/20	0.1/1		0.002/0.01
Jams/jellies			5/10	2/15		5/40	0.5/5		0.002/0.005
Meat products		0.02/0.2	100/500	15/100	0.4/4	1/5		23/46	0.02/0.10
Milk products	0.01/0.1		50/150	5/15		20/60	0.5/5		0.001/0.005
Nut products			75/225	15/100		5/20			0.01/0.05
Other grains		0.01/0.1	10/20	5/10		10/50			0.01/0.1
Processed fruits	0.01/0.05		10/30	2/15		5/20	0.5/5		0.001/0.005
Processed vegetables			5/10	3/5		5/20			0.10/0.50
Poultry		0.02/0.2	100/500	15/100		1/5			0.01/0.05
Reconstituted vegetables			5/10	5/25		5/20			0.02/0.10
Seasonings/ flavors			2,000/4,000	10/250	5/5	10/50			100.0/1,000
Snack foods		0.05/0.5	100/200	15/250		5/30			0.05/0.25
Soft candy	0.01/0.1	0.01/0.1	25/100	3/15		20/60	0.5/5	306/312	0.001/0.003
Soups		0.02/0.2	100/500	5/250		5/20			0.10/0.05
Sugar substitutes			10/20	3/15		1/10			
Sweet sauces			25/100	3/15		15/50	0.5/5		0.001/0.003

Table 2 **Use levels for new FEMA GRAS flavoring substances, *continued***

	Average usual ppm/Average maximum ppm								
	10	11	12	13	14	15	16	17	18
Category	Diethyl sulfide FEMA No. 3825	2,5-Dihydroxy-1,4-dithiane 3826	Diisopropyl disulfide 3827	2,4-Dimethylanisole 3828	(E)-2-(3,7-Dimethyl-2,6-octadienyl)-cyclopentanone 3829	(E)-3,7-Dimethyl-1,5,7-octatrien-3-ol 3830	1,4-Dithiane 3831	Ethyl 2,4,7-decatrienoate 3832	2-Ethylhexanethiol 3833
Baked goods	1/6	0.02/7.5	0.06/1	0.1/0.2	30/100		0.02/8		0.1/5
Beverages (nonalcoholic)	0.2/2		0.2/2		5/25	0.05/0.5			0.1/5
Beverages (alcoholic)	0.2/2					0.2/2			
Breakfast cereal								0.01/0.02	0.1/5
Cheese									
Chewing gum					300/1,000	5/50		0.05/0.1	
Condiments/relishes	0.2/2								
Confectionery frostings						0.2/2			
Egg products									
Fats/oils	0.01/0.04		0.01/0.04					0.01/0.03	
Fish products									
Frozen dairy	0.2/2			0.1/0.1		0.2/2			0.1/5
Fruit ices					25/30	0.2/2		0.02/0.05	
Fruit juices									
Gelatins/puddings	0.1/1		0.1/1			0.5/5			
Gravies	0.1/1		0.1/1						0.1/5
Hard candy					25/75	0.5/5		0.02/0.05	
Imitation dairy	0.1/0.1				15/30				
Instant coffee/tea						0.2/2			
Jams/jellies									
Meat products	4/44	0.02/2	0.4/4				0.02/2		0.1/5
Milk products				0.1/0.1		0.2/2		0.01/0.03	0.1/5
Nut products				0.1/0.3					
Other grains									
Processed fruits						0.1/1			
Processed vegetables									
Poultry									
Reconstituted vegetables									
Seasonings/flavors	1,000/1,000	620/620	6/6				20/20	0.005/0.01	100/1,000
Snack foods				0.1/0.3					
Soft candy	0.2/2			0.1/0.3	15/75	0.5/5		0.01/0.02	0.1/5
Soups		0.02/1					0.02/1		0.1/5
Sugar substitutes									
Sweet sauces									0.1/5

Table 2 **Use levels for new FEMA GRAS flavoring substances, *continued***

	Average usual ppm/Average maximum ppm								
	19	20	21	22	23	24	25	26	27
	Ethyl 2-(methyldithio) propionate	Ethyl 2-(methylthio) acetate	Ethyl 3-(methylthio) butyrate	Ethyl vanillin isobutyrate	Ethyl vanillin propylene glycol acetal	Farnesene	4-[(2-Furan-methyl)thio]-2-pentanone	(Z)-4-Hept-en-1-ol	1-Hexanethiol
Category	FEMA No. 3834	3835	3836	3837	3838	3839	3840	3841	3842
Baked goods	1/10	0.1/0.5	1/10	10/50	55/121	10/50	10/50		0.1/5
Beverages (nonalcoholic)		0.1/0.2			23/39	5/20	0.5/5	2/10	0.1/5
Beverages (alcoholic)		0.1/0.2			7/13	5/20	2.5/25	5/20	
Breakfast cereal					351/429	10/50	5/25		0.1/5
Cheese						2/10			
Chewing gum				20/50	49/49	30/90	20/50	50/100	
Condiments/ relishes					17/17	5/15			
Confectionery frostings		0.1/0.2		10/50	125/352	20/60	5/25		
Egg products									
Fats/oils					0.08/0.2	5/30			
Fish products						1/5			
Frozen dairy		0.1/0.2		10/30	16/35	5/40			0.1/5
Fruit ices						5/20			
Fruit juices									
Gelatins/ puddings		0.1/0.2		10/50	24/52	2/10			
Gravies	1/2	0.1/0.2	1/2			5/20			0.1/5
Hard candy		0.1/0.2		10/30	21/39	10/50	10/20	5/20	
Imitation dairy						1/5			
Instant coffee/tea						5/20	5/50	5/20	
Jams/jellies						2/10			
Meat products	1/10	0.1/0.5	1/10		5/5	1/5			0.1/5
Milk products				10/50	1,817/1,824	10/30	5/20	5/20	0.1/5
Nut products						5/20			
Other grains						10/50			
Processed fruits						5/30			
Processed vegetables	0.5/5		0.5/5			2/10			
Poultry						1/5			
Reconstituted vegetables						5/20			
Seasonings/ flavors	10/10	20/20	10/10			10/50			0.5/5
Snack foods						5/20			
Soft candy		0.1/0.2			74/116	10/30	5/20	5/20	0.1/5
Soups	1/10	0.1/0.5	1/10			5/20			0.1/5
Sugar substitutes						1/10			
Sweet sauces					133/224	2/10			0.1/5

Table 2 **Use levels for new FEMA GRAS flavoring substances, *continued***

	Average usual ppm/Average maximum ppm								
	28	29	30	31	32	33	34	35	36
	3-Hydroxy-2-oxopropionic acid	β-Ionyl acetate	α-Isomethyl ionyl acetate	Litsea cubeba berry oil	L-Lysine	*cis*-and *trans*-P-1(7), 8-Methadien-2-yl acetate	3-(*l*-Menthoxy)-2-methyl-propane-1, 2-diol	3-Mercapto-hexanol	3-Mercapto-hexyl acetate
Category	FEMA No. 3843	3844	3845	3846	3847	3848	3849	3850	3851
Baked goods	0/0	0.15/3	0.15/3	178/356	70/150		100/500	0.05/0.2	0.01/0.1
Beverages (nonalcoholic)	0.3/5	0.05/1	0.05/1	28/56	3/30	2/10	300/500	0.005/0.05	0.005/0.05
Beverages (alcoholic)	0/0			5.9/11.8	3/30	5/20	300/500	0.01/0.1	0.01/0.1
Breakfast cereal					30/150		100/500		
Cheese	0.5/5			0.2/0.4	70/150				
Chewing gum		0.5/5	0.5/5		5/25	50/100	3,000/4,000	0.05/0.3	0.05/0.3
Condiments/ relishes				10/20	10/30		25/100		
Confectionery frostings		0.1/2	0.1/2		15/25		100/500	0.01/0.1	0.01/0.1
Egg products					50/100				
Fats/oils	0.4/5				10/30				
Fish products					50/125				
Frozen dairy	0.7/5	0.1/2	0.1/2	33.6/67.2	70/150		100/500	0.01/0.1	0.01/0.1
Fruit ices	0.1/5	0.07/1.5	0.07/1.5		10/30		15/50	0.01/0.1	0.01/0.1
Fruit juices									
Gelatins/ puddings		0.2/2	0.2/2	210/520	10/25		500/1,000	0.01/0.1	0.01/0.1
Gravies				0.75/1.5	70/150		50/200		
Hard candy		0.25/4	0.25/4		10/30	5/20	250/500	0.01/0.1	0.01/0.1
Imitation dairy	0.1/5	0.1/2	0.1/2		70/150		100/500		
Instant coffee/tea					15/30	5/20	25/100		0.0001/0.001
Jams/jellies		0.1/2	0.1/2		15/25		50/250		
Meat products				2.25/4.5	70/150		10/25		
Milk products	0.5/5	0.1/2	0.1/2		70/150		20/50	0.01/0.1	0.01/0.1
Nut products					15/50				
Other grains					15/100				
Processed fruits	0.1/1				10/30		50/150	0.01/0.1	0.01/0.05
Processed vegetables	0.6/10				15/25		25/100		
Poultry					50/100				
Reconstituted vegetables	0.5/10				10/20				
Seasonings/ flavors	50/100				50/250				
Snack foods					50/250		20/100		
Soft candy		0.12/2.5	0.12/2.5	181/362	10/30	5/20	150/500		0.01/0.1
Soups					50/250		25/100		
Sugar substitutes	0.5/5				10/50				
Sweet sauces					10/25		25/100		

Table 2 **Use levels for new FEMA GRAS flavoring substances, *continued***

	Average usual ppm/Average maximum ppm								
	37	38	39	40	41	42	43	44	45
	3-Mercapto-hexyl butyrate	3-Mercapto-hexyl hexanoate	3-Mercapto-3-methyl-1-butanol	3-Mercapto-3-methyl-butyl formate	1-Mercapto-2-propanone	S-Methyl benzo-thioate	3-Methyl butane-thiol	Methyl (E)-2-(Z)-4-decadien-oate	Methyl ethyl sulfide
Category	FEMA No. 3852	3853	3854	3855	3856	3857	3858	3859	3860
Baked goods	0.02/0.2	0.02/0.2	0.02/0.05	0.0001/5	0.3/3	0.1/5	0.1/5	1/10	1/6
Beverages (nonalcoholic)	0.005/0.05	0.005/0.05	0.01/0.02	0.00001/5	0.3/3	0.1/5	0.1/5	0.2/2	0.2/2
Beverages (alcoholic)	0.01/0.1	0.01/0.1		0.0001/0.08				0.4/4	0.2/2
Breakfast cereal				0.02/5	0.3/3	0.1/5	0.1/5		
Cheese									
Chewing gum	0.05/0.3	0.05/0.3	0.1/0.5	0.0001/0.1				10/50	
Condiments/ relishes									0.2/2
Confectionery frostings	0.01/0.1	0.01/0.1	0.01/0.02	0.0001/0.04					
Egg products									
Fats/oils									0.04/0.04
Fish products									
Frozen dairy	0.01/0.1	0.01/0.1	0.01/0.02	0.03/5		0.1/5	0.1/5		0.2/2
Fruit ices	0.01/0.1	0.01/0.2						1/10	
Fruit juices									
Gelatins/ puddings	0.01/0.1		0.01/0.02						0.1/1
Gravies			0.02/0.05	0.1/5	0.3/3	0.1/5	0.1/5		0.1/1
Hard candy	0.01/0.1	0.01/0.1	0.02/0.05	0.0001/0.1				2/20	
Imitation dairy									0.01/0.1
Instant coffee/tea				0.0001/0.04				0.4/4	
Jams/jellies								2/20	
Meat products			0.02/0.05	0.1/5	0.3/3	0.1/5	0.1/5		4/44
Milk products	0.01/0.1	0.01/0.1	0.01/0.02	0.0001/5		0.1/5	0.1/5	1/10	
Nut products				0.0001/0.001					
Other grains									
Processed fruits	0.01/0.1	0.01/0.1						0.4/4	
Processed vegetables									
Poultry									
Reconstituted vegetables									
Seasonings/ flavors				100/1,000	5,000/10,000	100/1,000	0.2/2		1,000/1,000
Snack foods			0.02/0.05						
Soft candy	0.01/0.1	0.01/0.1	0.01/0.02	0.0001/5	0.3/3	0.1/5	0.1/5	2/20	0.2/2
Soups			0.02/0.05	0.1/5	0.3/3	0.1/5	0.1/5		
Sugar substitutes									
Sweet sauces				0.1/5	0.3/3	0.1/5	0.1/5		

Table 2 Use levels for new FEMA GRAS flavoring substances, *continued*

	Average usual ppm/Average maximum ppm								
	46	47	48	49	50	51	52	53	54
	Methyl ethyl trisulfide	S-Methyl hexane-thioate	2-(4-Methyl-2-hydroxyphenyl) propionic acid -γ-lactone	S-methyl-3-methyl-butane-thioate	Methyl-3-methyl-1-butenyl disulfide	2-Methyl-2-(methyldithio) propanal	S-Methyl 4-methyl pentane-thioate	(E)-7-Methyl-3-octen-2-one	3-Methyl-2-oxobutanoic acid
Category	FEMA No. 3861	3862	3863	3864	3865	3866	3867	3868	3869
Baked goods	0.06/1	0.1/5		1.5/7.5	0.06/1	0.1/1	0.1/5	0.2/1	0/0
Beverages (nonalcoholic)	0.2/2	0.1/5	1/5	0.1/5	0.2/2	0.1/0.5	0.1/5	0.1/1	0.5/10
Beverages (alcoholic)			2/10	0.005/0.015					1/10
Breakfast cereal		0.1/5		0.3/5			0.1/5	0.2/1	
Cheese				0.5/1.5				0.2/2	0.8/10
Chewing gum			10/50	0.01/0.03					5/10
Condiments/ relishes				0.02/0.10		0.1/0.2		0.2/1	1/5
Confectionery frostings				0.01/0.03				0.2/1	1/10
Egg products				0.2/0.6				0.2/1	
Fats/oils	0.01/0.04			0.2/0.6	0.01/0.04			0.3/1	0.5/5
Fish products				0.05/0.15				0.1/1	
Frozen dairy		0.1/5		0.2/5		0.1/0.5	0.1/5	0.3/2	1.2/10
Fruit ices				0.01/0.03				0.1/1	0.5/3
Fruit juices									
Gelatins/ puddings	0.1/1			0.01/0.03	0.1/1			0.1/1	0.7/5
Gravies	0.1/1	0.1/5		0.05/5	0.1/1	0.1/0.2	0.1/5	0.2/2	1/10
Hard candy			5/20	0.01/0.03					5/10
Imitation dairy				0.2/1.0				0.2/1	2/10
Instant coffee/tea			2/10	0.005/0.025				0.1/1	0.1/1
Jams/jellies				0.01/0.05					1/10
Meat products	0.4/4	0.1/5		0.05/5	0.4/4	0.1/1	0.1/5	0.3/2	
Milk products		0.1/5	2/10	0.05/5			0.1/5	0.2/1	0.5/5
Nut products				0.02/0.06				0.2/2	
Other grains				0.2/1.0				0.2/1	
Processed fruits				0.01/0.03				0.1/1	0.1/1
Processed vegetables				0.01/0.03		0.5/5		0.2/2	0.01/1
Poultry				0.05/0.15				0.2/1	
Reconstituted vegetables				0.01/0.10				0.1/1	0.6/10
Seasonings/ flavors	0.3/0.3	100/1,000		200/10,000	5/5	500/500	100/1,000	0.1/2	50.0/100
Snack foods				0.5/1.5				0.2/2	
Soft candy		0.1/5	5/20	0.01/5		0.1/0.5	0.1/5	0.1/1	0.5/5
Soups		0.1/5			0.02/5	0.5/5	0.1/5	0.2/2	1/10
Sugar substitutes								0.2/1	0.03/5
Sweet sauces		0.1/5		0.05/5			0.1/5	0.1/1	

Table 2 **Use levels for new FEMA GRAS flavoring substances, *continued***

	Average usual ppm/Average maximum ppm								
	55	56	57	58	59	60	61	62	63
	3-Methyl-2-oxopentanoic acid	4-Methyl-2-oxopentanoic acid	Methyl phenyl disulfide	Methyl phenyl sulfide	2-Methyl-1-propanethiol	Methyl sulfinyl methane	S-Methyl thioacetate	3-Methylthio-hexanol	*bis*-(Methylthio)-methane
Category	FEMA No. 3870	3871	3872	3873	3874	3875	3876	3877	3878
Baked goods			0.06/1	0.06/1	0.1/5	0.1/5	0.1/5	0.5/1	0.6/6
Beverages (nonalcoholic)	1.0/10	0.05/5	0.2/2	0.2/2	0.1/5	0.1/5	0.1/5	0.05/0.1	0.2/2
Beverages (alcoholic)	0.5/5	1/5						0.5/1	0.2/2
Breakfast cereal					0.1/5	0.1/5	0.1/5		
Cheese	0.5/5	1/10							
Chewing gum	1.0/5	0.5/5						1/5	
Condiments/ relishes	0.5/10	1/5							0.2/2
Confectionery frostings	1.0/5	1/5							
Egg products									
Fats/oils	0.3/10	0.5/5	0.01/0.04	0.01/0.04					0.04/0.04
Fish products									
Frozen dairy	1.0/10	0.5/10			0.1/5	0.1/5	0.1/5		0.2/2
Fruit ices	1.0/10	1/5						0.5/1	
Fruit juices									
Gelatins/ puddings	0.5/5	0.5/5	0.1/1	0.1/1					0.1/1
Gravies	1.0/5	1/5	0.1/1	0.1/1	0.1/5	0.1/5	0.1/5		0.1/1
Hard candy	1.0/5	0.1/5						0.5/2	
Imitation dairy	0.5/5	0.5/5							0.01/0.1
Instant coffee/tea	0.1/1	0.1/1							
Jams/jellies	1.0/5	1/5							
Meat products			0.4/4	0.4/4	0.1/5	0.1/5	0.1/5		4/44
Milk products	0.5/5	1/10			0.1/5	0.1/5	0.1/5	1/3	
Nut products									
Other grains									
Processed fruits	0.1/1	0.1/1							
Processed vegetables	0.1/1	0.1/1							
Poultry									
Reconstituted vegetables	1.0/5								
Seasonings/ flavors	50/100	50/100	5/5	0.5/1	3,000/10,000	100/1,000	100/1,000		1,000/1,000
Snack foods									
Soft candy	0.1/5	0.3/3			0.1/5	0.1/5	0.1/5	0.5/1	0.2/2
Soups	1.0/10	1/10			0.1/5	0.1/5	0.1/5		
Sugar substitutes	0.5/5	0.5/5							
Sweet sauces	1.0/10	1/10			0.1/5	0.1/5	0.1/5		

Table 2 Use levels for new FEMA GRAS flavoring substances, *continued*

	Average usual ppm/Average maximum ppm								
	64	65	66	67	68	69	70	71	72
	Methylthio-methyl butyrate	Methylthio-methyl hexanoate	4-(Methylthio)-2-oxobutan-oic acid	1-Methylthio-2-propanone	3-(Methylthio)-propyl acetate	(E)-3-(Z)-6-Nonadien-1-ol	(Z)(Z)-3, 6-Nonadien-1-ol	8-Ocimenyl acetate	(E)-2-Octen-1-ol
Category	FEMA No. 3879	3880	3881	3882	3883	3884	3885	3886	3887
Baked goods	1/10	1/10		0.1/1	0.1/0.5	0.3/0.6	0.3/0.6		
Beverages (nonalcoholic)				0.1/0.5	0.1/0.2	0.2/0.5	0.2/0.5	1/5	
Beverages (alcoholic)					0.1/0.2	0.2/0.2	0.2/0.2	2/10	
Breakfast cereal									
Cheese			0.5/5						0.01/0.1
Chewing gum								20/100	
Condiments/ relishes			0.1/5	0.1/0.2					
Confectionery frostings			0.1/5		0.1/0.2				
Egg products									
Fats/oils			0.3/5			0.05/0.05	0.05/0.05		
Fish products									
Frozen dairy				0.1/0.5	0.1/0.2	0.4/0.9	0.4/0.9		
Fruit ices									
Fruit juices									
Gelatins/ puddings					0.1/0.2	0.2/0.5	0.2/0.5		
Gravies	1/2	1/2		0.1/0.2	0.1/0.2	0.01/0.01	0.01/0.01		0.02/0.1
Hard candy								10/50	
Imitation dairy									
Instant coffee/tea			0.5/5					2/10	
Jams/jellies									
Meat products	1/10	1/10	0.5/5	0.1/1	0.1/0.5				0.01/0.1
Milk products			0.5/5					2/10	
Nut products									0.01/0.1
Other grains									
Processed fruits									
Processed vegetables	0.5/5	0.5/5	0.1/5	0.5/5		0.02/0.03	0.02/0.03		0.1/0.2
Poultry			0.3/5						0.01/0.1
Reconstituted vegetables									
Seasonings/ flavors	500/500	300/300		500/500	50/50				0.1/0.2
Snack foods						0.02/0.03	0.02/0.03		0.01/0.1
Soft candy				0.1/0.5	0.1/0.2	0.4/1.0	0.4/1.0		
Soups	1/10	1/10	1/5	0.5/5	0.1/0.5				0.01/0.1
Sugar substitutes									
Sweet sauces									

Table 2 **Use levels for new FEMA GRAS flavoring substances, *continued***

	Average usual ppm/Average maximum ppm								
	73	74	75	76	77	78	79	80	81
Category	(E)-2-Octen-4-ol	(E)-2-(2-Octenyl)-cyclopentanone	(Z)-5-Octenyl propionate	2-Oxopentanedioic acid	2-Oxo-3-phenylpropionic acid	2-Pentyl butyrate	Phenylethyl mercaptan	Prenyl thioacetate	Prenylthiol
	FEMA No. 3888	3889	3890	3891	3892	3893	3894	3895	3896
Baked goods	10/40	30/100					0.05/0.01	0.05/0.1	0.05/5
Beverages (nonalcoholic)	1/5	5/25	0.5/2	0.1/5	0.5/10	1/10	0.001/0.01	0.001/0.01	0.001/5
Beverages (alcoholic)	3/15		1/5			2/20	0.005/0.05	0.005/0.05	0.005/0.05
Breakfast cereal	5/20				1/5		0.01/0.05	0.01/0.05	0.01/5
Cheese				0.5/5	0.5/5				
Chewing gum	30/90	300/1,000	10/50		1/5	50/100	0.05/0.1	0.05/0.1	0.05/0.1
Condiments/relishes									
Confectionery frostings	10/40		5/10		1/5		0.001/0.01		0.01/0.05
Egg products									
Fats/oils				0.4/5					
Fish products									
Frozen dairy	5/20		5/10	1/5					0.1/5
Fruit ices	10/40	25/30	2/5		0.5/5				
Fruit juices									
Gelatins/puddings	5/20				0.5/5				
Gravies							0.005/0.05		0.1/5
Hard candy	10/40	25/75	5/20		1/5	5/50	0.01/0.05	0.01/0.05	0.01/0.05
Imitation dairy		15/30							
Instant coffee/tea						5/20	0.001/0.01	0.001/0.01	0.001/0.01
Jams/jellies									
Meat products							0.01/0.05	0.01/0.05	0.01/5
Milk products	3/15		5/10	0.5/5	0.5/5	5/50	0.005/0.05	0.005/0.05	0.005/5
Nut products									
Other grains					1/5				
Processed fruits	5/20		5/10	0.1/1	0.1/1				
Processed vegetables									
Poultry									
Reconstituted vegetables									
Seasonings/flavors					50/100				0.2/2
Snack foods							0.01/0.05		
Soft candy	5/20	15/75	5/10		1/5				0.1/5
Soups				0.1/5			0.001/0.01		0.1/5
Sugar substitutes					0.50/5				
Sweet sauces					1/5				0.1/5

Table 2 Use levels for new FEMA GRAS flavoring substances, *continued*

	Average usual ppm/Average maximum ppm								
	82	83	84	85	86	87	88	89	90
Category	2-Propanethiol FEMA No. 3897	1-Pyrroline 3898	Sarcodactylis oil 3899	Sodium Diacetate 3900	Sodium 3-mercaptooxo-propionate 3901	Tea tree oil 3902	2,3,4-Trimethyl-3-pentanol 3903	Vanillin 3-(*l*-menthoxy)-propane-1,2-diol acetal 3904	Vanillin propylene glycol acetal 3905
Baked goods	0.1/5		93/186			10/30	1/3	5/20	97/242
Beverages (nonalcoholic)	0.1/5	0.0005/0.0025	68.6/137.20			10/30	0.2/0.5	2/10	51/127
Beverages (alcoholic)		0.0025/0.005	91.1/182.2			10/50	0.2/0.5	2/10	39/61
Breakfast cereal	0.1/5					10/30		5/20	459/459
Cheese					0.8/5	10/30			
Chewing gum						10/50	1/5	10/20	106/578
Condiments/ relishes						10/50		5/20	
Confectionery frostings						10/30	0.5/1.5	5/10	775/999
Egg products					1/5	10/30		5/10	
Fats/oils					0.5/5	10/50			125/130
Fish products		0.0025/0.01				10/50		2/10	
Frozen dairy	0.1/5		49.5/99		0.1/3	10/30			35/72
Fruit ices						10/30			
Fruit juices									
Gelatins/ puddings			200/400		1/10	10/30		2/10	62/152
Gravies	0.1/5	0.01/0.1			1/10	10/50		10/20	
Hard candy						10/50		10/20	34/251
Imitation dairy						10/30		2/5	
Instant coffee/tea						10/30			
Jams/jellies						10/30		2/10	
Meat products	0.1/5	0.0001/0.001	150/300		1/5	10/50		2/10	2/4
Milk products	0.1/5				0.5/5	10/30			287/409
Nut products		0.0003/0.003				10/30	0.5/1.5	2/10	
Other grains						10/30		2/10	
Processed fruits						10/30	0.5/1.5		
Processed vegetables					0.01/1	10/50		5/10	
Poultry					1/10	10/30		2/10	
Reconstituted vegetables					0.5/5	10/50		2/10	
Seasonings/ flavors	20/200					10/30		10.0/20	
Snack foods		0.005/0.02		15,000/30,000		10/50		10/20	260/260
Soft candy	0.1/5		95.2/190.4			10/30		5/10	321/530
Soups	0.1/5	0.01/0.01				10/50		10/20	
Sugar substitutes						10/30			
Sweet sauces	0.1/5					10/30		2/10	465/472

Table 3 **Updated use levels for flavoring substances previously recognized as FEMA GRAS on which the FEMA Expert Panel based its judgments that the substances are generally recognized as safe. Superscript a represents a new use level**

	Average usual ppm/Average maximum ppm							
	1	2	3	4	5	6	7	8
	Methyl anthranilate	Sodium acetate	N-Ethyl-2-isopropyl-5-methyl-cyclohexane carboxamide	Thaumatin (Talin)	*l*-Menthyl lactate	*l*-Menthol ethylene glycol carbonate	*l*-Menthol propylene glycol carbonate	Neohesperidine dihydrochalcone
	FEMA No. 2682	3024	3455	3732	3748	3805	3806	3811
Category	**GRAS List No. 3**	**3**	**9**	**13**	**14**	**17**	**17**	**17**
Baked goods	38/38	15/15		0.5[a]/2[a]	60[a]/250[a]	60[a]/250[a]	60[a]/250[a]	4[a]/4[a]
Beverages (nonalcoholic)	40[a]/40[a]	1.5/1.5	10/10	0.2[a]/5[a]	30[a]/120[a]	30[a]/120[a]	30[a]/120[a]	2/3
Beverages (alcoholic)	0.2[a]/2	1.5/1.5	10/10	1[a]/10[a]	100[a]/400[a]	100[a]/400[a]	100[a]/400[a]	3[a]/3[a]
Breakfast cereal		0.01/60		1[a]/2[a]	15[a]/60[a]	15[a]/60[a]	15[a]/60[a]	3[a]/3[a]
Cheese				5[a]/10[a]	15[a]/60[a]	15[a]/60[a]	15[a]/60[a]	3[a]/4[a]
Chewing gum	200[a]/1,583		1,200/1,200	300/300	1,000[a]/2,000[a]	5,000/20,000	5,000/10,000	4/5
Condiments/relishes				5[a]/30[a]	100[a]/400[a]	100[a]/400[a]	100[a]/400[a]	2/3
Confectionery frostings			10/10	2[a]/10[a]	500[a]/2,000[a]	500/2,000	500[a]/2,000[a]	3[a]/3[a]
Egg products				0.5[a]/2[a]				2[a]/3[a]
Fats/oils		1/5						4/4
Fish products				0.5[a]/2[a]				2[a]/3[a]
Frozen dairy	40[a]/40[a]		10/10	1[a]/5[a]	30[a]/120[a]	30[a]/120[a]	30[a]/120[a]	2/3
Fruit ices	40[a]/40[a]		10/10	0.5[a]/3[a]	100[a]/400[a]	100[a]/400[a]	100[a]/400[a]	1/2
Fruit juices								
Gelatins/puddings	20/20		10/10	2[a]/10[a]	200[a]/800[a]	500/2,000	200[a]/800[a]	2/3
Gravies				0.5[a]/2[a]	25[a]/100[a]	25[a]/100[a]	25[a]/100[a]	3[a]/4[a]
Hard candy	80[a]/161	200/200	100[a]/100[a]	5[a]/10[a]	1,000[a]/2,000[a]	500/2,000	1,000/3,000	2/4
Ice cream/ices		15/15						
Imitation dairy				1[a]/10[a]	15[a]/60[a]	15[a]/60[a]	15[a]/60[a]	3/4
Instant coffee/tea				0.5[a]/2[a]	100[a]/400[a]	100[a]/400[a]	100[a]/400[a]	2[a]/3[a]
Jams/jellies	6[a]/6[a]	0.3/0.3		2[a]/10[a]				2/3
Meat products		0.5/1		0.5[a]/2[a]				2[a]/3[a]
Milk products				1[a]/5[a]	200[a]/800[a]	200[a]/800[a]	200[a]/800[a]	2/3
Nut products				0.5[a]/2[a]				3[a]/4[a]
Other grains		6/6		0.5[a]/2[a]				3[a]/4[a]
Processed fruits				1[a]/5[a]	100[a]/400[a]	100[a]/400[a]	100[a]/400[a]	2[a]/3[a]
Processed vegetables				0.5[a]/2[a]				2/3
Poultry				0.5[a]/2[a]				2[a]/3[a]
Reconstituted vegetables								2[a]/3[a]
Seasonings/flavors				0.5[a]/1[a]				3[a]/4[a]
Snack foods		15,000[a]/30,000[a]		0.5[a]/2[a]	25[a]/100[a]	25[a]/100[a]	25[a]/100[a]	3[a]/3[a]
Soft candy	80[a]/80[a]	0.9/0.9		2[a]/10[a]	500[a]/2,000[a]	500[a]/2,000[a]	500[a]/2,000[a]	2/3
Soups		0.1/0.5		0.5[a]/2[a]	25[a]/100[a]	25[a]/100[a]	25[a]/100[a]	1/2
Sugar substitutes								4[a]/4[a]
Sweet sauces				2[a]/10[a]				2/3