GRAS Flavoring Substances 21

The 21st publication by the Expert Panel of the Flavor and Extract Manufacturers Association on recent progress in the consideration of flavoring ingredients generally recognized as safe under the Food Additives Amendment

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The Expert Panel of the Flavor and Extract Manufacturers Association continues to perform its function of rigorously evaluating the safety of flavoring substances under conditions of intended use. Formed more than 40 years ago, the Expert Panel has maintained a program to respond to the provision in the 1958 Food Additives Amendment [Public Law 85-929, 72 Stat. 1784 (1958), codified at 21 USC Section 348 (1988)] to the Federal Food, Drug, and Cosmetic Act that exempted from food additive status those substances "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." Based on this, substances "generally recognized as safe" (GRAS) by the FEMA Expert Panel are not considered to be food additives, and are excluded from mandatory premarket approval by the Food and Drug Administration.

During a GRAS assessment of a substance, the Expert Panel evaluates a combination of relevant data, including data specific to the substance as well as data for the chemical group to which the substance belongs. For example, a pyrazine derivative is reviewed individually and in the context of its chemical group (42 other pyrazine derivatives) (Smith et al., 2002a). The analysis of food and flavor exposure data, pharmacokinetics, metabolism, and toxicology for the structurally related group of substances provides the comprehensive basis of the GRAS decision. The breadth of the safety evaluation allows the Expert Panel to arrive at a "weight of evidence" decision concerning the GRAS status of each candidate substance.

In addition to assessing the GRAS status of new flavoring substances, the Expert Panel operates an ongoing program to comprehensively reassess the GRAS status of existing flavoring substances. In this manner, the Expert Panel revaluates the safety for an individual substance or group of substances based on most recent scientific information. The current reassessment program, known as "GRAS reaffirmation" or "GRASr" began in 1994 and is scheduled for completion in December 2005. As part of the GRASr program, the Expert Panel regularly publishes reviews of key scientific data on structurally related groups of flavoring substances on which GRAS decisions are based (Adams et al., 1996, 1997, 1998; Newberne et al., 1999; Smith et al., 2002a, b).

This article, the 21st GRAS publication, includes the results of the Expert Panel's review of 45 new GRAS flavoring substances (Tables 1 and 2). In addition, the Expert Panel has determined that new use levels and food categories for three flavoring substances are consistent with their current GRAS status (Table 3). In this article, the Expert Panel also critically reviews the results of chronic two-year bioassay studies performed at the National Toxicology Program (NTP) for *trans,trans*-2,4-hexadienal (FEMA No. 3429) and *trans*-cinnamaldehyde (FEMA No. 2286).

Safety Assessment of *trans, trans*-2,4-Hexadienal (FEMA 3429)

trans,trans-2,4-Hexadienal (CAS No. 142-83-6) is a linear aliphatic α,β-unsaturated dienal. In concentrated form, it exhibits a powerful irritating odor, but at concentrations used in flavorings (<1 ppm) it provides a sweet-green aroma. Based on a reported annual volume of 1.4 kg (Lucas et al., 1999), the daily per-capita intake (PCI) for "eaters only" is estimated to be approximately 0.003 µg/kg body weight /day from its use as a flavoring substance. The intake for the U.S. population in 1995 (260 million) was calculated as follows:

$$PCI = \frac{(1.4 \text{ kg/year})(10^9 \text{ µg/kg})}{(260\times10^6)(10\%, \text{ eaters only})(0.8)(365 \text{ days/year})(60 \text{ kg})}$$
$$= 0.003 \text{ µg/kg bw/day}$$

where 0.8 represents the assumption that only 80% of the flavor volume was reported in the survey (Lucas et al., 1999).

trans,trans-2,4-Hexadienal occurs naturally in a wide variety of foods, including kiwifruit, mango, peanuts, clams, and beer (Maarse et al., 1999). Based on quantitative data for its presence in traditional foods, human consumption of this aldehyde as a natural component of food has been estimated to be approximately 1,000 times its consumption from use as a flavoring substance (Stofberg and Grundschober, 1987).

In a two-year bioassay (NTP, 2001a), groups of 50 F344/N rats of both sexes were administered oral doses of 0, 22.5, 45, or 90 mg/kg bw/day of *trans,trans*-2,4-hexadienal by gavage for 105 weeks. Groups of B6C3F1 mice of both sexes were administered oral doses of 0, 30, 60, or 120 mg/kg bw/day of *trans,trans*-2,4-hexadienal by gavage for 105 weeks. The NTP subcommittee concluded:

"Under the conditions of these 2-year gavage studies, there was clear evidence of carcinogenic activity of 2,4-hexadienal in male and female F344/N rats and male and female B6C3F1 mice based on increased incidences of squamous cell neoplasms of the forestomach. The occurrence of squamous cell carcinoma of the oral cavity (tongue) in male B6C3F1 mice may have been related to the administration of 2,4-hexadienal."

In F344/N rats, the neoplastic response reported in the NTP study included statistically significant increases in the incidence of squamous cell papillomas of the forestomach at 45 ($P < 0.001$) and 90 mg/kg bw/day ($P < 0.001$) in males and at 45 ($P = 0.031$) and 90 mg/kg bw/day ($P < 0.001$) in females. There were also statistically significant ($P < 0.001$) increases in the incidence of forestomach epithelial hyperplasia at all dose levels in both sexes. There was no statistically significant increase in the incidence of squamous cell carcinomas of the forestomach in either males or females at any dose level.

Similarly, in B6C3F1 mice, there were statistically significant increases in the incidence of epithelial hyperplasia ($P = 0.007$) and squamous cell papillomas ($P = 0.030$) of the forestomach at 120 mg/kg bw/day in males and statistically significant increases in the incidence of epithelial hyperplasia ($P = 0.033$ at 60 mg/kg bw/day and $P < 0.001$ at 120 mg/kg bw/day) and squamous cell papillomas ($P = 0.004$ at 60 mg/kg bw/day and $P = 0.001$ at 120 mg/kg bw/day) at 60 and 120 mg/kg bw/day in females. At the highest dose level in females, a statistically significant ($P < 0.05$) increase (7/50) in the incidence of squamous cell carcinomas was reported. There were no other carcinomas observed in the two lower dose or control groups.

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The appearance of forestomach hyperplasia and squamous cell papillomas in rodents is a regular occurrence in bioassay gavage studies in which high concentrations of an irritant material in corn oil is delivered daily by dosing tube into the forestomach. These phenomena are consistently associated with administration of high concentrations of aldehydes, e.g., malonaldehyde, furfural, benzaldehyde, and *trans,trans*-2,4-hexadienal (NTP, 1988, 1990a, 1993a, 2001a) and other irritating substances, e.g., ethyl acrylate, dihydrocoumarin, and coumarin (NTP, 1990b, 1992) in corn oil by gavage. Squamous cell papillomas are benign lesions associated with squamous epithelium surfaces. A majority of papillomas arise as a result of chronic irritation, or from infection from some strains of viruses (Smith and Ford, 1993). Given these results, high irritating concentrations of aldehyde administered by gavage over the lifetime of a rodent may progress to malignant neoplasms, as was observed in the high-dose group of female mice.

Apparently, the combination of daily introduction of a dosing tube into the forestomach and delivery of high concentrations of an irritating test material in corn oil, which itself is a mild irritant and mitogen, was, in all probability, the source of the papillomas in the rodent forestomach. Gavage administration provides a bolus dose that exerts a traumatic effect on the forestomach epithelium. When repeated in chronic studies, it leads to chronic inflammation and regenerative hyperplasia. In contrast, the same total doses administered to rodents in the diet achieve maximum concentrations in the stomach and circulation that are significantly lower than those achieved by a bolus gavage dose. Therefore, the effects resulting from gavage administration would not be expected when 2,4-hexadienal is administered in the diet.

This conclusion is supported by the observation that the occurrence of squamous cell papillomas and forestomach hyperplasia following gavage administration of an irritant in corn oil for two years (NTP, 1986a) do not develop when the same substance is administered at similar intake levels in the diet (NTP, 1993b). In addition, recent two-year bioassays performed with both aliphatic and aromatic aldehydes [*trans*-cinnamaldehyde and 3,7-dimethyl-2,6-octadienal (citral)] administered microencapsulated in the diet at higher concentrations than those used in the gavage studies mentioned above show no evidence of either forestomach hyperplasia, forestomach papillomas or forestomach carcinomas (NTP, 2001b, 2002).

The relevance of the appearance of forestomach tumors in rodents to potential carcinogenic targets in humans has been the subject of much investigation (Clayson et al., 1990; Grice, 1988; Wester and Kroes, 1988). Although it has been suggested that the mucosa of the rodent forestomach is similar to that of the human esophagus, this is clearly not the case. The rodent forestomach has a storage function and contains mucosa of keratinizing squamous epithelium that is constantly exposed to the strong acid medium of the gastric contents. Conversely, the esophagus has no storage capacity and contains non-keratinizing squamous epithelium that is extremely sensitive to the adverse effects of strong acid medium. The esophagus has no significant contact with food contents, in that it is a muscle that exerts a motive action on food contents propelling them from the pharynx to the stomach.

Therefore, the appearance of these lesions in the two-year rodent bioassay in which the test material was administered at high concentration by gavage has doubtful relevance to humans consuming *trans,trans*-2,4-hexadienal as a flavoring substance. The FEMA Expert Panel concludes that *trans,trans*-2,4-hexadienal is GRAS under conditions of intended use as a flavoring substance and does not present a carcinogenic hazard to humans.

NTP reached a similar conclusion in a recent reevaluation of the results of a two-year NTP gavage study for ethyl acrylate. The study (NTP, 1986b) concluded that ethyl acrylate was carcinogenic due to dose-related increase in the incidence of benign and malignant forestomach neoplasms in rats and mice. Based primarily on the results of the study, ethyl acrylate was listed as "reasonably anticipated to be a human carcinogen."

However, in 2000, ethyl acrylate was delisted as a human carcinogen, based on the facts that "1) the forestomach tumours induced in animal studies were seen only when the chemical was administered by gavage at high concentrations that induced marked local irritation and cellular proliferation, 2) animal studies by other routes of administration including inhalation were negative, and 3) because significant chronic human oral exposure to high concentrations of ethyl acrylate monomer is unlikely" (NTP, 2000).

An independent analysis of the NTP data for the incidence of forestomach papillomas and carcinomas in male and female rats and mice treated with 2,4-hexadienal revealed that no tumors would be produced by $10^{20.2}$ molecules/kg/day (Waddell, 2002). Estimates of daily per capita intake ("eaters only") (Lucas et al., 1999) of 0.003 µg/kg bw/day of *trans, trans*-2,4-hexadienal corresponds to intake of $10^{10.27}$ molecules/kg bw/day. Therefore, no tumors would have been produced in the rodents even if rats or mice had been fed a daily dose of *trans, trans*-2,4-hexadienal that was more than ten billion times the daily intake by an "eaters only" population (i.e., 10% of the population consumes 100% of the annual volume of *trans, trans*-2,4-hexadienal used as a flavoring ingredient).

Safety Assessment of *trans*-Cinnamaldehyde (FEMA No. 2286)

trans-Cinnamaldehyde is an aromatic aldehyde chemically recognized as (E)-3-phenylpropenal (CAS No. 104-55-2). It occurs naturally as the major constituent of cinnamon shrubs and trees (family *Lauraceae*) and is therefore the major constituent of cassia oil (ca. 90%) (*Cinnamonium cassia*) (Lawrence, 1994a) and cinnamon bark oil (ca. 75%) (*Cinnamonium zeylanicum*) (Lawrence, 1994b). It is used as a flavor ingredient in foods up to an average level of 700 ppm in candy and up to 4,900 ppm in chewing gum (Hall and Oser, 1965). Based on a reported annual volume of 450,400 kg (Lucas et al., 1999), the estimated per-capita intake is 0.099 mg/kg bw/day or "eaters only" intake of 0.99 mg/kg bw/day.

In an NTP (2002) bioassay, groups of 50 male and female F344/N rats and B6C3F1 mice each were administered dietary concentrations of 1,000, 2,100, or 4,100 ppm of microencapsulated *trans*-cinnamaldehyde for two years. These dietary concentrations correspond to average daily doses of approximately 50, 100 or 200 mg/kg bw/day in male and female rats, respectively, and 125, 270, or 550 mg/kg bw/day in male and female mice, respectively. Additional groups of 50 male and 50 female animals of each species were administered untreated feed or feed containing placebo microencapsules. The NTP Board of Scientific Counselors Technical Report Review Subcommittee met for a peer review of the recently issued draft NTP Technical Report on *trans*-cinnamaldehyde (NTP, 2002). The Subcommittee concluded, "Under the conditions of these 2-year feed studies there was no evidence of carcinogenic activity of trans-cinnamaldehyde in male or female F344/N rats or B6C3F1 mice."

The lack of any evidence of carcinogenicity in either rats or mice at levels exceeding 1% of the diet is consistent with the results of other bioassays in which other aldehydes (e.g., citral) (NTP, 2001b) or reactive substances (e.g., benzyl acetate) (NTP, 1993b) were provided in microencapsulated form administered in the diet. A comparison of the two-year bioassay results for dietary administration of microencapsulated cinnamaldehyde to the gavage administration of a structurally related aldehyde, benzaldehyde (NTP, 1993a), provides a basis for evaluating the effect of mode of administration on selected carcinogenic endpoints, specifically the increased incidence of forestomach papillomas and squamous cell carcinomas in rodent species. The increased incidence of forestomach hyperplasia, papillomas, and eventually the appearance of squamous cell carcinomas in the gavage study using high concentrations of an irritating aldehyde confirm the impact of the mode of administration on the toxicological sequelae in the rodent forestomach (see "Safety Assessment of *trans,trans*-2,4-Hexadienal" above). Future design of two-year bioassay studies with low-molecular-weight irritant substances should avoid the use of gavage as a mode of administration.

The negative results in the two-year bioassay for *trans*-cinnamaldehyde provide insight into the mechanism by which hepatic neoplasms are induced in B6C3F1 mice exposed to high dose levels of a related ester, cinnamyl anthranilate, for two years (NTP, 1980). At low dose levels, cinnamyl anthranilate is adequately hydrolyzed to cinnamyl alcohol and anthranilic acid; cinnamyl alcohol is then readily oxidized primarily in the liver to cinnamaldehyde and then cinnamic acid (Keyhanfar and Caldwell, 1996). However, at elevated dietary levels, those exceeding 15,000 ppm in mice, the hydrolysis of cinnamyl anthranilate approaches saturation leading to accumulation of unhydrolyzed

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ester in the liver compartment. This phenomenon is accompanied by a pattern of hepatic enzyme induction that is characteristic of peroxisome proliferation (Caldwell, 1992; Caldwell and Viswalingam, 1989; Keyhanfar and Caldwell, 1996; Viswalingam et al., 1988).

In an earlier GRAS article (Newberne et al., 2000), the Panel concluded that the hepatic neoplasms in the B6C3F1 mouse in the NTP bioassay are secondary responses to peroxisome proliferation, a rodent-specific and dose-dependent phenomenon induced by the intact ester cinnamyl anthranilate (Caldwell, 1992; Caldwell and Viswalingam, 1989; Keyhanfar and Caldwell, 1996; Viswalingam et al., 1988). If the intact ester is responsible for induction of peroxisome proliferation and subsequent appearance of liver neoplasms, then the hydrolysis products (anthranilic acid and cinnamyl alcohol) or their liver metabolites (cinnamaldehyde or cinnamic acid) should show no evidence of hepatocarcinogenicity in bioassay studies in the same species and strain at similar or higher exposure levels.

Two bioassays, one on anthranilic acid and the other on the intermediary metabolite of cinnamyl alcohol, cinnamaldehyde, indicate that this is the case. An intake of 15,000 ppm (i.e., the LOAEL for peroxisome proliferation in the cinnamyl anthranilate study) corresponds to a potential production of 7,945 ppm of cinnamyl alcohol and 8,240 ppm of anthranilic acid, calculated as [(molecular weight of alcohol or acid)/(molecular weight of ester)] × (dietary level in ppm). There was no evidence of carcinogenicity reported when B6C3F1 mice were maintained on diets of (1) 25,000 or 50,000 ppm anthranilic acid 5 days/week for 78 weeks and then observed for an additional 26–27 weeks (NCI, 1980) or (2) 1,000, 2,100, or 4,100 ppm of microencapsulated *trans*-cinnamaldehyde for 2 years (NTP, 2002). Given the similar levels of exposure, the lack of liver carcinogenicity for the hydrolysis products supports a mechanism of action in which high concentrations of the intact ester are associated with the onset of peroxisome proliferation and the eventual appearance of liver tumors.

The Expert Panel concurs with NTP's conclusion that *trans*-cinnamaldehyde exhibits no carcinogenic potential in either species of rodent maintained on diets containing up to and including 4,100 ppm of *trans*-cinnamaldehyde for two years. Therefore, *trans*-cinnamaldehyde is considered GRASr as a flavoring substance by the Expert Panel, given its historically low level of use by the flavor industry (Lucas et al., 1999; NAS, 1970, 1982, 1987).

Correction

In the "Safety Assessment of Citral" section of "GRAS Flavoring Substances 20" (Smith et al., 2001), the FEMA number for citral was incorrectly listed as 2045. The correct FEMA number for citral is 2303.

Expert Panel Member Changes

In January 2002, Samuel M. Cohen, Professor of Pathology and Microbiology at the University of Nebraska Medical Center joined the Expert Panel.

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Table 1—Primary names (in boldfaced capital letters, listed alphabetically) and synonyms (in lower case)

FEMA No.	Substance primary name and synonyms
4024	**ACETALDEHYDE DIISOAMYL ACETAL** Butane, 1,1'-[ethylidenebis(oxy)]bis[3-methyl]- 3-Methyl-1-[1-(3-methyl-butoxy)-ethoxy]-butane
4025	**AMYL METHYL DISULFIDE** Disulfide, methyl pentyl 1-Methyldisulfanylpentane 2,3-Dithiaoctane
4026	**BENZYL HEXANOATE** Hexanoic acid, phenylmethyl ester Hexanoic acid, benzyl ester Benzyl caproate
4027	**BUTYL ETHYL DISULFIDE** Disulfide, butyl ethyl 1-Ethyldisulfanylbutane 3,4-Dithiaoctane
4028	***beta*-CYCLODEXTRIN** *beta*-CD Cycloheptapentylose Cycloamylose Cyclodextrin Cycloheptaglucosan
4029	**DIETHYL TRISULFIDE** Trisulfide, diethyl 1-Ethyltrisulfanylethane 3,4,5-Trithiaheptane
4030	**(+/-)-*cis*- and *trans*-3,5-DIETHYL-1,2,4-TRITHIOLANE** 1,2,4-Trithiolane, 3,5-diethyl-, (+/-)
4031	**(+/-)-DIHYDROFARNESOL** 3,7,11-Trimethyl-6,10-dodecadien-1-ol, (+/-) 2,3-Dihydrofarnesol, (+/-)
4032	**(+/-)-DIHYDROMINTLACTONE** 2(3H)-Benzofuranone, hexahydro-3,6-dimethyl 3,6-Dimethylcyclohexylacetolactone 2-(2-Hydroxy-4-methylcyclohexyl)propionic acid gamma lactone
4033	**DIHYDROXYACETONE** 2-Propanone, 1,3-dihydroxy (monomer) 1,3-Dihydroxyacetone alpha,alpha-Dihydroxyacetone (monomer) (Bis)hydroxymethylketone (monomer) Chromelin (monomer) 1,4-Dioxane-2,5-dimethanol, 2,5-dihydroxy (2R,5S) (dimeric form) 1,4-Dioxane-2,5-dimethanol, 2,5-dihydroxy-, *trans* (dimeric form)
4034	**2,5-DIMETHYL-3-FURANTHIOL ACETATE** Ethanethioic acid, S-(2,5-dimethyl-3-furanyl) ester S-(2,5-Dimethyl-3-furyl) ethanethioate S-(2,5-Dimethylfuran-3-yl) ethanethioate S-(2,5-Dimethylfur-3-yl) thioacetate Thioacetic acid S-(2,5-dimethylfuran-3-yl) ester 2,5-Dimethyl-3-thioacetoxyfuran 3-Thioacetyl-2,5-dimethylfuran 3-Acetylthio-2,5-dimethylfuran 3-(Acetylthio)-2,5-dimethylfuran
4035	**2,5-DIMETHYLTHIAZOLE** Thiazole, 2,5-dimethyl-
4036	**(Z)-4-DODECENAL** *cis*-4-Dodecenal Tangerinal
4037	**4,5-EPOXY-(E)-2-DECENAL** 3-(3-Pentyloxiran-2-yl)prop-(E)-2-enal 2-Propenal, 3-(3-pentyloxiranyl), (2E)-
4038	**(+/-)-ETHYL 3-ACETOXY-2-METHYLBUTYRATE** Butanoic acid, 3-(acetyloxy)-2-methyl, ethyl ester 3-Acetoxy-2-methylbutyric acid, ethyl ester
4039	**S-ETHYL 2-ACETYLAMINOETHANETHIOATE** (Acetylamino)ethanethioic acid, S-ethyl ester S-Ethyl 2-acetamidoethanethiolate N-Acetylthioglycine, S-ethyl ester N-Acetylglycinethiol ethyl ester S-Ethyl 2-acetylaminoethanethiolate
4040	**ETHYL METHYL DISULFIDE** Disulfide, ethyl methyl Methyldisulfanylethane 2,3-Dithiapentane
4041	**ETHYL PROPYL DISULFIDE** Disulfide, ethyl propyl 1-Ethyldisulfanylpropane 3,4-Dithiaheptane
4042	**ETHYL PROPYL TRISULFIDE** Trisulfide, ethyl propyl 3,4,5-Trithiaoctane
4043	**O-ETHYL S-(2-FURYLMETHYL)THIOCARBONATE** O-Ethyl S-(furan-2-ylmethyl)thiocarbonate O-Ethyl S-(2-furanylmethyl)thiocarbonate Carbonothioic acid, O-ethyl S-(2-furanylmethyl) ester O-Ethyl S-(2-furanylmethyl)carbonothioate Ethoxy carbonyl furfurylthiol
4044	**GERANYL TIGLATE** 2-Butenoic acid, 2-methyl 3,7-dimethyl-2,6-octadienyl ester, (E,E)- Tiglic acid, 3,7-dimethyl-2,6-octadienyl ester Tiglic acid, geraniol ester
4045	**GRAPE SEED EXTRACT** Oligomeric Proanthocyanidins
4046	***trans*-4-HEXENAL** (E)-4-Hexenal *trans*-Hex-4-enal 4-Hexenal, trans-
4047	**(E)-2-HEXENAL DIETHYL ACETAL** 2-Hexene, 1,1-diethoxy-, (2E)-
4048	**2-HEXYL-4,5-DIMETHYL-1,3-DIOXOLANE** 1,3-Dioxolane,2-hexyl-4,5-dimethyl- Heptanal 2,3-butandiol acetal

Table 1 continued on page 53 ▶

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Table 1—Primary names and synonyms, *continued*

FEMA No.	Substance primary name and synonyms
4049	**4-HYDROXY-3,5-DIMETHOXYBENZALDEHYDE** Benzaldehyde, 4-hydroxy-3,5-dimethoxy- Syringic aldehyde Syringaldehyde Gallaldehyde 3,5-dimethyl ether
4050	**4-HYDROXY-2,3-DIMETHYL-2,4-NONADIENOIC ACID GAMMA LACTONE** Bovolide 2(5H)-Furanone, 3,4-dimethyl-5-pentylidene- 3,4-Dimethyl-5-pentylidene-5H-furan-2-one 5-Pentylidene-3,4-dimethyl-2,5-dihydrofuran-2-one
4051	**4-HYDROXY-4-METHYL-5-HEXENOIC ACID GAMMA LACTONE** Lilac lactone 2(3H)-Furanone, 5-ethenyldihydro-5-methyl- 5-Methyl-5-vinyl-dihydrofuran-2-one 4-Methyl-5-hexen-1,4-olide
4052	**3-HYDROXY-4-PHENYLBUTAN-2-ONE** 2-Butanone, 3-hydroxy-4-phenyl-
4053	***p*-MENTHANE-3,8-DIOL** Cyclohexanemethanol,2-hydroxy-alpha,alpha,4-trimethyl- 2-(2'Hydroxypropan-2'-yl)-5-methylcyclohexanol 2-Hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol
4054	**1-MENTHYL METHYL ETHER** Cyclohexane, 2-methoxy-4-methyl-1-(1-methylethyl)-,(1S,2R,4R)- 1-Isopropyl-2-methoxy-4-methylcyclohexane 2-Isopropyl-5-methylcyclohexyl methyl ether
4055	**(+/-)-METHYL 5-ACETOXYHEXANOATE** Hexanoic acid, 5-(acetyloxy)-, methyl ester 5-Acetoxyhexanoic acid methyl ester
4056	**(+/-)-3-[(2-METHYL-3-FURYL)THIO]-2-BUTANONE** 2-Butanone, 3-[(2-methyl-3-furanyl)thio]- 3-[(2-Methyl-3-furyl)sulfanyl]-2-butanone 3-[(2-Methyl-3-furanyl)sulfanyl]-2-butanone 3-(2-Methyl-3-furylthio)-2-butanone
4057	**3-METHYL-2,4-NONANEDIONE** 3-Methylnonane-2,4-dione
4058	**(+/-)-2-(5-METHYL-5-VINYLTETRAHYDROFURAN-2-YL)PROPIONALDEHYDE** 2-Furanacetaldehyde, 5-ethenyltetrahydro-alpha,5-dimethyl-, (+/-) Lilac aldehyde, (+/-)
4059	**9-OCTADECENAL** Olealdehyde Elialdehyde Octadecenyl aldehyde Oleic Aldehyde
4060	**2,3-OCTANEDIONE** Octan-2,3-dione
4061	**(+/-)-1-PHENYLETHYLMERCAPTAN** Benzenemethanethiol, alpha-methyl, (+/-) 1-Phenylethanethiol, (+/-)
4062	**(Z)-4-PROPENYLPHENOL** Phenol, 4-(1-propenyl)- Isochavicol
4063	**2-PROPIONYLPYRROLINE** 1-(3,4-Dihydro-2H-pyrrol-5-yl)-1-propanone
4064	**2-PROPIONYL-2-THIAZOLINE** 1-Propanone, 1-(4,5-dihydro-2-thiazolyl)- 1-(4,5-Dihydro-1,3-thiazol-2-yl)-1-propanone 1-Propanone, 1-(2-thiazolin-2-yl)-
4065	**2-PROPYLPYRIDINE** Pyridine, 2-propyl-
4066	**(Z)-8-TETRADECENAL** (Z)-Tetradec-8-enal 8-Tetradecenal, (Z)-
4067	**TUBEROSE LACTONE** 2(3H)-Furanone, dihydro-5-(2,5-octadienyl)-, (Z,Z)- 6,9-Dodecadien-4-olide, (Z,Z)-
4068	**2-UNDECEN-1-OL** 1-Hydroxy-2-undecene *trans*-2-Undecenol

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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	10
	Acetaldehyde diisoamyl acetal	Amyl methyl disulfide	Benzyl hexanoate	Butyl ethyl disulfide	*beta*-Cyclodextrin	Diethyl trisulfide	(+/-)-3,5-*cis*- and *trans*-Diethyl-1,2,4-trithiolane	(+/-)-Dihydro farnesol	(+/-)-Dihydromint lactone	Dihydroxy acetone
Category	**FEMA No. 4024**	**4025**	**4026**	**4027**	**4028**	**4029**	**4030**	**4031**	**4032**	**4033**
Baked goods	25/50	0.8/1.5		0.1/0.2	5,000/5,000	0.15/0.3	0.4/1		1/3	50/200
Beverages (nonalcoholic)	10/20	0.4/0.8	1/5	0.05/0.1	3,000/3,000	0.05/0.1	0.008/0.08	30/100	1/3	
Beverages (alcoholic)	10/20			0.05/0.1		0.05/0.1	0.04/0.2	60/600	0.3/1	
Breakfast cereal					5,000/5,000				0.3/1	120/600
Cheese					4,000/4,000					
Chewing gum				0.3/0.6	5,000/5,000	0.4/0.8		300/1,000	3/10	
Condiments/ relishes		0.4/0.8		0.05/0.1		0.05/0.1	0.03/0.3			300/1,200
Confectionery frostings								60/600	0.3/1	
Egg products										
Fats/oils							0.04/0.2			
Fish products	10/20						0.04/0.2			
Frozen dairy	15/30	0.3/0.6		0.06/0.12		0.07/0.15			1/3	80/320
Fruit ices	10/20	0.4/0.8		0.05/0.1		0.05/0.1		30/100	0.3/1	
Gelatins/ puddings	15/30			0.05/0.1	5,000/5,000	0.05/0.1		60/200	0.5/2	40/240
Granulated sugar										
Gravies		0.4/0.8		0.05/0.1		0.05/0.1	0.04/0.2			80/240
Hard candy	20/40	0.8/1.5		0.1/0.2	4,000/4,000	0.1/0.2		60/600	1/3	300/1,200
Imitation dairy							0.04/0.2			
Instant coffee/tea					3,000/3,000					
Jams/jellies								60/200		
Meat products		0.4/0.8				0.05/0.1	0.04/0.2			20/200
Milk products	10/20	0.4/0.8	1/5	0.05/0.1		0.05/0.1	0.016/0.08		0.3/1	40/200
Nut products										
Other grains										
Poultry										
Processed fruits										
Processed vegetables							0.04/0.2			80/240
Reconstituted vegetables										
Seasonings/ flavors	10/20						0.04/0.2	3,000/10,000		400/2,400
Snack foods	10/20	0.4/0.8		0.05/0.1	5,000/5,000	0.5/0.1	0.08/0.5			
Soft candy	15/30	0.3/0.6		0.06/0.12		0.07/0.15		60/600	0.3/1	
Soups	15/30	0.3/0.6		0.05/0.1	2,000/2,000	0.05/0.1	0.01/0.1			
Sugar substitutes										
Sweet sauces								60/600		

Table 2 continued on page 56 ▶

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

	Average usual ppm/Average maximum ppm										
	11	12	13	14	15	16	17	18	19	20	21
	2,5-Dimethyl-3-furanthiol acetate	2,5-Dimethyl thiazole	(Z)-4-Dodecenal	4,5-Epoxy-(E)-2-decenal	(+/-)-Ethyl 3-acetoxy-2-methyl butyrate	*S*-Ethyl 2-acetylamino ethanethioate	Ethyl methyl disulfide	Ethyl propyl disulfide	Ethyl propyl trisulfide	O-Ethyl S-(2-furylmethyl) thiocarbonate	Geranyl tiglate
Category	**FEMA No. 4034**	**4035**	**4036**	**4037**	**4038**	**4039**	**4040**	**4041**	**4042**	**4043**	**4044**
Baked goods		5/10	0.1/0.2	0.1/1	20/40	0.05/1	3/6	0.5/1	0.05/0.1	0.03/0.06	
Beverages (nonalcoholic)		2/4	0.05/0.1	0.001/0.1	10/20		1/2	0.2/0.4	0.02/0.05	0.03/0.06	20
Beverages (alcoholic)		3/6	0.08/0.16	0.001/0.1	10/20		1/2	0.2/0.4	0.02/0.05	0.03/0.06	20
Breakfast cereal		3/6	0.1/0.2	0.001/0.1						0.03/0.06	
Cheese				0.1/1		0.05/1					
Chewing gum			4/8	0.001/0.1	40/80		4/8	1/2	0.1/0.2	0.03/0.06	
Condiments/ relishes	0.01/0.03			0.1/1	10/20		2/4	0.2/0.4	0.03/0.06		
Confectionery/ frostings			1/2	0.001/0.1							100
Egg products				0.1/1							
Fats/oils				0.1/1		0.1/2					
Fish products				0.1/1							
Frozen dairy		3/6	0.08/0.16	0.01/0.5	15/30		2/4	0.3/0.6	0.03/0.06	0.03/0.06	50
Fruit ices		2/4	0.08/0.16	0.01/0.5	10/20		1/2	0.2/0.4	0.02/0.05		50
Gelatins/ puddings		2/4	0.05/0.1	0.01/0.5	15/30					0.03/0.06	
Granulated sugar				0.001/0.1							
Gravies	0.02/0.04	2/4		0.1/1		0.1/2	1/2	0.3/0.6	0.03/0.06		
Hard candy		4/8	0.1/0.2	0.001/0.1	20/40		2/4	0.4/0.8	0.04/0.08	0.03/0.06	100
Imitation dairy				0.1/1			1/2	0.2/0.4	0.02/0.04	0.03/0.06	50
Instant coffee/tea				0.1/1			1/2			0.03/0.06	
Jams/jellies			0.04/0.08	0.001/0.1							
Meat products	0.02/0.05	3/6		0.1/1		0.1/2	2/4	0.2/0.4	0.03/0.06		
Milk products		2/4		0.1/1	10/20		1/2	0.2/0.4	0.02/0.05	0.03/0.06	50
Nut products				0.01/1							
Other grains				0.01/1							
Poultry	0.02/0.05			0.1/1		0.05/1					
Processed fruits				0.01/1							
Processed vegetables				0.01/1		0.02/0.5					
Reconstituted vegetables				0.01/1							
Seasonings/ flavors		2/4		2/10		1/2					
Snack foods	0.01/0.02	2/4	0.1/0.2	0.1/1		0.1/1	1/2	0.3/0.6	0.03/0.06		
Soft candy		3/6	0.1/0.2	0.001/0.1	15/30		2/4	0.3/0.6	0.03/0.06	0.03/0.06	100
Soups	0.005/0.01	2/4		0.1/1		0.05/1	1/2	0.3/0.6	0.03/0.06		
Sugar substitutes				0.001/0.1							
Sweet sauces				0.1/1							

Table 2 continued on page 57 ▶

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

	Average usual ppm/Average maximum ppm									
	22	23	24	25	26	27	28	29	30	31
	Grape seed extract	*trans*-4-Hexenal	(E)-2-Hexenal diethyl acetal	2-Hexyl-4,5-dimethyl-1,3-dioxolane	4-Hydroxy-3,5-dimethoxy benzaldehyde	4-Hydroxy-2,3-dimethyl-2,4-nonadienoic acid gamma lactone	4-Hydroxy-4-methyl-5-hexenoic acid gamma lactone	3-Hydroxy-4-phenyl butan-2-one	*p*-Menthane-3,8-diol	1-Menthyl methylether
Category	**FEMA No. 4045**	**4046**	**4047**	**4048**	**4049**	**4050**	**4051**	**4052**	**4053**	**4054**
Baked goods		0.008/0.1		5/10	12/60	3/6	100/200	20/40		50/250
Beverages (nonalcoholic)	100/200		1/15	2/4	4/20	1/2	50/100	10/20	5/25	1/10
Beverages (alcoholic)	100/200			2/4		1/2	50/100	10/20	5/25	4/20
Breakfast cereal							100/200		5/20	1/10
Cheese	100/200								5/25	
Chewing gum					15/75	5/10		50/100	75/150	500/2,000
Condiments/ relishes	100/200					1/2			5/25	
Confectionery frostings									5/25	2/20
Egg products										2/20
Fats/oils									5/25	2/20
Fish products										
Frozen dairy	100/200			3/6	6/30	2/4	75/150	15/30	5/25	20/100
Fruit ices						1/2	50/100		5/25	10/50
Gelatins/ puddings	100/200			2/4			50/100	15/30	10/50	10/50
Granulated sugar										10/50
Gravies						1/2			5/35	
Hard candy		0.008/0.1		3/6	6/30	2/4	100/200	20/40	30/100	10/50
Imitation dairy	100/200			2/4				10/20	5/35	5/10
Instant coffee/tea	100/200									2/10
Jams/jellies		0.01/0.2							10/50	10/50
Meat products						1/2				
Milk products	100/200			2/4	4/20	1/2	50/100			2/10
Nut products									10/50	
Other grains										
Poultry		0.01/0.1								
Processed fruits									5/25	2/10
Processed vegetables		0.008/0.1							5/25	
Reconstituted vegetables		0.008/0.1							5/25	
Seasonings/ flavors	100/200									1,000/30,000
Snack foods		0.01/0.2		2/4		1/2			5/25	
Soft candy				3/6		2/4	75/150	15/30	10/50	3/50
Soups	100/200	0.008/0.5				1/2			7/35	4/0
Sugar substitutes	100/200									3/50
Sweet sauces									5/50	

Table 2 continued on page 58 ▶

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

	Average usual ppm/Average maximum ppm									
	32	33	34	35	36	37	38	39	40	41
	(+/-)-Methyl 5-acetoxy hexanoate	(+/-)-3-[(2-Methyl-3-furyl)thio]-2-butanone	3-Methyl-2, 4-nonedione	(+/-)-2-(5-Methyl-5-vinyl-tetrahydro furan-2-yl)-propion aldehyde	9-Octadecenal	2,3-Octanedione	(+/-)-1-Phenyl ethyl mercaptan	(Z)-4-Propenyl phenol	2-Propionyl pyrroline	2-Propionyl-2-thiazoline
Category	**FEMA No. 4055**	**4056**	**4057**	**4058**	**4059**	**4060**	**4061**	**4062**	**4063**	**4064**
Baked goods	20/40			8/16	1/20	20/20	0.002/0.04	2/5	60/300	0.4/1
Beverages (nonalcoholic)	10/20		0.0003/0.001	3/6		8/16	0.001/0.02	1/2	1.2/12	0.01/0.08
Beverages (alcoholic)	10/20			4/8		8/16	0.0005/0.005	1/2	6/50	0.04/0.2
Breakfast cereal									10/100	0.01/0.05
Cheese										
Chewing gum	40/80						0.002/0.015	4/8	60/300	0.04/1
Condiments/ relishes	10/20		0.1							
Confectionery frostings									6/30	0.04/0.2
Egg products									6/30	
Fats/oils									8/40	0.04/0.20
Fish products								2/4		
Frozen dairy	15/30		0.001	6/12		12/24		2/4	20/100	0.16/0.8
Fruit ices	10/20			3/6						
Gelatins/ puddings	15/30			5/10		12/24	0.001/0.008		10/50	
Granulated sugar										
Gravies		0.004/0.04			1/20	8/16		2/4		0.02/0.1
Hard candy	20/40			6/12		16/32	0.002/0.025	2/4	10/50	0.08/0.8
Imitation dairy						8/16		1/2		
Instant coffee/tea			0.001						10/50	
Jams/jellies									10/50	
Meat products		0.001/0.01	0.025/0.3		2/40	8/16		2/4	10/50	0.04/0.4
Milk products	10/20		0.001/0.001			8/16			10/50	0.02/0.08
Nut products								1/2		
Other grains									10/50	
Poultry		0.001/0.01			3/20					
Processed fruits										
Processed vegetables					1/20				10/50	
Reconstituted vegetables					1/20					
Seasonings/ flavors		10/100				8/16	0.001/1	2/4	10/50	0.08/0.8
Snack foods		0.001/0.01			0.5/40	8/16	0.002/0.04	2/4	50/250	0.08/0.8
Soft candy	15/30			5/10		12/24		2/4	10/50	0.08/0.8
Soups		0.003/0.03	0.1/1		0.5/20	8/16	0.005/1	2/4		
Sugar substitutes										
Sweet sauces									6/30	

Table 2 continued on page 59 ▶

GRAS Flavoring Substances 21

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

	Average usual ppm/Average maximum ppm			
	42	43	44	45
	2-Propyl pyridine	(Z)-8-Tetradecenal	Tuberose lactone	2-Undecen-1-ol
Category	FEMA No. 4065	4066	4067	4068
Baked goods	0.6/1	0.01/0.1	5/10	
Beverages (nonalcoholic)	0.2/0.4	0.001/0.05	2/4	0.5/5
Beverages (alcoholic)		0.001/0.05	10/20	
Breakfast cereal		0.001/0.1	10/20	
Cheese		0.01/0.1		
Chewing gum		0.001/0.1	50/100	
Condiments/relishes		0.01/0.1		
Confectionery frostings		0.001/0.1	4/8	
Egg products		0.001/0.1		
Fats/oils		0.01/0.2	2/5	
Fish products		0.01/0.2		
Frozen dairy	0.3/0.5	0.001/0.1	3/6	
Fruit ices		0.001/0.1	4/8	
Gelatins/puddings	0.3/0.6	0.001/0.1	5/10	
Granulated sugar		0.001/0.1		
Gravies	0.3/0.6	0.01/0.2		
Hard candy	0.4/0.8	0.001/0.1	10/20	
Imitation dairy		0.005/0.2	5/10	
Instant coffee/tea		0.01/0.2		
Jams/jellies		0.001/0.01	5/10	
Meat products	0.2/0.4	0.005/0.5	5/10	
Milk products		0.005/0.2	5/10	
Nut products	0.3/0.6	0.005/0.1	3/8	
Other grains		0.005/0.1	5/10	
Poultry		0.01/0.2		
Processed fruits		0.005/0.1	10/20	
Processed vegetables		0.001/0.3		
Reconstituted vegetables		0.005/0.3		
Seasonings/flavors	0.3/0.6	0.5/5		
Snack foods	0.3/0.6	0.01/0.2	5/10	
Soft candy	0.3/0.6	0.001/0.1	5/10	
Soups	0.2/0.4	0.01/0.2	2/5	0.5/5
Sugar substitutes		0.001/0.05		
Sweet sauces		0.05/0.2		

Table 3—Updated use levels for flavoring substances previously recognized as FEMA GRAS. Superscript a represents a new use level.

	Average usual ppm/Average maximum ppm		
	Ethanethioic acid, S-(2-methyl-3-furanyl) ester	12-Methyl tridecanal	2,3,5-Trithia-hexane
Category	FEMA No. 3973	4005	4021
	GRAS List 20	20	20
Baked goods	5/10	35/70	2/10
Beverages (nonalcoholic)	0.1/1	0.7/7	0.1/0.8
Beverages (alcoholic)			0.3/2
Breakfast cereal	0.1/0.5	0.7/3.5	
Cheese	0.01/0.1	0.1/5[a]	0.1/0.2[a]
Chewing gum			2/10
Condiments/relishes	0.001/0.01	0.1/0.5[a]	0.1/0.2[a]
Confectionery frostings		1/5[a]	0.3/2
Egg products		3.5/35	0.3/2
Fats/oils	0.5/5	3.5/35	0.3/2
Fish products	0.5/5	0.25/5[a]	0.1/0.2[a]
Frozen dairy			0.5/6
Fruit ices			0.2/1
Gelatins/puddings			0.2/1
Granulated sugar			
Gravies	0.5/5	3.5/35	0.3/2
Hard candy	0.5/5	3.5/35	0.5/2
Imitation dairy			0.1/0.2[a]
Instant coffee/tea			0.1/0.8
Jams/jellies			0.5/3
Meat products	0.5/5	3.5/35	0.4/5
Milk products	0.1/1	0.7/7	0.2/1
Nut products	0.5/5		
Other grains			
Poultry	0.05/0.3[a]	0.25/5[a]	
Processed fruits			
Processed vegetables	0.1/1	0.1/1[a]	
Reconstituted vegetables	0.003/0.03		
Seasonings/flavors	1/5[a]	200/500[a]	0.5/5
Snack foods	1/5	7/35	0.5/3
Soft candy			0.5/3
Soups	0.1/1	0.7/7	0.1/1
Sugar substitutes			
Sweet sauces			