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# GRAS

# FLAVORING SUBSTANCES 24

The 24th publication by the FEMA Expert Panel presents safety and usage data on 236 new generally recognized as safe flavoring ingredients.

t is now half of a century since passage of the 1958 Food Additives Amendment (FAA) to the Federal Food, Drug, and Cosmetic Act—Public Law 85-929, 72 Stat. 1784 (1958), codified at 21 U.S.C. Sec. 348 (1988)—that exempted from food additive status those substances "generally recognized as safe" (GRAS) under conditions of intended use. In order for the use of a substance to qualify for GRAS status, the safety of the substance must be evaluated by experts qualified by training and experience and adequately shown through scientific procedures to be "generally recognized as safe." For almost five decades, the Expert Panel of the Flavor and Extract Manufacturers Association (FEMA) has maintained an independent program to evaluate the safety of substances for their intended use as flavor ingredients. During that time, more than 2,600 flavor ingredients achieved GRAS status, approximately 200 candidates were withdrawn from GRAS consideration due to lack of available data or safety concerns, and 11 substances had their previous GRAS status revoked (or "DeGRASed") due to specific safety concerns or an absence of requested safety data.

At the beginning of the FEMA GRAS Program, FEMA flavor manufacturers submitted data on approximately 1,400 flavoring substances that had been in commerce in the United States at the time the 1958 Amendment was adopted. In the first round of safety evaluations, the Expert Panel systematically considered data on these chemically defined substances and concluded that 1,124 of these flavor ingredients were GRAS under conditions of their intended use in food flavorings. In accordance with the provisions of the 1958 Amendment that the use of these substances be "generally recognized as safe," the Expert Panel published the first list of GRAS flavoring substances in 1965 (Hall and Oser, 1965). This began a tradition of periodic publication of GRAS lists of flavoring substances, including their principal name, synonyms, and their recommended average added usual and maximum use levels. In addition, there was a desire to publish the background scientific data upon which GRAS deliberations were based. Under contract to the U.S. Food and Drug Administration (FDA), relevant safety data



were compiled on approximately 1,300 substances and published in a series of Scientific Literature Reviews (SLRs) between 1974 and 1979. Each SLR was organized into groups of structurally related flavoring ingredients that participated in common pathways

flavoring substances, suggesting that there may be an upper limit to the number of commercially viable flavoring substances.

However, two mutually connected initiatives drastically altered the rate of GRAS evaluations. First, in 1994, the Expert Panel began a

# The FEMA Expert Panel published the first list of GRAS flavoring substances in 1965.

of metabolism and exhibited similar toxicological potential.

These reviews served as the foundation for the first comprehensive re-evaluation and affirmation of the GRAS status of more than 1,740 flavor ingredients in a program known as GRAS affirmation (GRASa). The GRASa Program began in 1975 and was completed in 1985. In the next 10-year period (1985–1995), relatively few new substances (approximately 75) were GRASed for use as

second comprehensive evaluation of the safety of all chemically defined GRAS flavoring substances in a program designated GRAS reaffirmation (GRASr). Second, in conjunction with FDA, the flavor industry supported a new, more-comprehensive initiative to expedite the global evaluation of all existing flavoring substances. After more than 30 years of evaluating the safety of individual flavoring substances, the World Health Organization and United Nations

Food and Agriculture Organization Joint Expert Committee on Food Additives (JECFA) adopted a novel flavor evaluation procedure in 1995 that allowed for the systematic evaluation of chemical groups of flavoring ingredients beginning in 1996. These chemical groups of flavor ingredients had been previously evaluated by the FEMA Expert Panel in the GRASr program. Every year since 1996, FDA has requested that the Codex Committee on Food Additives (CCFA) place groups of GRAS flavor ingredients on the JECFA agenda for evaluation at its annual meeting. As of 2008, JECFA has evaluated more than 1,750 substances and concluded that these flavoring agents are "safe under current conditions of intake." The JECFA list is updated annually following each JECFA meeting.

The consistent conclusions rendered by the FEMA Expert Panel and JECFA have, to a considerable extent, created an open positive list of flavoring substances

# FEMA GRAS LISTS

# published in Food Technology, in chronological order

Hall, R.L. 1960. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. Food Technol. 14: 488-495.

Hall, L. and Oser, B.L. 1961. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. II. Food Technol. 15(12): 20, 22-26.

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.

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 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., Ford, R.A., and Bernard, B.K. 1984. Recent progress in the 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.

Burdock, G.A., Wagner, B.M., Smith, R.L., Munro, I.C., and Newberne, P.M. 1990. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 15. GRAS substances. Food Technol. 44(2): 78, 80, 82, 84, 86.

Smith, R.L. and Ford, R.A. 1993. Recent progress in the 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.

Newberne, P., Smith, R.L., Doull, J., Goodman, J.I., Munro, I.C., Portoghese, P.S., Wagner, B.M., Weil, C.S., Woods, L.A., Adams, T.B., Hallagan, J.B., and Ford, R.A. 1998. GRAS flavoring substances 18. Food Technol. 52(9): 65-66, 68, 70, 72, 74, 76, 79-92.

Newberne, P., Smith, R.L., Doull, J., Goodman, J.I., Munro, I.C., Portoghese, P.S., Wagner, B.M., Weil, C.S., Woods, L.A., Adams, T.B., Hallagan, J.B., and Ford, R.A. 1999. Correction to GRAS flavoring substances 18. Food Technol. 53(3): 104.

Newberne, P., Smith, R.L., Doull, J., Feron, V.J., Goodman, J.I., Munro, I.C., Portoghese, P.S., Waddell, W.J., Wagner, B.M., Weil, C.S., Adams, T.B., and Hallagan, J.B. 2000. GRAS flavoring substances 19. Food Technol. 54(6): 66, 68-69, 70, 72-74, 76-84.

Smith, R.L., Doull, J., Feron, V.J., Goodman, J.I., Munro, I.C., Newberne, P.M., Portoghese, P.S., Waddell, W.J., Wagner, B.M., Adams, T.B., and McGowen, M.M. 2001. GRAS flavoring substances 20. Food Technol. 55(12): 34-36, 38, 40, 42, 44-55.

Smith, R.L., Cohen, S.M., Doull, J., Feron, V.J., Goodman, J.I., Marnett, I.J., Portoghese, P.S., Waddell, W.J., Wagner, B.M., and Adams, T.B. 2003. GRAS flavoring substances 21. Food Technol. 57(5): 46-48, 50, 52-54, 56-59.

Smith, R.L., Cohen, S.M., Doull, J., Feron, V.J., Goodman, J.I., Marnett, I.J., Portoghese, P.S., Waddell, W.J., Wagner, B.M., and Adams, T.B. 2005. GRAS flavoring substances 22. Food Technol. 59(8): 24-28, 31-32, 34, 36-62.

Waddell, W.J., Cohen, S.M., Feron, V.J., Goodman, J.I., Marnett, L.J., Portoghese, P.S., Rietjens, I.M.C.M., Smith, R.L., Adams, T.B., Gavin, C. L., McGowen, M.M., and Williams, M.C. 2007. GRAS flavoring substances 23. Food Technol. 61(8): 22-24, 26-28, 30-49. for use in the U.S. and in WHO member countries that wish to adopt the FEMA and/or JECFA lists. In other industrialized regions, such as the European Union (EU) and Japan, open positive lists of flavoring substances either are being developed or are currently in existence. In the EU, a positive list is being compiled based on the safety evaluations performed by JECFA prior to 2000 and thereafter by the European Food Safety Authority. In Japan, the Ministry of Health, Labor, and Welfare maintains a list of currently approved flavoring substances, and recent safety evaluations of specific groups of flavor ingredients (e.g., pyrazine derivatives) have added new groups of structurally related substances to the existing list.

As the JECFA list has developed, flavor manufacturers in these other industrialized regions (Europe and Asia) have, quite understandably, taken an interest in having existing flavoring ingredients specific to their regions added to the FEMA and JECFA lists. Hence, both EU and Japanese flavor manufacturers have, through their respective international and national trade associations, submitted these substances for safety evaluation, first by the FEMA Expert Panel and then by JECFA. As a result, there has been renewed interest in the GRAS Program.

Beginning with the publication of GRAS 18 in 1998, there has been a significant increase in the number of substances GRASed annually, GRAS 22 (published in 2005) and GRAS 23 (published in 2007) contain 185 and 175 new flavor ingredients, respectively. The vast majority of GRAS applications for substances in GRAS 22 and 23 were submitted on behalf of EU and Japanese manufacturers. In this publication (i.e., GRAS 24), 236 new flavor ingredients, mostly of Japanese origin, have been granted GRAS status. Therefore, in a four-year span, the GRAS list of chemically defined flavor ingredients has increased by approximately 25%. It is anticipated that the majority of flavor ingredients historically used in these regions have now been recognized as GRAS and future GRAS lists will contain mainly flavor ingredients resulting from global manufacturer research and development pipelines. >>>>

# Genotoxicity Assays and Flavor Safetu Evaluation

The Panel has now concluded its second comprehensive re-evaluation (GRASr) of the current safety data related to the use of GRAS substances as flavor ingredients. Because these evaluations were performed on groups of structurally related substances, it provided the Panel with the opportunity to screen robust datasets that included in vitro and in vivo genotoxicity assays. The Panel considered the relevance of this genotoxicity data in the context of existing information on the biochemical fate of the flavor ingredients and animal toxicology and carcinogenicity. For example, for a group of structurally related benzyl derivatives (e.g., benzyl alcohol, benzaldehyde, benzoic acid, benzyl acetate), the Panel was able to compare the results of more than 100 in vitro and 17 in vivo genotoxicity assays with in vivo data on metabolism, short- and long-term toxicity, and lifetime carcinogenicity studies for five principal flavor ingredients in the group (Adams et al., 2005). Although there were isolated reports of clastogenicity or mutations in in vitro chromosomal aberration, sister chromatid exchange, and mouse

lymphoma assays, these studies could not be confirmed in repeat assays. Additionally, there was no evidence of genotoxicity in any of the 17 in vivo assays performed on the same members of the group of benzyl derivatives. When these data are combined with the observations that benzyl derivatives 1) undergo high-capacity enzyme-catalyzed oxidative metabolism in animals to yield benzoic acid derivatives that are readily excretable as glycine conjugates, 2) show low oral toxicity in short- and long-term studies in mice and rats, and 3) exhibit no evidence of carcinogenicity relevant to human health, it can be concluded that the few isolated reports of a genotoxic response in vitro are not relevant to the safety of these substances when consumed at low levels as added flavoring substances.

During the past 15 years, the Panel has evaluated safety data, including genotoxicity data, on more than 50 groups of structurally related flavoring substances. Two chemical groups, the  $\alpha,\beta$ -unsaturated aldehydes (Adams et al., 2008) and heterocyclic  $\alpha$ -ketoenols (JECFA, 2006) are mutagenic in the reverse bacterial assays in some strains of *Salmonella typhimurium* (Ames TA100, TA102,

and TA104) and in some mammalian cell forward mutation assays (mouse lymphoma), and show evidence of clastogenicity in the sister chromatid exchange and chromosomal aberration assays. In a majority of in vitro genotoxicity assays involving  $\alpha$ ,  $\beta$ -unsaturated aldehydes, high concentrations (20 to 40 µM) in cell lines poor in detoxication capacity provide opportunity for either direct interaction of the  $\alpha$ , $\beta$ -unsaturated aldehyde with DNA or lead to indirect formation of DNA damage due to oxidative stress, which ultimately leads to single DNA strand breaks but no cross-linking of DNA. The oxidative stress caused by depletion of GSH due to reaction with high concentrations of α,β-unsaturated aldehydes may also lead subsequent release of nucleocytolytic enzymes, causing DNA fragmentation, cellular damage, and apoptosis. However, in vivo, there is no evidence of mutagenicity and genotoxicity in the mouse micronucleus test for 2-hexenal. 2-octenal, and 2-decenal, and no indication of unscheduled DNA synthesis for 2-hexenal in the liver (Adams et al., 2008). In addition, there is no evidence of DNA adduct formation in the liver of animals exposed to high dose levels (200 and 500 mg/kg body weight) of 2-hexenal for up to 28 days (Stout et al., 2008) and no evidence of hepatocarcinogenicity in rats or mice exposed to high dose levels of 2,4-hexadienal for up to 2 years (NTP, 2003). Based on these observations, the fact that normal human consumption of  $\alpha$ ,  $\beta$ -unsaturated aldehydes is many orders of magnitude less than those showing no effects in animals, and the rapid metabolism of these aldehydes in the high-capacity \( \beta \-oxidation \) pathway in humans, it is concluded that use of the substances are GRAS under intended conditions of intake as flavor ingredients.

The other group of structurally related substances that shows evi-



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dence of genotoxicity in both in vitro and in some in vivo genotoxicity assays is alicyclic or heterocyclic alpha-ketoenols. These substances induce DNA damage in vitro by generating free radicals that induce strand scission (JECFA, 2006). In order to produce these cytotoxic effects, the structures must contain specific structural features. The alpha-ketoenol moiety must be present to bind the metal ion (Fe3<sup>+</sup> or Cu2<sup>+</sup>) and the molecule must have a source of electrons from an electron donating group (e.g., an alkyl ring substituent or a heteroatom in the ring). Hence, similar biochemical behaviour has been reported for furaneol (4-hydroxy-2,5-dimethyl2(3*H*)furanone) (Murakami et al., 2007); maltol (3-hydroxy-2-methyl-4-pyrone) (Murakami et al., 2005a, 2005b, 2006); hinokitiol (2-hydroxy-4isopropyl-2,4,6-cycloheptatrienone) (Murakami et al. 2005a); and 3-hydroxy-1,2-dimethylpyridin-4(1H)-one (Moridani and O'Brien, 2001) (see Figure 1). It has been reported that metal chelating ability does not strictly correlate to metal ion reduction ability (Murakami et al., 2007). The donation of electrons, either from an alkyl substituent or the ring itself allows the alpha-ketoenol to act as an alpha-hydroxyenolate that readily complexes with metal ions and provides an electron for metal reduction.

In one pathway, the alpha-ketoenol reduces the metal ion, which subsequently reduces molecular oxygen to produce superoxide ion. Superoxide dismutase catalyzes the conversion of superoxide ion to hydrogen peroxide that is then converted to hydroxyl radicals by Fe2<sup>+</sup> in

the Fenton reaction (see Figure 2). Hydrogen peroxide also oxidizes glutathione (GSH), leading to a decreased GSH/GSSG ratio and an increase in cellular oxidative stress.

Support for this pathway has been reported when various cell lines have been incubated with furaneol (Hiramoto, 1998), maltol (Murakami, 2005b), and hinokitiol (Ido et al., 2002; Inamori et al., 1993). In these experiments, the ketoenol/ iron complex led to inactivation of aconitase, an iron-sulfur cluster-containing enzyme with high sensitivity to reactive oxygen species. The inactivation of aconitase was metal ion-dependent, and prevented by 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy (TEMPOL), a scavenger of reactive oxygen species and superoxide dismutase, suggesting that the ketoenol/iron-mediated generation of superoxide anion is responsible for the inactivation of aconitase. Addition of furaneol or maltol to calf thymus DNA stimulated the formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG), an indicator for the presence of hydroxyl radicals, and addition of catalase, an enzyme that converts hydrogen peroxide, a hydroxyl radical precursor, to water and oxygen, completely inhibits formation of 8-OHdG (Murakami, 2005b, 2007).

In one experiment, hinokitiol induced DNA fragmentation in teratocarcinoma F9 cells in a concentration and time dependent manner. In contrast, hinokitiol methyl ether and hinokitiol-Fe3<sup>+</sup>complex showed no DNA fragmentation in cells in culture or in cell-free systems. Hinokitiol activated caspase-3, one of the key enzymes in the apoptotic cascade

Figure 1. Alicyclic and heterocyclic alpha-ketoenols that form alpha-hydroxyenolates that readily complex with metal ions

Figure 2. Mechanism of in vitro furanone derivative oxidation

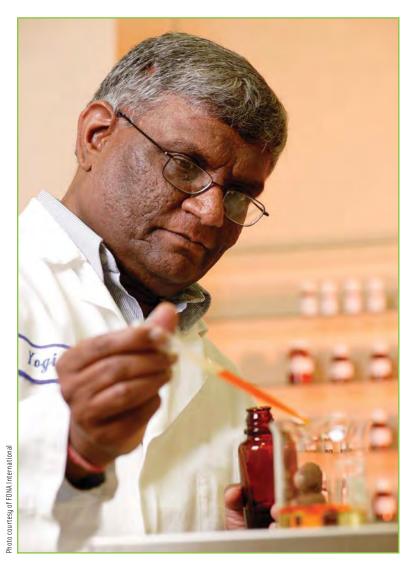
H<sub>3</sub>C CH<sub>3</sub> + Fe<sup>+++</sup> + O<sub>2</sub>

H<sub>3</sub>C CH<sub>3</sub> + Fe<sup>++</sup> + O<sub>2</sub>

$$O_2^{--}$$

Superoxide dismutase

 $O_2^{--}$ 
 $O_2^{--$ 



(Ido et al., 2002). In conclusion, evidence of DNA reactivity in these genotoxicity assays is the result of reduction of intracellular metal ions by high cellular concentrations of alpha-ketoenols eventually leading to production of OH radicals leading to DNA damage and eventually apoptosis.

Despite the fact that these substances exhibit genotoxicity, they do not produce carcinogenic effects in rodents. Three studies, one on ethyl maltol, one on furaneol and the other on a structurally related furanone, show no evidence of carcinogenicity at intake levels at least four orders of magnitude greater than the

intake of these substances added as flavouring agents (Kelly and Bolte, 2003; Munday and Kirkby, 1973; Gralla et al., 1969). Furthermore, vitamin C, a furanone containing a dihydroxyenol moiety with a genotoxicity test profile similar to that of DMHF, does not demonstrate carcinogenicity (NRC, 1996). In humans, furaneol (Roscher et al., 1997) and maltol (Rennhard, 1971) are rapidly absorbed in the gastrointestinal tract, conjugated with glucuronic acid in the liver and excreted in the urine. Free furaneol is not detected in the blood of human volunteers to whom it is administered as a constituent of strawberries; its glucuronic acid

conjugate is the principal urinary metabolite (Roscher et al., 1997). At low levels of intake as flavouring substances, it is highly unlikely that these substances would exhibit the genotoxic potential observed under in vitro conditions at much higher cellular concentrations or in vivo at severely toxic levels (>oral LD<sub>50</sub> levels). Based on the available data, it is highly unlikely that these substances pose any significant genotoxic risk to humans under conditions of use as flavouring agents.

For the other chemical groups containing more than 2,000 substances, there is no consistent positive evidence of mutagenicity or genotoxicity in a specific in vitro assay or in a group of standard in vitro assays (bacterial reverse mutation [Ames], mouse lymphoma, sister chromatid exchange, and chromosomal aberration). In cases where raw data are available for the in vitro assays, positive evidence of mutations, clastogenicity, or genotoxicity occurs at concentrations in which there is measurable evidence of cytotoxicity. Positive evidence of mutagenicity or genotoxicity in a single in vitro assay is not confirmed upon repeat analysis or by standardized in vivo assays (e.g., mouse micronucleus, unscheduled DNA synthesis) using oral administration.

Among the standard battery of genotoxicity assays, the in vitro chromosome aberration test, the sister chromatid exchange assay, and the mouse lymphoma assay, all show higher incidences of positive evidence of genotoxicity. While all of the standardized assays have value in detecting relevant genotoxicity under experimental conditions, there is no supportive evidence for DNA reactivity for a considerable number of in vitro clastogens in the chromosomal aberration or sister chromatid exchange assays or forward mutations in the mouse lymphoma assay. In fact, the clastogenic response



of cells when exposed to flavoring substances is strongly correlated with cytotoxicity. This may invoke the need to alter the protocol for assessing clastogenicity in vitro. Decreasing the level of cytotoxicity (e.g., from 50% to 10-20%) at which clastogenic responses are still considered valid and lowering the upper limits of test substance concentration, irrespective of cytotoxicity, may help ensure sufficient reliability of future genotoxicity testing with mammalian cells in vitro. These recommendations have recently been proposed by the International Conference on Harmonisation (ICH) and in the Organization for Economic Co-Operation & Economic Development's (OECD) guidelines to create a common ground of understanding for interpretation of in vitro (positive) test results (Kirkland et al., 2005, 2007a, 2007b; Meintieres and Marzin, 2004; Muller and Sufuni, 2000; Thybaud et al., 2007).

# Safety Assessment of Isoeugenol (FEMA No. 2468)

Isoeugenol (CAS No. 97-54-1) is trans-4hydroxy-3-methoxy-1-propenylbenzene. Together with a number of structurally related derivatives, isoeugenol occurs in a wide variety of plants and plant extracts, including savory basil, clove, mace, dill seed, and nutmeg. As a flavoring agent, it has been added to flavor formulations for nonalcoholic beverages, candy, and chewing gum. The annual reported volume of use as a flavor ingredient is 236 kg in the U.S. and 426 kg in Europe (Gavin et al., 2008; EFFA, 2005).

In a 2-year bioassay sponsored by National Toxicology Program (NTP, 2008), groups of 50 F344/N rats or B6C3F, mice of both sexes were administered oral doses of 0, 75, 150, or 300 mg/kg body weight per day of isoeugenol by gavage, 5 days/week for 105 weeks. The NTP Subcommittee that reviewed the study concluded that:

"Under the conditions of these 2-year gavage studies, there was equivocal evidence of carcinogenic activity of isoeugenol in male F344/N rats based on increased incidences of rarely occurring thymoma and mammary gland carcinoma. There was no evidence of carcinogenic activity in female F344/N rats.... There was clear evidence of carcinogenic activity of isoeugenol in male B6C3F, mice based on increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and

hepatocellular adenoma or carcinoma (combined). There was equivocal evidence of carcinogenic activity of isoeugenol in female B6C3F, mice based on increased incidences of histiocytic sarcoma."

The primary neoplastic effects reported in the 2-year NTP gavage study were associated with the liver of control and treated male mice. The high incidence of hepatocellular adenomas, carcinomas, and adenomas and carcinomas (combined) in both control and treated groups of male mice is indicative of the sensitivity of the B6C3F, male mouse liver to toxicity and eventually neoplastic changes. Although the incidence of hepatocellular adenomas (control, 24/50; dosed groups, 35/50 at 75 mg/kg bw, 37/50 at 150 mg/kg bw, and 33/50 at 300 mg/kg bw), hepatocellular carcinomas (control, 8/50; dosed groups, 18/50 at 75 mg/kg bw, 19/50 at 150 mg/kg bw, and 18/50 at 300 mg/kg bw), and combined hepatocellular adenomas and carcinomas (control, 28/50; dosed groups, 43/50 at 75 mg/kg bw, 43/50 at 150 mg/ kg bw, and 43/50 at 300 mg/kg bw) in all groups of treated male mice was greater than in the control group, the effects were not dose-dependent and the incidence of malignant neoplasms (14/50) of all types (hepatocellular carcinomas, hemangiosarcoma, hepatocholangiocarcinomas, and hepatoblastomas) in the control group was similar to the incidences in the treated groups. No liver neoplastic effects were reported in rats.

This pattern of neoplastic responses is consistent with the historically high levels of background hepatocellular neoplasms in male B6C3F, mice (Maronpot et al., 1987). The historical spontaneous incidence of liver neoplasms in control male B6C3F, mice has revealed background incidences of combined hepatocellular adenoma and carcinomas of 32.4% for males with a range of 20-47% (NTP, 2006). A higher incidence was reported in the control group of the isoeugenol study (56%). It



is generally well accepted that male and female B6C3F, mouse liver tumors that arise in 2-year bioassays with various agents (e.g., chloroform) are an indirect result of dose-related chronic toxicity and resulting cellular proliferation. In the absence of this chronic toxicity in humans, these tumors are not considered to represent a risk for humans (Cohen et al., 2004).

There is substantial evidence that the appearance of male B6C3F, mouse liver tumors is not relevant to a human risk. First, there was no statistical evidence of an increased incidence of hepatic tumors in female mice or male or female rats related to administration of isoeugenol. Second, all dose groups of male B6C3F, mice suffered chronic hepatic toxicity prior to the development of either liver adenomas or carcinomas, as evidenced by the results of the 90-day and 2-year studies. Hepatocellular adenomas and carcinomas also occurred late in the life span of males. From a biological perspective, the increase in the incidence of

tumors in male B6C3F, mice reflects the impact of high-dose liver damage to an organ already prone to spontaneous development of liver neoplasms (Haseman et al., 1986, 1990).

Therefore, it can be concluded that the carcinogenic potential in this sensitive breed and sex of laboratory rodent is a secondary biological response to dose-dependent hepatotoxicity, and is not relevant to humans who consume isoeugenol at low non-toxic levels (<0.1 mg/kg bw per day) from intended use as a flavoring ingredient. These levels of intake are at least six orders of magnitude less than those used in the NTP study.

The only other neoplastic effect reported was in female mice. There was an increased incidence of histiocytic sarcoma in dosed compared to control females (control, 0/50; dosed groups, 1/50 at 75 mg/kg bw; 1/50 at 150 mg/kg bw; 4/50 at 300 mg/kg bw.) Although no evidence of histiocytic sarcoma was reported in control females, the incidence of histiocytic sarcomas  $(1.5\% \pm 2.2\%$ , range 0–8%) and incidences of

tumors in the isoeugenol study (2% and 8%) are well within the historical control range for the NTP female mouse historical database.

In order to evaluate the relevance of these tumors to the potential cancer risk for humans consuming isoeugenol as a flavoring agent, it is important to note that a significant increase in histiocytic sarcomas was reported at dose levels inducing liver toxicity and even necrosis (8/50 at 300 mg/kg bw per day). Increased incidences of splenic extramedullary hematopoiesis and splenic cellular depletion are additional evidence of damage to the hematopoietic system.

Clearly, low incidences of histiocytic sarcomas occurred in only one sex, and only at dose levels inducing toxicity, rendering it highly likely that the occurrence of these tumors is a high-dose phenomenon that manifests itself in severely affected livers of female mice. The estimated daily per capita intake of isoeugenol as a flavoring agent in the U.S. (0.00002 mg/kg bw/day) is more than 3,750,000 times lower than the dose levels in the NTP study. Therefore, the occurrence of these neoplasms in the present study is considered a high-dose phenomenon without any relevance for assessing the potential cancer risk of the use of isoeugenol as a food flavor ingredient. FT

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References on p. 62. »»

# **CORRECTION & CHANGES**

- Alternate Citronella Source. Citronella oil (FEMA 2308) reported in GRAS 3 (Hall and Oser, 1965) incorrectly listed only one species, Cymbopogon nardus Rendle, as the accepted botanical source. An alternate species, Cymbopogon winterianus Jowitt, is also an accepted botanical source for GRAS approved citronella oil.
- DeGRAS of Acetamide. The substance acetamide (FEMA No. 4251) was reviewed by the Expert Panel and found to require additional data, including chronic toxicity testing, for the continuation of its GRAS status. Based on a survey of the flavor industry, there was insufficient interest to support the acquisition of the requested data. Therefore, the flavor ingredient acetamide has been removed from the GRAS list.
- Expert Panel Member Change. Nigel Gooderham, Professor of Pharmacology and Toxicology at University of London, joined the Panel in January 2009.
- · Consultant Change. Ian Munro, a Panel member from 1983 to 2001 and a Panel consultant beginning in 2001, retired from the Panel in October 2008. He has spent more than a quarter of a century in service to the Expert Panel and the flavor industry. His experience in toxicology, international food and flavor safety, and food and flavor regulation provided the Panel with a unique expertise that contributed significantly to successful operation of the Panel.

# REFERENCES

Adams, T.B., Cohen, S.M., Doull, J., Feron, V.J., Goodman, J.I., Marnett, L.J., Munro, I.C., Portoghese, P.S., Smith, R.L., Waddell, W.J., and Wagner, B.M. 2005. The FEMA GRAS assessment of benzyl derivatives used as flavor ingredients. Food Chem, Toxicol. 43: 1207-1240.

Adams, T.B., Gavin, C.L., Taylor, S.V., Waddell, W.J., Cohen, S.M., Feron, V.J., Goodman, J.I., Rietjens, I.M.C.M., Marnett, L.J., Portoghese, P.S., and Smith, R.L. 2008. The FEMA GRAS assessment of alpha, beta-unsaturated aldehydes and related substances used as flavor ingredients. Food Chem. Toxicol. 49: 2935-2967.

Cohen, S.M., Klaunig J., Meck, M.E., Hill, R.N., Pastoor, T., Lehman-McKeeman, L., Bucher, J., Longfellow, D.G., Seed, J., and Dellarco, V. 2004. Evaluating the human relevance of chemically induced animal tumors. Toxicol. Sci. 78: 181-186.

EFFA. 2005. European Flavour and Fragrance Association European inquiry on volume use. Private communication to the Flavor and Extract Manufacturers Association (FEMA).

Gavin, C.L., Williams, M.C., and Hallagan, J.B. 2008. FEMA 2005 poundage and technical effects update survey. Flavor and Extract Manufacturers Association, Washington, D.C.

Gralla, E. J., Stebbins, R.B., Coleman G.L., and Delahunt, C.S. 1969. Toxicity studies with ethyl maltol. Toxicol. App. Pharmacol. 15(3): 604-613.

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

Haseman, J.K., Winbush, J.S., and O'Donnell, Jr., M.W. 1986. Use of dual control groups to estimate false positive rates in laboratory animal carcinogenicity studies. Fundamental and Applied Toxicol. 7: 573-584.

Haseman, J.K., Zeiger, E., Shelby, M.D., Margolin, B.H., and Tennant, R.W. 1990. Predicting rodent carcinogenicity from four in vitro genetic toxicity assays: an evaluation of 114 chemicals studied by the National Toxicology Program. J. Am. Statistical Assoc. 85(412): 964-971.

Hiramoto, K., Kato, T., Takahashi, Y., Yugi, K., and Kikugawa, K. 1998. Absorption and induction of micronucleated peripheral reticulocytes in mice after oral administration of fragrant hydroxyfuranones generated in the Maillard reaction. Mutat. Res. 415: 79-83.

Ido, Y., Muto, N., Inada, A., Kohroki, J., Mano, M., Odani, T., Itoh, N., Yamamoto, K., and Tanaka, K. 2002. Induction of apoptosis by hinokitiol, a potent iron chelator, in teratocarcinoma F9 cells is mediated through the activation of caspase-3. Cell Proliferation 32(1): 63-73.

Inamori, Y., Tsujibo, H., Ohishi, H., Ishii, F., Mizugaki, M., Aso, H., and Ishida, N. 1993. Cytotoxic effect of hinokitiol and tropolone on the growth of mammalian cells and on blastogenesis of mouse splenic T cells. Biol. Pharm. Sci. 16(5): 521-523. JECFA. 2006. Safety evaluation of certain food additives. Report of the Joint FAO/

food additives. Report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series No. 54. World Health Org., Geneva.

Kelly, C.M. and Bolte, H.F. 2003. ST 07 C99: a 24-month dietary carcinogenicity study in rats. Final report. Study No. 99-2644. Huntingdon Life Sciences, East Millstone N.J. Private communication to the Flavor and Extract Manufacturers Association.

Kirkland, D., Aardema, M., Henderson., L., and Muller, L. 2005. Evaluation of the ability of a battery of three in vitro genotoxicity tests to discriminate rodent carcinogens and non-carcinogens I. Sensitivity, specificity, and relative predictivity. Mutat. Res. 584(1-2): 1-256.

Kirkland, D., Pfuhler, S., Tweats, D.,
Aardema, M., Corvi, R., Darroudi,
F., Elhajouji, A., Glatt, H., Hastwell,
P., Hayashi, M., Kasper, P., Kirchner,
S., Lynch, A., Marzin, D., Maurici, D.,
Meunier, J.R., Müller, L., Nohynek, G.,
Parry, J., Parry, E., Thybaud, V., Tice, R.,
van Benthem, J., Vanparys, P., and White, P.
2007a. How to reduce false positive results
when undertaking in vitro genotoxicity
testing and thus avoid unnecessary followup animal tests: Report of an ECVAM
Workshop. Mutat. Res. 628(1): 31-55.

Kirkland, D., Aardema, M., Banduhn, N., Carmichael, P., Fautz, R., Meunier, J., and Pfuhler, S. 2007b. In vitro approaches to develop weight of evidence (WoE) and mode of action (MoA) discussions with positive in vitro genotoxicity results. Mutagenesis 22(3): 161-175.

Maronpot, R.R., Haseman, J.K., Boorman, G.A., Eustis, S.E., Rao, G.N., and Huff, J.E. 1987. Liver lesions in B6C3F, mice: the National Toxicology Program, experience and position. Arch. Toxicol. 10: 10-26.

Meintieres, S. and Marzin, D. 2004. Apoptosis may contribute to false-positive results in the in vitro micronucleus test performed in extreme osmolality, ionic strength, and pH conditions. Mutat. Res. 560: 101-118.

Moridani, M.Y. and O'Brien, P.J. 2001. Ion complexes of deferiprone and dietary plant catechols as cytoprotective superoxide radical scavengers. Biochem. Pharmacol. 62: 1579-1585.

Muller, L. and Sofuni, T. 2000. Appropriate levels of cytotoxicity for genotoxicity tests using mammalian cells in vitro. Environ. Mol. Mutagen. 35: 202-205.

Munday, R. and Kirkby, W. 1973. Unpublished report. Biological evaluation of a flavor cocktail. III. One-year feeding study in rats. Private communication to FEMA, Washington, D.C.

Murakami, K., Ohara, Y., Haneda, M., Tsubouchi, R., and Yoshino, M. 2005a. Prooxidant Action of Hinokitiol: Hinokitiol-Iron Dependent Generation of Reactive Oxygen Species. Basic Clin. Pharmacol. Toxicol. 97(6): 392-394.

Murakami, K., Ishida, K., Watakabe, K., Tsubouchi, R., Haneda, M., and Yoshino M. 2005b. Prooxidant action of maltol: Role of transition metals in the generation of reactive oxygen species and enhanced formation of 8-hydroxy-2'-deoxyguanosine formation in DNA. BioMetals 19: 253-257.

Murakami, K., Ishida, K., Watakabe, K., Tsubouchi, R., Naruse, M., and Yoshino, M. 2006. Maltol/iron-mediated apoptosis in HL60 cells: Participation of reactive oxygen species. Toxicol. Lett. 161(2): 102-107.

Murakami, K., Haneda, M., Makino, T., and Yoshino, M. 2007. Prooxidant action of furanone compounds: Implication of reactive oxygen species in the metal-dependent strand breaks and the formation of 8-hydroxy-2'-deoxyguanosine in DNA. Food Chem. Toxicol. 45: 1258-1262.

NRC. 1996. Carcinogens and anticarcinogens in the human diet; a comparison of naturally occurring and synthetic substances. National Academy Press, 91-92. National Research Council, Washington, D.C.

NTP. 2003. Technical Report on the Toxicology and Carcinogenesis Studies of 2,4-Hexadienal (CAS No. 142-83-6) in F344/N Rats and B6C3F, Mice. NTPTR 509. NIH Publication No. 04-4443. Natl. Toxicology Program, Research Triangle Park, N.C. http://ntp.niehs.nih.gov/

NTP. 2006. Technical Report on the Toxicology and Carcinogenesis Studies of Benzophenone (CAS NO. 119-61-9) in F344/N Rats and B6C3F<sub>1</sub> Mice. NTPTR 533. NIH Publication No. 06-4469. Natl. Toxicology Program, Research Triangle Park, N.C. http://ntp.niehs.nih.gov/

NTP. 2008. Draft Report: Technical Report on the Toxicology and Carcinogenesis Studies of Isoeugenol (CAS NO. 97-54-1) in F344/N Rats and B6C3F, Mice. NTP TR 551. Natl. Toxicology Program, Research Triangle Park, N.C.

Rennhard, H.H. 1971. The metabolism of ethyl maltol and maltol in the dog. J. Agric. Food Chem. 19(1): 152-154.

Roscher, R., Koch, H., Herderich, M., Schreier, P., and Schwab, W. 1997. Identification of 2,5-Dimethyl-4-hydroxy-3[2H]-franone beta-D-Glucuronide as the Major Metabolite of Strawberry Flavour Constituent in Humans. Food Chem. Toxicol. 35: 777-782.

Stout, M., Bodes, E., Schoonhoven, R., Upton, P., Travlos, G., and Swenberg, J. 2008. Toxicity, DNA binding, and cell proliferation in male F344 rats following short-term gavage exposures to trans-2hexenal. Toxicology Pathology 36(2): 232-246.

Thybaud, V., Aardema, M., Clements, J., Dearfield, K., Galloway, S., Hayashi, M., Jacobson-Kram, D., Kirkland, D., MacGregor, J., Marzin, D., Ohyama, W., Schuler, M., Suzuki, H., and Zeiger, E. 2007. Strategy for genotoxicity testing: Hazard identification and risk assessment in relation to in vitro testing. Mutat. Res. 627: 41-58.

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4430	<b>3,4-Dihydroxybenzoic acid</b> Protocatechuic acid
4431	<b>3-Hydroxybenzoic acid</b> <i>m</i> -Hydroxybenzoic acid <i>m</i> -Salicylic acid
4432	(+/-)-Acetaldehyde ethyl isopropyl acetal 2-(1-Ethoxyethoxy)propane 1-Ethoxy-1-isopropoxyethane 1-Ethoxy-1-(2-propoxy)ethane
4433	(+/-)-6-Methyloctanal
4434	<b>5-Ethyl-2,3-dimethylpyrazine</b> 2-Ethyl-5,6-dimethylpyrazine
4435	<b>2-Hydroxy-4-methoxybenzaldehyde</b> 2-Formyl-5-methoxyphenol 2-Hydroxy- <i>p</i> -anisaldehyde 4-Methoxysalicylaldehyde
4436	3-(Methylthio)propyl hexanoate 3-(Methylsulfanyl)propylhexanoate Hexanoic acid, 3-(methylthio)propyl ester Methionyl hexanoate
4437	Sodium lauryl sulfate Sodium dodecyl sulfate Sulfuric acid monododecyl ester sodium salt
4438	beta-Angelicalactone 5-Methylfuran-2(5H)-one 4-Methyl-2-butenolide 4-Hydroxy-2-pentenoic acid gamma-lactone
4439	<b>7-Decen-4-olide</b> 4-Hydroxydec-7-enoic acid lactone 5-(3-Hexenyl)dihydro-2(3H)-furanone 5-(Hex-3-en-1-yl)dihydrofuran-2(3H)-one
4440	9-Decen-5-olide 6-(Pent-4-en-1-yl)tetrahydro- 2H-pyran-2-one Tetrahydro-6-(4-penten-1- yl)-2H-pyran-2-one 5-Hydroxydec-9-enoic acid lactone
4441	8-Decen-5-olide 6-(Pent-3-en-1-yl)tetrahydro- 2H-pyran-2-one Tetrahydro-6-(3-penten-1- yl)-2H-pyran-2-one 5-Hydroxydec-8-enoic acid lactone
4442	6-[5(6)-Decenoyloxy]decanoic acid 5(6)-Decenoic acid, 1-butyl- 5-carboxypentyl ester
4443	Ethyl 5-acetoxyoctanoate Octanoic acid, 5-(acetyloxy)-, ethyl ester delta-Acetoxyoctanoic acid, ethyl ester Ethyl 5-(acetyloxy)octanoate
4444	Ethyl 5-hydroxydecanoate Decanoic acid, 5-hydroxy-, ethyl ester
4445	9-Dodecen-5-olide 6-(Hept-4-en-1-yl)tetrahydro- 2H-pyran-2-one 5-Hydroxydec-9-enoic acid lactone
4446	gamma-Octadecalactone 4-Hydroxyoctadecanoic acid lactone Dihydro-5-tetradecyl-2(3H)-furanone 5-Tetradecyldihydro-3H-furan-2-one gamma-Stearolactone 4-Octadecanolide

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4447	deltα-Octadecalactone 5-Hydroxyoctadecanoic acid lactone Tetrahydro-6-tridecyl-2H-pyran-2-one 6-Tridecyltetrahydro-2H-pyran-2-one deltα-Stearolactone 5-Octadecanolide
4448	9-Tetradecen-5-olide 5-Hydroxytetradec-9-enoic acid lactone Tetrahydro-6-(4-nonenyl)-2H-pyran-2-one 6-(Non-4-en-1-yl)tetrahydro- 2H-pyran-2-one
4449	Orin lactone (+/-)-4,8-Dimethylnon-7-en-4-olide 5-Methyl-5-(4-methyl-3-pentenyl)- 4,5-dihydro-2(3H)-furanone 5-Methyl-5-(4-methyl-3-penten- 1-yl)dihydrofuran-2(3H)-one
4450	Methyl 3-hydroxybutyrate (+/-)-Methyl 3-hydroxybutanoate 3-Hydroxybutyric acid methyl ester
4451	Methyl 3-acetoxy-2-methylbutyrate Methyl 3-(acetyloxy)-2-methylbutanoate Butanoic acid, 3-(acetyloxy)- 2-methyl-, methyl ester
4452	Ethyl 2-acetylhexanoate 2-Acetylhexanoic acid ethyl ester alphα-Acetylcaproic acid ethyl ester
4453	Ethyl 3-hydroxyoctanoate 3-Hydroxyoctanoic acid ethyl ester beta-Hydroxycaprylic acid ethyl ester
4454	Methyl 3-acetoxyoctanoate 3-(Acetyloxy)octanoic acid methyl ester Methyl 3-(acetyloxy)octanoate
4455	5-Oxooctanoic acid
4456	5-Oxodecanoic acid
4457	Ethyl 5-oxodecanoate 5-Oxodecanoic acid ethyl ester
4458	<b>5-Oxododecanoic acid</b> 5-Oxolauric acid
4459	Ethyl 2-acetyloctanoate Ethyl 2-acetylcaprylate 2-Acetyloctanoic acid ethyl ester
4460	<b>2-0xo-3-ethyl-4-butanolide</b> 4-Ethyldihydro-2,3-furandione 4-Ethyldihydrofuran-2,3-dione
4461	3-Isopropenyl-6-oxoheptanoic acid 3-(1-Methylethenyl)-6-oxo-heptanoic acid 6-0xo-3-(prop-1-en-2-yl)heptanoic acid
4462	Hydroxyacetone 1-Hydroxy-2-propanone 1-Hydroxypropan-2-one 2-Oxopropanol Acetol
4463	1-Hydroxy-4-methyl-2-pentanone
4464	Propyleneglycol diacetate 1,2-Propanediol diacetate 1,2-Diacetoxypropane Propane-1,2-diyl diacetate
4465	Propyleneglycol dipropionate 1,2-Propanediol dipropanoate Propylene glycol 1,2-dipropionate Propane-1,2-diyl dipropionate

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4466	Propyleneglycol dibutyrate 1,2-Propanediol dibutyrate Propane-1,2-diyl dibutyrate Dibutyryl 1,2-propyleneglycol Butanoic acid, 1,1'-(1-methyl- 1,2-ethanediyl) ester
4467	Propyleneglycol mono-2-methylbutyrate 2-Hydroxypropyl-2-methylbutanoate Butanoic acid, 2-methyl-, 2-hydroxy-1-methylethyl ester Butanoic acid, 2-methyl-, 2-hydroxypropyl ester
4468	Propyleneglycol di-2-methylbutyrate Propane-1,2-diyl bis(2-methylbutanoate)
4469	Propyleneglycol monohexanoate 2-Hydroxypropyl hexanoate Hexanoic acid, 2-hydroxypropyl ester Hexanoic acid, 2-hydroxy- 1-methylethyl ester
4470	Propyleneglycol dihexanoate 1,2-Propanediol dihexanoate 1,2-Propylene glycol dicaproate Propane-1,2-diyl dihexanoate
4471	Propyleneglycol dioctanoate 1,2-Propanediol dioctanoate 1,2-Propylene glycol dicaprylate Propane-1,2-diyl dioctanoate
4472	Dimethyl adipate Dimethyl hexanedioate Hexanedioic acid, dimethyl ester Adipic acid, dimethyl ester
4473	<b>Dipropyl adipate</b> Dipropyl hexanedioate Hexanedioic acid, dipropyl ester Adipic acid, dipropyl ester
4474	<b>Diisopropyl adipate</b> Hexanedioic acid, <i>bis</i> (1-methylethyl) ester Adipic acid, diisopropyl ester
4475	<b>Diisobutyl adipate</b> Hexanedioic acid, <i>bis</i> (2-methylpropyl) ester Adipic acid, diisobutyl ester
4476	<b>Dioctyl adipate</b> Hexanedioic acid, dioctyl ester Adipic acid, dioctyl ester Di- <i>n</i> -octyl adipate
4477	Ethyl acetoacetate ethyleneglycol ketal 2-Methyl-1,3-dioxolane-2- acetic acid ethyl ester Ethyl (2-methyl-1,3-dioxolan-2-yl) acetate Ethyl 2-methyl-1,3-dioxolane-2-acetate Ethyl 3-oxobutyrate ethylene ketal
4478	Methyl levulinate Methyl 4-oxovalerate Methyl 4-oxopentanoate 4-Oxopentanoic acid methyl ester Levulinic acid methyl ester
4479	Ethyl levulinate propyleneglycol ketal 2-Methyl-1,3-dioxane-2- propanoic acid ethyl ester Ethyl 3-(2,4-dimethyl-1,3- dioxolan-2-yl)propanoate
4480	Propyl levulinate 4-0xo-pentanoic acid propyl ester Levulinic acid propyl ester

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4481	Isoamyl levulinate Isopentyl levulinate Pentanoic acid, 4-oxo-, 3-methylbutyl ester Levulinic acid, isopentyl ester
4482	Dodecyl lactate Propanoic acid, 2-hydroxy-, dodecyl ester Lactic acid, dodecyl ester Lauryl lactate
4483	Hexadecyl lactate Propanoic acid, 2-hydroxy-, hexadecyl ester Lactic acid, hexadecyl ester Cetyl lactate
4484	Propyl pyruvate Propanoic acid, 2-oxo-, propyl ester Pyruvic acid, propyl ester Propyl 2-oxopropionate
4485	Hydroxycitronellal propyleneglycol acetal 2,6-Dimethyl-1,3-dioxolane-2-heptanol 4-Methyl-1,3-dioxolane-1-(6-hydroxy-2,6-dimethylheptyl)
4486	Citral glyceryl acetal 2-(2,6-Dimethyl-1,5-heptadien-1- yl)-1,3-dioxolane-4-methanol
4487	Mushroom oil, distilled Oils, Agaricus bisporus
4488	Propyleneglycol monobutyrate
4489	cis-3-Hexenyl acetoacetate (3Z)-Hex-3-en-1-yl 3-oxobutanoate
4490	2-Methoxy-6-(2-propenyl)phenol
4491	Myricitrin 3,3',4',5,5',7-Hexahydroxyflavone, 3- rhamnoside Myricetin 3-o-alpha-L-rhamnopyranoside Myricetin 3-o-alpha-L-rhamnoside 5,7-Dihydro-4-oxo-2-(3,4,5- trihydroxyphenyl)-4H-chromen-3-yl 6-deoxy-alpha-L-rhamnopyranoside
4492	( <i>R</i> )-(-)-1-Octen-3-ol (3 <i>R</i> )-1-Octen-3-ol Matsutake alcohol
4493	cis-3-Hexenoic acid (Z)-3-Hexenoic acid
4494	Ammonia (also includes ammonium chloride)
4495	Naringin dihydrochalcone 3,5-Dihydroxy-4-(p- hydroxyhydrocinnamoyl)phenyl 2-o-(6- deoxy-alpha-L-mannopyranosyl)-, beta-D-glucopyranoside 4'-(2-o-alpha-L-rhamno-beta- D-glucopyranoside)phloretin
4496	N-p-Benzeneacetonitrile- menthanecarboxamide N-[4-(Cyanomethyl)phenyl]-5-methyl-2- (1-methylethyl)-cyclohexanecarboxamide N-(4-Cyanomethylphenyl)-p- menthanecarboxamide
4497	Cubebol Cubeb camphor (35,3aR,3bR,45,7R,7aR)-3,7-Dimethyl- 4-(propan-2-yl)octahydro-1H- cyclopenta[1,3]cyclopropa[1,2]benzen-3-ol

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4498	6-Methylheptanal
4499	(+/-)-cis- and trαns-2-Pentyl- 4-propyl-1,3-oxathiane
4500	Choline chloride (also includes choline) (2-Hydroxyethyl)- trimethylammonium chloride (beta-Hydroxyethyl)- trimethylammonium chloride
4501	3-[(2-Methyl-3-furyl)thio]butanal Methylthiofuryl butanal 3-[(2-Methylfuran-3-yl)sulfanyl]butanal
4502	(-)-Sclareol  1-Naphthalenepropanol, alpha- ethenyldecahydro-2-hydroxy- alpha-2,5,5,8a-pentamethyl- (alpha-R,1R,2R,4a5,8a5)- Labd-14-ene-8,13-diol
4503	(+)-Cedrol  1H-3a,7-Methanoazulen-6-ol, octahydro- 3,6,8,8-tetramethyl-, (3R,3a5,6R,7R,8a5)- 8-beta-H-Cedran-8-ol alpha-Cedrol
4504	d-Limonen-10-ol (+)-(R)-p-Mentha-1,8(10)-dien-9-ol (+)-Limonene-10-ol 2-[(1R)-4-Methylcyclohex-3- en-1-yl]prop-2-en-ol
4505	(2,4)- and (3,5)- and (3,6)-Dimethyl- 3-cyclohexenylcarbaldehyde Dimethyl-3-cyclohexene-1-carboxaldehyde
4506	1,3-p-Menthadien-7-al 4-(1-Methylethyl)-1,3- cyclohexadiene-1-carboxaldehyde 4-Isopropyl-1,3-cyclohexadiene- 1-carboxaldehyde 4-(Propan-2-yl)cyclohexa-1,3- diene-1-carbaldehyde alpha-Terpinen-7-al p-Mentha-1,3-dien-7-al
4507	p-Menthan-7-ol 4-(1-methylethyl)-cyclohexanemethanol 4-lsopropylcyclohexylmethanol
4508	p-Menth-1-en-9-ol 2-(4-Methylcyclohex-3- en-1-yl)propan-1-ol
4509	Menthyl formate 2-Isopropyl-5-methylcyclohexyl formate Formic acid, menthyl ester
4510	Menthyl propionate 2-Isopropyl-5-methylcyclohexyl propionate
4511	Cyclotene propionate 3-Methyl-2-(1-oxopropoxy)- 2-cyclopenten-1-one 2-Methyl-5-oxocyclopent- 1-en-1-yl propanoate
4512	3,3,5-Trimethylcyclohexyl acetate Homomenthol acetate
4513	dl-Camphor (+/-)-1,7,7-Trimethylbicyclo[2.2.1] heptan-2-one

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4514	<b>2-Cyclopentylcyclopentanone</b> 1,1'-Bi(cyclopentyl)-2-one
4515	Carvyl palmitate Carvyl hexadecanoate
4516	Cyclohexanone diethyl ketal 1,1-Diethoxycyclohexane
4517	<b>2-Cyclohexenone</b> 2-Cyclohexen-1-one
4518	8,9-Dehydrotheaspirone (5)-2,6,10,10-Tetramethyl-1- oxaspiro[4.5]deca-2,6-dien-8-one
4519	I-Fenchone L-1,3,3-Trimethylbicyclo[2.2.1] heptan-2-one
4520	Ethylenediaminetetraacetic acid disodium salt Glycine, N,N'-1,Z-ethanediylbis[N-(carboxymethyl)-, disodium salt, dihydrate Acetic acid, (ethylenedinitrilo)tetra-, disodium salt, dihydrate Disodium dihydrogen ethylenediaminetetraacetate dihydrate Disodium EDTA dihydrate Ethylenediaminetetraacetic acid disodium salt dihydrate
4521	2,2,6,7-Tetramethylbicyclo[4.3.0]nona- 4,9(1)-dien-8-ol
4522	2,2,6,7-Tetramethylbicyclo[4.3.0]nona- 4,9(1)-dien-8-one
4523	<b>6-Hydroxycarvone</b> 3-Hydroxy-2-methyl-5-(prop-1- en-2-yl)cyclohex-2-en-1-one
4524	I-Menthyl butyrate L-5-Methyl-2-(1-methylethyl)- cyclohexyl butyrate
4525	Pinocarvyl isobutyrate 2(10)-Pinen-3-yl isobutyrate 6,6-Dimethyl-2-methylidenebicyclo[3.1.1]- hept-3-yl-2-methylpropanoate
4526	2-Pentenyl-4-propyl-1,3-oxathiane (mixture of isomers) 2-(Pent-2-enyl)-4-propyl-[1,3]-oxathiane
4527	Acetaldehyde di-isobutylacetal 1,1-Diisobutoxyethane
4528	Acetaldehyde ethyl isobutyl acetal 1-Ethoxy-1-isobutoxyethane 1-(1-Ethoxyethoxy)-2-methylpropane
4529	4-(2,2,3-Trimethylcyclopentyl)butanoic acid
4530	Perillaldehyde propyleneglycol acetal 4-Methyl-2-[4-(1-methylethenyl)- 1-cyclohexen-1-yl]-1,3-dioxolane
4531	<b>2,6,6-Trimethyl-2-hydroxycyclohexanone</b> 2-Hydroxy-2,6,6-trimethylcyclohexanone
4532	Acetoin propyleneglycol ketal 1-(2,4-Dimethyl-1,3-dioxolan-2-yl)ethanol
4533	4,5-Octanedione

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4534	Ethyl maltol isobutyrate 2-Ethyl-3-[(3-methylbut-1-en- 2-yl)oxy]-4 <i>H</i> -pyran-4-one
4535	2-Tetrahydrofurfuryl 2-mercaptopropionate Tetrahydrofuran-2-yl methyl 2-sulfanylpropanoate
4536	Nerolidol oxide 5-Ethenyltetrahydro-alpha-5-dimethyl-alpha-(4-methyl-3-pentenyl)- 2-furanmethanol Tetrahydro-alpha-5-dimethyl-alpha-(4-methyl-3-pentenyl)- 5-vinyl-furfuryl alcohol
4537	Furfural propyleneglycol acetal 2-(2-Furyl)-4-methyl-1,3-dioxolane
4538	Methyl 3-(furfurylthio)propionate  Methyl 3-(2-furylmethyl- sulfanyl)propanoate  Propanoic acid, 3-[(2-furanyl- methyl)thio]-, methyl ester
4539	Furfuryl decanoate
4540	Di-2-furylmethane Furan, 2,2'-methylenebis- 2,2'-Difurylmethane 2,2'-Methylenedifuran 2-(2-Furfuryl)furan
4541	(E)-Ethyl 3-(2-furyl)acrylate 2-Propenoic acid, 3-(2-furanyl)-, ethyl ester, (2E)- (E)-Ethyl 3-(2-furyl)-2-propenoate (E)-Ethyl 3-(2-furyl)acrylate
4542	Furfuryl formate Furfuryl alcohol, formate 2-Furfuryl formate
4543	<b>2-Methylbenzofuran</b> 2-Methylbenzo[b]furan
4544	5-Methylfurfuryl alcohol 5-Methyl-2-furanmethanol (5-Methyl-2-furyl)methanol 5-Methyl-2-furfuryl alcohol
4545	2-Methyl-3-furyl 2-methyl-3- tetrahydrofuryl disulfide
4546	Ethyl 2,5-dimethyl-3-oxo- 4(2H)-furyl carbonate
4547	Acai berry extract Assai palm Fats and glyceridic oils, Euterpe oleracea
4548	4-(2-Propenyl)phenyl-beta- D-glucopyranoside p-Allylphenyl-beta-D-glucopyranoside Chavicol-beta-D-glucoside
4549	N-(2-(Pyridin-2-yl)ethyl)-3- p-menthanecarboxamide 2-Isopropyl-5-methyl-N-[2-(pyridin- 2-yl)ethyl]cyclohexanecarboxamide
4550	(+/-)-N-Lactoyl tyramine 2-Hydroxy-N-[2-(4-hydroxyphenyl)- ethyl]-propanamide
4551	cis,cis-3,6-Nonadienyl acetate (Z,Z)-3,6-Nonadienyl acetate 3,6-Nonadien-1-ol, acetate, (3Z,6Z)-Acetic acid, (Z,Z)-3,6-nonadienyl ester

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4552	trans-2-Nonenyl acetate (E)-2-Nonenyl acetate 2-Nonen-1-ol, 1-acetate (2E)-
4553	cis-3-Nonenyl acetate (Z)-3-Nonenyl acetate 3-Nonen-1-ol, acetate, (3Z)-
4554	cis-6-Nonenyl acetate (Z)-6-Nonenyl acetate 6-Nonen-1-ol, acetate, (6Z)-
4555	Dihydrogalangal acetate 4-(Acetyloxy)-alpha- ethylbenzenemethanol acetate 1-[4-(Acetyloxy)phenyl]propyl acetate
4556	2,3,3-Trimethylindanone 2,3,3-Trimethyl-2,3-dihydro- 1 <i>H</i> -inden-1-one 2,3-Dihydro-2,3,3-trimethyl- 1 <i>H</i> -inden-1-one Safraleine
4557	N-Ethyl-2,2-diisopropylbutanamide N,2-diethyl-2-(isopropyl)- 3-methylbutyramide
4558	Cyclopropanecarboxylic acid (2-isopropyl- 5-methyl-cyclohexyl)-amide Cyclopropanecarboxylic acid (15,25,5R)- (2-isopropyl-5-methylcyclohexyl)-amide Cyclopropanecarboxylic acid (1R,2R,5S)- (2-isopropyl-5-methylcyclohexyl)-amide
4559	Magnolol 5,5'-Di(prop-2-en-1-yl)biphenyl-2,2'-diol 5,5'-Diallyl-2,2'-biphenyldiol 2,2'-Bichavicol Magnolia bark extract
4560	2-(Methylthio)ethyl acetate 2-(Methylsulfanyl)ethyl acetate 2-Acetoxyethyl methyl sulfide
4561	3-(Methylthio)propyl mercaptoacetate 3-(Methylsulfanyl)propyl sulfanylacetate Acetic acid, mercapto-,3- (methylthio)propyl ester
4562	Ethyl 2-hydroxyethyl sulfide Ethanol, 2-(ethylthio) - 2-(Ethylthio)-1-ethanol 2-Ethylmercaptoethanol Ethyl 2-hydroxyethyl thioether
4563	Ethyl 3-(methylthio)-cis-2-propenoate Ethyl 3-(methylthio)-(2Z)-propenoate 2-Propenoic acid, 3-(methylthio)-, ethyl ester, (2Z)-
4564	Ethyl 3-(methylthio)-trans-2-propenoate Ethyl 3-(methylthio)-(2E)-propenoate 2-Propenoic acid, 3-(methylthio)-, ethyl ester, (2E)-
4565	Ethyl 3-(methylthio)-2-propenoate Ethyl 3-(methylsulfanyl)-2-propenoate 2-Propenoic acid, 3-(methylthio)-, ethyl ester
4566	4-Methyl-2-(methylthiomethyl)-2-hexenal 4-Methyl-2-[(methylsulfanyl)- methyl]hex-2-enal
4567	5-Methyl-2-(methylthiomethyl)-2-hexenal 5-Methyl-2-[(methylsulfanyl)- methyl]hex-2-enal

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4568	4-Methyl-2-(methylthiomethyl)-2-pentenal 4-Methyl-2-[(methylsulfanyl)- methyl]pent-2-enal
4569	1-(3-(Methylthio)-butyryl)- 2,6,6-trimethyltyclohexene 3-(Methylthio)-1-(2,6,6-trimethyl- 1-cyclohexen-1-yl)-1-butanone
4570	2-0xothiolane Dihydro-2(3H)-thiophenone 4-Butyrothiolactone Thiacyclopentan-2-one Thiolan-2-one
4571	Butyl beta-(methylthio)acrylate Butyl 3-(methylsulfanyl)acrylate 2-Propenoic acid, 3-(methylthio)-, butyl ester
4572	Ethyl 3-(ethylthio)butyrate Ethyl 3-(ethylsulfanyl)butanoate Butanoic acid, 3-(ethylthio)-, ethyl ester
4573	Methyl octyl sulfide 1-(Methylthio)-octane 1-(Methylsulfanyl)octane 2-Thiadecane
4574	Methyl 1-propenyl sulfide 1-(Methylthio)-1-propene 1-(Methylsulfanyl)prop-1-ene Methyl propenyl sulfide
4575	Diisoamyl disulfide Bis(3-methylbutyl) disulfide 2,9-Dimethyl-5,6-dithiadecane Diisopentyl disulfide
4576	bis(2-Methylphenyl) disulfide 1,1'-Disulfanediyl bis(2-methylbenzene) Di-o-tolyl disulfide
4577	Mixture of butyl propyl disulfide and propyl and butyl disulfide
4578	Di-sec-butyl disulfide Bis(1-methylpropyl) disulfide 3,6-Dimethyl-4,5-dithiaoctane
4579	<b>Methyl 2-methylphenyl disulfide</b> Methyl <i>o</i> -tolyl disulfide
4580	<b>Diisoamyl trisulfide</b> Bis(3-methylbutyl)trisulfane Trisulfide, bis(3-methylbutyl)-
4581	Dodecanethiol 1-Dodecanethiol 1-Dodecyl mercaptan Lauryl mercaptan
4582	<b>2-Hydroxyethanethiol</b> 2-Mercaptoethyl alcohol beta-Mercaptoethanol
4583	4-Mercapto-4-methyl-2-hexanone 4-Methyl-4-sulfanylhexan-2-one
4584	3-Mercapto-3-methylbutyl isovalerate Butanoic acid, 3-methyl-, 3-mercapto-3-methylbutyl ester
4585	3-Mercaptohexanal

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4586	Methyl isobutanethioate S-Methyl 2-methylpropanethioate Propanethioic acid, 2-methyl-, S-methyl ester
4587	3-Mercaptopropionic acid 3-Mercaptopropanoic acid beta-Mercaptopropionic acid
4588	2-Ethylhexyl 3-mercaptopropionate Propanoic acid, 3-mercapto-, 2-ethylhexyl ester 2-Ethylhexyl 3-mercaptopropanoate 2-Ethylhexyl beta-mercaptopropionate 3-Mercaptopropionic acid 2-ethylhexyl ester
4589	Butanal dibenzyl thioacetal 1,1'-[Butane-1,1-diyl- bis(sulfanediylmethanediyl)]dibenzene Butyraldehyde, dibenzyl mercaptal
4590	Methional diethyl acetal 1,1-Diethoxy-3-(methylsulfanyl)propane Propane, 1,1-diethoxy-3-(methylthio)
4591	Ethyl linalyl ether Linalool ethyl ether 3-Ethoxy-3,7-dimethyl-1,6-octadiene 3,7-Dimethylocta-1,6-dien-3-yl ethyl ether
4592	Myrcenyl methyl ether 7-Methoxy-7-methyl-3- methylidene-oct-1-ene
4593	Linalool oxide pyranoid 6-Ethenyltetrahydro-2,2,6- trimethyl-2 <i>H</i> -pyran-3-ol 6-Ethenyl-2,2,6-trimethyltetrahydro- 2 <i>H</i> -pyran-3-ol 2,2,6-Trimethyl-6-vinyltetrahydro- 2 <i>H</i> -pyran-3-ol
4594	<b>2-Hydroxy-5-methylacetophenone</b> 1-(2-Hydroxy-5-methylphenyl)ethanone 2-Acetyl-4-methylphenol o-Acetyl-p-cresol
4595	2-Phenylpropanal propyleneglycol acetal 4-Methyl-2-(1-phenylethyl)-1,3-dioxolane
4596	Cinnamaldehyde propyleneglycol acetal 4-Methyl-2-(2-phenylethenyl)- 1,3-dioxolane 4-Methyl-2-styryl-1,3-dioxolane
4597	Ethyl alpha-acetylcinnamate Ethyl 2-benzylidene-3-oxobutanoate Butanoic acid, 3-oxo-2- (phenylmethylene)-, ethyl ester
4598	Ethyl 2-hydroxy-3-phenylpropionate Ethyl-2-hydroxy-3-phenylpropanoate Benzenepropanoic acid, alpha- hydroxy-, ethyl ester
4599	3-(3,4-Methylenedioxyphenyl)- 2-methylpropanal alpha-Methyl-3,4-(methylenedioxy) hydrocinnamaldehyde 2-Methyl-3-(3,4-methyenedioxyphenyl) propanal 2-Methyl-3-(3,4-methyenedioxyphenyl) propionaldehyde

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4600	Trehalose, dihydrate alpha-D-Glucopyranosyl-alpha- D-glucopyranoside, dihydrate 2-(Hydroxymethyl)-6-[3,4,5-trihydroxy-6-(hydroxymethyl))oxan-2-yl] oxyoxane-3,4,5-triol, dihydrate alpha,alpha-Trehalose alpha-D-Trehalose D-(+)-Trehalose D-Trehalose Mycose
4601	Rebaudioside A
4602	N-(2-Hydroxyethyl)-2,3-dimethyl- 2-isopropylbutanamide N-(2-Hydroxyethyl)-2,3-dimethyl- 2-(1-methylethyl) butanamide N-(2-Hydroxyethyl)-2-isopropyl- 2,3-dimethylbutanamide
4603	N-(1,1-dimethyl-2-hydroxyethyl)- 2,2-diethylbutanamide 2,2-Diethyl-N-(2-hydroxy-1,1- dimethylethyl) butanamide
4604	Dimenthyl glutarate Pentanedioic acid, bis[5-methyl-2- (1-methylethyl)cyclohexyl] ester Glutaric acid, di-(p-menth-3-yl) ester
4605	<b>trans-3-Nonen-1-ol</b> (E)-3-Nonen-1-ol
4606	4-Formyl-2-methoxyphenyl2- hydroxypropanoate Vanillyl lactate
4607	<b>Guaiacol butyrate</b> Butanoic acid, 2-methoxyphenyl ester Butyric acid, <i>o</i> -methoxyphenyl ester 2-Methoxyphenyl butyrate
4608	Guaiacol isobutyrate 2-Methoxyphenyl-2-methyl propanoate Propanoic acid, 2-methyl-, 2-methoxyphenyl ester
4609	Guaiacol propionate Propionic acid, o-methoxyphenyl propionate Phenol, o-methoxy-, propionate 2-Methoxyphenyl propionate
4610	Ethyl 5-hydroxyoctanoate
4611	Isopropylideneglyceryl 5-hydroxydecanoate 5-Hydroxydecanoic acid, glycerol acetone ketal ester Decanoic acid, 5-hydroxy-, (2,2-dimethyl- 1,3-dioxolan-4-yl)methyl ester
4612	<b>2-Ethyl-2-hexenal</b> 2-Ethylhexenal
4613	Ethyl 2-hexenoate 2-Hexenoic acid, ethyl ester
4614	Propyl sorbate trans,trans-2,4-Hexadienoic acid, propyl ester 2,4-Hexadienoic acid, propyl ester, (E,E)-
4615	<i>cis-</i> 2-0ctenol <i>cis-</i> 2-0cten-1-ol (Z)-2-0cten-1-ol
4616	<b>2-Hexylidenehexanal</b> 2-Butyl-2-octenal

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4617	trans-2-Tridecenol trans-2-Tridecen-1-ol (E)-2-Tridecen-1-ol
4618	<b>2-Phenoxyethyl propionate</b> 2-Phenoxyethyl propanoate
4619	Propyl 4-tert-butylphenylacetate
4620	<b>2-Phenoxyethanol</b> beta-Phenoxyethanol 1-Hydroxy-2-phenoxyethane Ethylene glycol monophenyl ether
4621	Phenyl butyrate Butanoic acid, phenyl ester Butyric acid, phenyl ester Phenyl butanoate
4622	Piperonal propyleneglycol acetal 4-(4-Methyl-1,3-dioxolan- 2-yl)-1,3-benzodioxole 4-Methyl-2-(3,4-methylenedioxyphenyl)- 1,3-dioxolane
4623	Benzyl levulinate Benzyl 4-oxopentanoate Pentanoic acid, 4-oxo-, phenylmethyl ester
4624	<b>4-Methylbenzyl alcohol</b> p-Methylbenzyl alcohol 4-(Hydroxymethyl)toluene p-Tolualcohol
4625	Phenylacetaldehyde diethyl acetal (2,2-Diethoxyethyl)benzene 1,1-Diethoxy-2-phenylethane Benzeneacetaldehyde, diethyl acetal
4626	<b>Benzyl nonanoate</b> Nonanoic acid, phenylmethyl ester Nonanoic acid, benzyl ester
4627	Anisaldehyde propyleneglycol acetal 2-(4-Methoxyphenyl)-4-methyl-1,3-dioxolane 2-(p-Methoxyphenyl)-4-methyl-1,3-dioxolane
4628	4-Methylbenzaldehyde propyleneglycol acetal 4-Methyl-2-(4-methylphenyl)- 1,3-dioxolane 4-Methyl-2-p-tolyl-1,3-dioxolane
4629	Phenylacetaldehyde propyleneglycol acetal 4-Methyl-2-(phenylmethyl)-1,3-dioxolane 2-Benzyl-4-methyl-1,3-dioxolane
4630	2-Ethylhexyl benzoate 2-Ethyl-1-hexanol benzoate Ethylhexyl benzoate Benzoic acid, 2-ethylhexyl ester 1-Hexanol, 2-ethyl-, benzoate
4631	2-Ethyl-3-methylthiopyrazine 2-(Ethyl-3-(methylsulfanyl)pyrazine 2-(Methylthio)-3-ethylpyrazine
4632	<b>2-Ethoxy-3-isopropylpyrazine</b> 2-Ethoxy-3-(1-methylethyl) pyrazine
4633	2-Ethoxy-3-ethylpyrazine
4634	Butyl beta-naphthyl ether 2-Butoxynaphthalene beta-Naphthol butyl ether

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4635	Isoamyl phenethyl ether Phenethyl isoamyl ether 2-Phenylethyl isoamyl ether [2-(3-Methylbutoxy)ethyl] benzene
4636	<b>2-Acetyl-4-isopropenylpyridine</b> [4-(1-Methylethenyl)-2- pyridinyl]ethanone
4637	4-Acetyl-2-isopropenylpyridine [2-(1-Methylethenyl)-4- pyridinyl]ethanone
4638	<b>2-Acetyl-4-isopropylpyridine</b> [4-(1-Methylethyl)-2-pyridinyl]ethanone
4639	2-Methoxypyridine
4640	6-Methoxyquinoline
4641	<b>2-Pentylthiazole</b> 2- <i>n</i> -Amylthiazole
4642	2-Thienylmethanol 2-Thiophenemethanol (Thiophen-2-yl)methanol 2-(Hydroxymethyl) thiophene
4643	<b>2-Acetyl-5-methylthiophene</b> (5-Methyl-2-thienyl) ethanone
4644	<b>4-Methyl-3-thiazoline</b> 4-Methyl-2,5-dihydrothiazole
4645	3,4-Dimethylthiophene
4646	1-(2-Thienyl)ethanethiol 2-(1-Mercaptoethyl)thiophene (Thiophen-2-yl)ethanethiol
4647	4,5-Dimethyl-2-isobutylthiazole 4,5-Dimethyl-2-(2-methylpropyl)thiazole 2-lsobutyl-4,5-dimethylthiazole
4648	Cyclotene butyrate 2-Methyl-5-oxopent-1-en-1-yl butanoate Butanoic acid, 2-methyl-5-oxo- 1-cyclopenten-1-yl ester Butyric acid, 2-methyl-5-oxo-1- cyclopenten-1-yl ester
4649	3-(Methylthio)propylamine 3-(Methylthio)-1-propanamine 1-Amino-3-(methylthio)propane 3-(Methylmercapto)propylamine 3-(Methylsulfanyl)propylamine 3-Aminopropyl methyl sulfide
4650	<b>4-Methyl-</b> <i>cis</i> <b>-2-pentene</b> <i>cis</i> <b>-</b> 1-lsopropylpropene 4-Methyl-(2Z)-pentene (Z)-4-Methyl-2-pentene
4651	1-Nonene alpha-Nonene
4652	1,3,5,7-Undecatetraene
4653	Ethyl alpha-ethyl-beta-methyl-beta-phenylglycidate Ethyl trans-2-ethyl-3-methyl-3- phenyloxirane-2-carboxylate Oxiranecarboxylic acid, 2-ethyl-3- methyl-3-phenyl-, ethyl ester, trans- Hydrocinnamic acid, alpha,beta-epoxy- alpha-ethyl-beta-methyl-, ethyl ester

FEMA No.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4654	Methyl beta-phenylglycidate Methyl-3-phenyloxirane-2-carboxylate (+/-)-Methyl 2,3-epoxycinnamate Glycidic acid, 3-phenyl-, methyl ester
4655	d-8-p-Menthene-1,2-epoxide D-1,2-Epoxylimonene D-Limonene 1,2-epoxide (4R)-1-Methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptane
4656	L-8.p-Menthene-1,2-epoxide L-1,2-Epoxylimonene L-Limonene 1,2-epoxide (45)-1-Methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptane
4657	<b>2,3-Epoxyoctanal</b> 3-Pentyl oxirane-2-carboxaldehyde
4658	<b>2,3-Epoxyheptanal</b> 3-Butyl oxirane-2-carboxaldehyde
4659	<b>2,3-Epoxydecanal</b> 3-Heptyl oxirane-2-carboxaldehyde
4660	Hydroxy(4-hydroxy-3- methoxyphenyl)acetic acid alpha-4-Dihydroxy-3- methoxybenzeneacetic acid (4-Hydroxy-3-methoxyphenyl) glycolic acid 3-Methoxy-4- hydroxyphenylhydroxyacetic acid (+/-)-Vanilmandelic acid (+/-)-4-Hydroxy-3-methoxymandelic acid
4661	4-Hydroxy-4-(3-hydroxy-1-butenyl)- 3,5,5-trimethyl-2-cyclohexen-1-one 4-(1-Hydroxy-4-keto-2,6,6-trimethyl- 2-cyclohexen-1-yl)-3-buten-2-ol
4662	(+/-)-2,6,10,10-Tetramethyl-1- oxaspiro[4.5]deca-2,6-dien-8-one (+/-)-8,9-Dehydrotheaspirone
4663	4-(2-Butenylidene)-3,5,5- trimethylcyclohex-2-en-1-one 4-(2-Buten-1-ylidene)-3,5,5- trimethyl-2-cyclohexen-1-one (4E)-4-[(2E/Z)-Butenylidene]-3,5,5- trimethylcyclohex-2-en-1-one Megastigmatrienone
4664	Digeranyl ether 1,1'-0xybis[3,7-dimethyl-(2E)-octadiene] Bis(3,7-dimethyl-2,6-octadienyl) ether
4665	1-(4-Hydroxy-3-methoxyphenyl) decan-3-one 1-(4-Hydroxy-3-methoxyphenyl)- 3-decanone Paradol [6]-Paradol
4666	alpha-Bisabolol alpha-(-)-Bisabolol (-)-alpha-Bisabolol (-)-(1'5,25)-alpha-Bisabolol (-)-(45,85)-alpha-Bisabolol 5-Hepten-2-ol, 6-methyl-2-(4-methyl-3-cyclohexen-1-yl), (-)- (2R)-6-Methyl-2-[(1R)-4-methylcyclohex-3-en-1-yl]hept-5-en-2-ol

	3,4-Dihydroxy- benzoic acid	3-Hydroxyben- zoic acidt	(+/-)-Acetal- dehyde ethyl isopropyl acetal	(+/-)-6-Methyl- octanal	5-Ethyl-2,3- dimethylpyr- azine	2-Hydroxy- 4-methoxy- benzaldehyde	3-(Methylthio) propyl hexanoate	Sodium lauryl sulfate	betα- Angelica- lactone	7-Decen-4-olide	9-Decen-5-olide	8-Decen-5-olide
Category	FEMA No. 4430	4431	4432	4433	4434	4435	4436	4437	4438	4439	4440	4441
Baked goods				0.1/0.3	3.1/6	10/100	1/5	0.001/0.01	0.4/2	0.3/3	50/250	1/10
Beverages (nonalcoholic)	300/500	300/500	20/30	0.1/0.3	1.9/2.5	5/50	1/5			0.3/3		0.3/3
Beverages (alcoholic)			20/30	0.1/0.3	0.3/1	20/50	2/10			0.5/5		
Breakfast cereal						10/100	1/5	0.001/0.01				
Cheese				0.1/0.3			1/10	0.001/0.01			5/25	1/10
Chewing gum	500/2,000	500/2,000		0.1/0.3		20/100	5/20	0.001/0.01		1/15	10/50	
Condiments/ relishes							1/10	0.001/0.01				
Confectionery frostings	300/500	300/500		0.1/0.3		10/50	1/5	0.001/0.01		0.3/3		
Egg products												
Fats/oils				0.1/0.5							20/100	2/10
Fish products				0.1/0.5								
Frozen dairy				0.1/0.3	1.7/3.6	10/50	1/5			0.1/1		0.2/1
Fruitices			20/30	0.1/0.3						0.1/1		
Gelatins/ puddings				0.1/0.3	1.1/2.3	10/50	1/5			1/3		
Granulated sugar				0.1/0.3								
Gravies								0.001/0.01				
Hard candy				0.1/0.3		20/100	2/5			1/10		
lmitation dairy								0.001/0.01		0.1/1		
Instant coffee/tea			20/30	0.1/0.3		10/25		0.001/0.01				
Jams/jellies				0.1/0.3						0.3/3		
Meat products					2/4		1/5		0.4/2			
Milk products				0.1/0.3		10/50			0.4/2	0.2/2	5/25	1/10
Nut products				0.1/0.2								
Other grains								0.001/0.01	0.4/2			
Poultry				0.1/0.3								
Processed fruits				0.1/0.3								
Processed vegetables				0.1/0.3			1/10		0.4/2			
Reconstituted vegetables				0.1/0.3			1/10					
Seasonings/ flavors						100/1,000	1/100	0.001/0.1	1.5/7.5			
Snack foods							2/10	0.001/0.01				1/10
Soft candy	300/500	300/500		0.1/0.3	2.9/6	10/50	2/5			0.2/2		
Soups							1/10	0.001/0.01	1/5			
Sugar substitutes								0.001/0.01				
Sweet sauces				0.1/0.3		10/50	1/5	0.001/0.01		0.3/3		

Baser Space   Secretary   Se		6-(5(6)- Decenoyloxy) decanoic acid	Ethyl 5-acetoxyocta- noate	Ethyl 5- hydroxydeca- noate	9-Dodecen- 5-olide	gαmmα- Octadeca- lactone	delta- Octadeca- lactone	9-Tetradecen- 5-olide	Orin lactone	Methyl 3-hydroxybu- tyrate	Methyl 3-acetoxy-2- methylbutyrate	Ethyl 2-acetylhexa- noate	Ethyl 3-hydroxyocta- noate
Secretaria   Sec	Category	4442	4443	4444	4445	4446	4447	4448	4449	4450	4451	4452	4453
Consideration   Consideratio	Baked goods				50/250	5/10	0.5/3	50/250				5/50	
Content		0.05/0.2	8/75	1/10			0.1/1		1/5	0.02/1	1/5	1/10	0.05/0.2
Content	Beverages (alcoholic)		8/75	1/10			0.1/1		2/10		0.5/2.5		0.0001/0.001
Chemistry   Chem													
Canadinariaty   Carlottering   Caryon   Caryon	Cheese	0.05/0.2			5/25	5/10		5/25					
Contesting   Con	Chewing gum		10/50	5/50	10/50		0.5/3	10/50	10/50				0.0001/0.001
Festing   Martin													
Fats/elis   0.02/0.1   0.02/0.1   0.02/0.1   0.02/0.0   0.02/0.1   0.02/0.5   0.02/0.1   0.02/0.5   0.02/0.1   0.02/0.5   0.02/0.1   0.02/0.5   0.02/0.1   0.02/0.5	Confectionery frostings	0.02/0.1	8/50										
Frozendating   0.0270.1   0.0500   0.0171   0.	Egg products												
Frest dairy   0.02/0.1   0.05/0.5   0.01/1   0	Fats/oils	0.02/0.1			20/100	5/10		20/100					
Freitices   8/50   8/50   1/5   1/	Fish products												
Gelatins/ puddings   8/50	Frozen dairy	0.02/0.1					0.1/1						
Craudited   Crau	Fruitices		8/50								1/5		
Sugar			8/50						2/10				0.2/2
Hard candy   0.02/1   8/70   5/50													
Instant coffee/tea	Gravies						0.1/3						
Instant coffee/tea	Hard candy	0.02/1	8/70	5/50					4/20	0.06/1	5/25	5/50	
Lams/jellies   8/70   2/10	Imitation dairy	0.02/1		0.05/0.5									
Meat products         0.02/1         0.05/0.5         5/25         5/10         0.1/3         5/25 </th <td></td>													
Milk products         0.02/1         0.05/0.5         5/25         5/10         0.1/3         5/25 </th <td>Jams/jellies</td> <td></td> <td>8/70</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>2/10</td> <td></td> <td></td>	Jams/jellies		8/70								2/10		
Nut products													
Other grains	Milk products	0.02/1		0.05/0.5	5/25	5/10	0.1/3	5/25					
Poultry Processed fruits Processed vegetables Reconstituted vegetables Seasonings/ flavors Snack foods Soft candy 0.02/1 8/100 5/50													
Processed fruits	-												
Processed vegetables	Processed												
Reconstituted vegetables	Processed												
Seasonings	Reconstituted												
Snack foods         5/10           Soft candy         0.02/1         8/100         5/50	Seasonings/												
Soft candy 0.02/1 8/100 5/50						5/10							
	Soft candy	0.02/1	8/100	5/50									
	Soups						0.1/1						
Sugar substitutes													
Sweetsauces	Sweet sauces												

	Methyl 3-acetoxyocta- noate	5- Oxooctanoic acid	5- Oxodecanoic acid	Ethyl 5-oxodecanoate	5-Oxododeca- noic acid	Ethyl 2-acetylocta- noate	2-0xo-3-ethyl- 4-butanolide	3-Isopropenyl- 6-oxoheptanoic acid	Hydroxyacetone	1-Hydroxy- 4-methyl-2- pentanone	Propyleneglycol diacetate	Propyleneglycol dipropionate
Category	4454	4455	4456	4457	4458	4459	4460	4461	4462	4463	4464	4465
Baked goods				4/8		5/50			0.002/1.5	1/5	4/9	3/7
Beverages (nonalcoholic)	1/5					4/10			2/10		1/1.5	10/50
Beverages (alcoholic)	0.5/2.5					0.5/10			4/20			
Breakfast cereal												
Cheese												
Chewing gum						50/500		0.1/0.5			10/250	50/250
Condiments/ relishes									0.001/0.8	1/5		
Confectionery frostings						1/5		0.05/0.25	0.002/1.5			
Egg products				2/4								
Fats/oils				20/50		5/50	10/20					10/50
Fish products												
Frozen dairy				4/6		0.5/5					1/2	10/50
Fruit ices	1/5					4/5					1/2	
Gelatins/ puddings						0.7/7			4/20			
Granulated sugar												
Gravies				2/4								
Hard candy	5/25			2/4		5/50		0.05/0.25	0.002/1.5		0.4/50	10/50
lmitation dairy		0.01/0.05	0.01/0.05	20/30	0.01/0.05							
Instant coffee/tea									10/50			
Jams/jellies	2/10								0.001/0.8			
Meat products												
Milk products		0.01/0.05	0.01/0.05	15/30	0.01/0.05	0.7/7						
Nut products												
Other grains												
Processed fruits												
Processed vegetables												
Reconstituted Vegetables												
Seasonings/ flavors									0.002/1.5	0.5/2.5		
Snack foods				2/4						0.5/2.5		
Soft candy						0.3/5		0.1/0.5	10/50			
Soups									0.0004/0.3			
Sugar substitutes												
Sweet sauces									0.001/0.8			

# GRAS FLAVORING SUBSTANCES 24

	Propylene- glycol dibutyrate	Propylene- glycol mono-2- methylbutyrate	Propylene- glycol di-2- methylbutyrate	Propylene- glycol mono- hexanoate	Propyleneglycol dihexanoate	Propyleneglycol dioctanoate	Dimethyl adipate	Dipropyl adipate	Diisopropyl adipate	Diisobutyl adipate	Dioctyl adipate	Ethyl acetoacetate ethylene glycol ketal
Category	4466	4467	4468	4469	4470	4471	4472	4473	4474	4475	4476	4477
Baked goods	5/12	20/50	5/15	20/50	20/50	3/7	5/10	556/600	200/400	5/10	20/40	1/20
Beverages (nonalcoholic)	1/2	1/10	1/2	1/10	1/10			0.1/2	0.1/2		0.1/2	
Beverages (alcoholic)	1/2	3/20	1/2	3/20	3/20	0.5/1						
Breakfast cereal												
Cheese		5/30		5/30	5/30		5/10			5/10		
Chewing gum	10/70	20/50	10/100	20/50	30/50	50/250						1/20
Condiments/ relishes												
Confectionery frostings												
Egg products												
Fats/oils						3/7	5/10			5/10		
Fish products	1/2											
Frozen dairy	1/2	3/20	1/2	3/20	3/20	0.5/1						
Fruitices	1/2	2/10	1/2	2/10	2/10	0.5/1						1/10
Gelatins/ puddings		2/10	1/2	2/10	2/10							0.5/5
Granulated sugar												
Gravies												
Hard candy	5/30	10/30	5/50	10/30	10/30	10/50						1/20
Imitation dairy												
Instant coffee/tea												
Jams/jellies												
Meat products  Milk products							5/10			5/10		
Nut products							3/10			3/10		
Other grains												
Poultry												
Processed fruits												
Processed vegetables												
Reconstituted vegetables												
Seasonings/ flavors												
Snack foods							5/10			5/10		
Soft candy	4/30	20/50	4/40	20/50	20/50							1/20
Soups												
Sugar substitutes												
Sweet sauces												

# GRAS FLAVORING SUBSTANCES 24

Category		glycol ketal	levulinate	Isoamyl Ievulinate	Dodecyl lactate	Hexadecyl lactate	Propyl pyruvate	Hydroxy- citronellal propylene- glycol acetal	Citral glyceryl acetal	Mushroom oil, distilled	Propylene- glycol monobutyrate	cis-3- Hexenyl acetoacetate
		4.170	4400		4400	4405		4405	4400			
	4478	4479	4480	4481	4482	4483	4484	4485	4486	4487	4488	4489
Baked goods	3/10	10/200	5/10	0.01/0.1	50/250	2/50	1/5	0.1/1			20/50	15/160
Beverages (nonalcoholic)	0.01/0.1	1/10	1/3	1/10		0.1/1		0.1/1	50/250		1/10	8/80
Beverages (alcoholic)	0.3/3		5/10	0.1/0.7				0.1/3	100/500		3/20	5/50
Breakfast cereal												
Cheese	3/10						1/5				5/30	
Chewing gum		100/500		0.2/2		20/250		0.5/5	200/1,000		20/50	
Condiments/ relishes										2/10		
Confectionery frostings												
Egg products										2/10		
Fats/oils	3/10	10/50			2/50	2/50	1/5					
Fish products												
Frozen dairy	0.05/5	5/50	5/10		0.2/3	0.2/2		0.2/2			3/20	8/80
Fruit ices	0.6/6			0.2/2		0.2/2					2/10	
Gelatins/ puddings		2/20	5/10	0.2/1.5				0.1/1	50/500		2/10	8/80
Granulated sugar												
Gravies										4/20		
Hard candy	0.1/50	10/100			1/20			0.1/3	50/250		10/30	
Imitation dairy												
Instant coffee/tea												
Jams/jellies												
Meat products										2/10		
Milk products	3/10						1/5					
Nut products										2/10		
Other grains												
Poultry										2/10		
Processed fruits												
Processed vegetables										2/10		
Reconstituted vegetables												
Seasonings/ flavors										100/1,000		
Snack foods	3/10						1/5			4/20		10/100
Soft candy		10/50	3/10					0.1/2			20/50	
Soups										4/20		
Sugar substitutes												
Sweet sauces												

	2-Methoxy-6- (2-propenyl)- phenol	Myricitrin	(R)-(-)-1-Octen- 3-ol	<i>cis</i> -3-Hexenoic acid	Ammonia (also includes ammonium chloride)	Naringin dihydrochalcone	N-p-Benzene- acetonitrile- menthane carboxamide	Cubebol	6-Methyl- heptanal	(+/-)-cis- and trans-2-Pentyl- 4-propyl-1,3- oxathiane	Choline chloride (also includes choline)	3-[(2-Methyl- 3-furyl)thio] butanal
Category	4490	4491	4492	4493	4494	4495	4496	4497	4498	4499	4500	4501
Baked goods	0.2/1	10/30	4/11	7/16				1/30	0.1/0.3		2,500/4,000	0.05/0.1
Beverages (nonalcoholic)		10/30	1/1	2/4		50/60	1/5	1/30	0.1/0.3	0.5/3		0.002/0.005
Beverages (alcoholic)		10/30	0.5/1	2/4		50/60		1/30	0.1/0.3	0.5/3		0.005/0.01
Breakfast cereal	0.2/1					150/200		1/30			300/600	0.005/0.01
Cheese	0.5/2.5								0.1/0.3			
Chewing gum	1/5	100/150	0.02/0.02			200/200	200/800	1/30	0.1/0.3	1/5		0.05/0.1
Condiments/ relishes	0.3/1.5		2/5									0.005/0.01
Confectionery frostings	0.2/1	10/30			500/1,500			1/30	0.1/0.3	0.5/3		0.005/0.01
Egg products					1,000/3,000							0.005/0.01
Fats/oils	0.2/1	10/30							0.1/0.5			0.05/0.1
Fish products	0.2/1				1,000/3,000				0.1/0.5		600/1,200	0.05/0.1
Frozen dairy	0.5/2.5	10/30	1/1	4/8		50/60		1/20	0.1/0.3	0.5/3		0.005/0.01
Fruitices	0.5/2.5	10/30				50/60			0.1/0.3	0.5/3		0.001/0.003
Gelatins/ puddings		10/30	1/2	2/5		50/60			0.1/0.3	0.5/3		
Granulated sugar								1/20	0.1/0.3			
Gravies	0.3/1.5		2/3								600/1,200	
Hard candy	1/5	10/30			1,000/3,000	50/60	150/250	1/20	0.1/0.3	1/5		0.001/0.002
lmitation dairy						50/60						0.001/0.002
Instant coffee/tea								1/20	0.1/0.3			0.001/0.002
Jams/jellies						50/60		1/10	0.1/0.3	0.5/3		0.001/0.002
Meat products	0.2/1		4/5		1,000/3,000						600/1,200	0.05/0.2
Milk products	0.5/2.5	10/30			1,000/3,000	50/60		1/10	0.1/0.3			0.005/0.01
Nut products								1/10	0.1/0.2			0.001/0.003
Other grains	0.2/1											0.001/0.002
Poultry	0.2/1								0.1/0.3		600/1,200	0.05/0.1
Processed fruits	0.4/2					50/60			0.1/0.3			0.001/0.003
Processed vegetables	0.4/2		12/20			50/60			0.1/0.3			0.001/0.003
Reconstituted vegetables	0.4/2								0.1/0.3			0.001/0.003
Seasonings/ flavors	0.3/1.5				1,000/3,000							5/20
Snack foods	2/10	10/30	0.5/0.5								2,500/4,000	0.001/0.003
Soft candy	1/5	10/30	1/2	7/15		50/60		1/30	0.1/0.3	1/5		0.002/0.005
Soups	0.3/1.5		3/5								600/1,200	0.05/0.1
Sugar substitutes								1/30				
Sweet sauces						50/60		1/30	0.1/0.3			0.02/0.05

# GRAS FLAVORING SUBSTANCES 24

	(-)-Sclareol	(+)-Cedrol	d-Limonen-10-ol	(2,4)- and (3,5)- and (3,6)-Dimethyl- 3-cyclohexenyl- carbaldehyde	1,3-p- Mentha- dien-7-al	p-Menthan-7-ol	p-Menth-1- en-9-ol	Menthyl formate	Menthyl propionate	Cyclotene propionate	3,3,5- Trimethylcy- clohexyl acetate	dl-Camphor
Category	4502	4503	4504	4505	4506	4507	4508	4509	4510	4511	4512	4513
Baked goods	10/50	10/50		0.2/4						1/3		1/10
Beverages (nonalcoholic)	5/25	5/25	0.005/0.05	0.5/5	0.1/0.5	0.5/2.5	0.1/0.5	1/5	1/5		0.2/1	0.01/0.2
Beverages (alcoholic)	5/25	5/25			0.2/1		0.2/1	1/5	1/5		0.2/1	
Breakfast cereal	5/25	5/25										
Cheese	7/35	7/35										
Chewing gum				5/50	1/5		1/5	20/500	5/25		5/25	20/100
Condiments/ relishes	20/100	20/100				1/5						
Confectionery frostings	10/50	10/50										
Egg products												
Fats/oils	5/25	5/25		0.5/4								1/10
Fish products	2/10	2/10										
Frozen dairy	7/35	7/35		0.5/10								
Fruitices	10/50	10/50		0.5/10								0.02/2
Gelatins/ puddings	10/50	10/50	0.02/1		0.2/1		0.2/1			2/3		
Granulated sugar												
Gravies	5/25	5/25										
Hard candy	10/50	10/50	0.1/5	0.2/5	0.5/2.5	1/5	0.5/2.5	10/50	5/25	10/20	5/25	5/50
lmitation dairy	7/35	7/35										
Instant coffee/tea	5/25	5/25								0.1/0.3		
Jams/jellies	7/35	7/35								1/3		
Meat products	2/10	2/10										
Milk products	7/35	7/35										
Nut products	5/25	5/25										
Other grains	5/25	5/25										
Poultry	2/10	2/10										
Processed fruits	7/35	7/35										
Processed vegetables	7/35	7/35										
Reconstituted vegetables	7/35	7/35										
Seasonings/ flavors	5/25	5/25							0.5/10			
Snack foods	10/50	10/50								1/3		
Soft candy	10/50	10/50						10/50	5/25	1/3	5/25	
Soups	5/25	5/25							3/20			
Sugar substitutes												
Sweet sauces	5/25	5/25										

# GRAS FLAVORING SUBSTANCES 24

	2-Cyclopen- tylcyclo- pentanone	Carvyl palmitate	Cyclohexanone diethyl acetal	2-Cyclohexe- none	8,9- Dehydrothea- spirone	<i>I</i> -Fenchone	Ethylenedia- minetetraacetic acid disodium salt	2,2,6,7- Tetramethyl- bicyclo[4.3.0]- nona-4,9(1)- dien-8-ol	2,2,6,7-Tetra- methyl- bicyclo[4.3.0]- nona-4,9(1)- dien-8-one	6-Hydroxy- carvone	<i>I</i> -Menthyl butyrate	Pinocarbyl isobutyrate
Category	4514	4515	4516	4517	4518	4519	4520	4521	4522	4523	4524	4525
Baked goods	15/100		5/30									
Beverages (nonalcoholic)	1/10				5/25	0.01/0.1		1/5	1/5		1/5	0.5/5
Beverages (alcoholic)	1/10				10/50			2/10	2/10		1/5	0.5/5
Breakfast cereal			0.5/3									
Cheese										0.1/0.5		
Chewing gum		0.1/0.5			50/250	0.1/5		10/50	10/50		10/50	45/100
Condiments/ relishes										0.05/0.25		
Confectionery frostings		0.05/0.25										
Egg products												
Fats/oils				5/25								
Fish products												
Frozen dairy	2/20		0.5/2		20/100							
Fruit ices	2/20											
Gelatins/ puddings	3/30											
Granulated sugar												
Gravies												
Hard candy	5/50	0.05/0.25	0.5/2			0.05/0.5				0.05/0.25	5/25	15/50
Imitation dairy												
Instant coffee/tea												
Jams/jellies								5/25	5/25			
Meat products				1/5								
Milk products	3/30				20/100			2/10	2/10			
Nut products												
Other grains												
Poultry Processed fruits												
Processed vegetables												
Reconstituted vegetables												
Seasonings/ flavors				10/50			100/120					
Snack foods			2/30	1/5								
Soft candy	5/50	0.1/0.5	0.1/1							0.1/0.5	5/25	15/50
Soups				1/5								
Sugar substitutes												
Sweet sauces	3/30											

	2-Pentenyl- 4-propyl-1,3- oxathiane	Acetaldehyde di-isobutyl- acetal	Acetaldehyde ethyl isobutyl- acetal	4-(2,2,3- Trimethyl- cyclopentyl) butanoic acid	Perillaldehyde propylene- glycol acetal	2,6,6-Trimethyl- 2-hydroxy- cyclohexanone	Acetoin propylene glycol acetal	4,5-Octane- dione	Ethyl maltol isobutyrate	2-Tetrahydro- furfuryl 2-mercapto- propionate	Nerolidol oxide	Furfural propylene- glycol acetal
Category	4526	4527	4528	4529	4530	4531	4532	4533	4534	4535	4536	4537
Baked goods							1/10	0.01/1	5/50			5/10
Beverages (nonalcoholic)	0.5/3	25/30	20/30	10/30	0.01/2	0.01/0.1					5/25	5/10
Beverages (alcoholic)	0.5/3	25/30	20/30								10/50	
Breakfast cereal												
Cheese												
Chewing gum	1/5										50/250	5/250
Condiments/ relishes					0.01/2					0.02/0.2		
Confectionery frostings	0.5/3			10/40		0.01/0.1	1/5					
Egg products												
Fats/oils								0.01/1	5/50			5/10
Fish products												0.1/1
Frozen dairy	0.5/3										20/100	5/10
Fruitices	0.5/3	25/30	20/30									5/10
Gelatins/ puddings	0.5/3							0.01/1		1/10		
Granulated sugar												
Gravies												
Hard candy	1/5							0.01/1	5/50			5/10
Imitation dairy												
Instant coffee/tea		25/30	20/30	10/30		1/5	5/10					
Jams/jellies	0.5/3										10/50	
Meat products												
Milk products				10/30			1/10					
Nut products												
Other grains												
Poultry												
Processed fruits												
Processed vegetables												
Reconstituted vegetables												
Seasonings/ flavors					0.01/2					0.02/0.2		
Snack foods					0.01/2			0.01/1	5/50	0.02/0.2		
Soft candy	1/5											2/10
Soups										1/10		
Sugar substitutes				10/40								
Sweet sauces												

	Methyl 3-(furfurylthio) propionate	Furfuryl decanoate	Di-2- furylmethane	(E)-Ethyl 3-(2- furyl)acrylate	Furfuryl formate	2-Methylbenz- ofuran	5-Methyl- furfuryl alcohol	2-Methyl-3- furyl 2-methyl- 3-tetrahydro- furyl disulfide	Ethyl 2,5-dimethyl-3- oxo-4(2 <i>H</i> )-furyl carbonate	Acai berry extract	4-(2-Propenyl)- phenyl- <i>beta-D</i> - glucopyranoside	N-(2-(Pyridin- 2-yl)ethyl)-3- p-menthanecar- boxamide
Category	4538	4539	4540	4541	4542	4543	4544	4545	4546	4547	4548	4549
Baked goods		1/10		0.4/2							200/500	
Beverages (nonalcoholic)									1/5	10/50	100/800	1/5
Beverages (alcoholic)										10/50	200/800	
Breakfast cereal										10/50	150/600	
Cheese											200/600	
Chewing gum						0.1/0.5					200/1,000	100/300
Condiments/ relishes												
Confectionery frostings	0.1/1									5/30	100/500	
Egg products												
Fats/oils											100/500	
Fish products											100/500	
Frozen dairy							0.01/0.1			20/100	100/500	
Fruit ices	0.1/1						0.02/0.1		1/5			
Gelatins/ puddings					0.01/0.1					20/100	100/500	
Granulated sugar												
Gravies											100/500	
Hard candy					0.1/1	0.05/0.25				10/50	100/800	80/150
lmitation dairy											100/600	
Instant coffee/tea			0.03/0.1		0.02/0.1						100/400	
Jams/jellies				0.2/1		0.1/0.5					100/800	
Meat products								0.01/0.05			100/600	
Milk products											100/400	
Nut products												
Other grains												
Poultry												
Processed fruits												
Processed vegetables												
Reconstituted vegetables												
Seasonings/ flavors										500/2,000	200/1,000	
Snack foods	0.1/1						0.01/0.05	0.05/0.1		10/50	200/800	
Soft candy												
Soups			0.2/1					0.1/0.5			100/600	
Sugar substitutes				0.2/1		0.1/0.5						
Sweet sauces				0.1/0.5		0.05/0.25					100/800	

	(+/-)-N-Lactoyl tyramine	<i>cis,cis-</i> 3,6- Nonadienyl acetate	trans-2-Nonenyl acetate	<i>cis</i> -3-Nonenyl acetate	<i>cis</i> -6-Nonenyl acetate	Dihydrogalangal acetate	2,3,3- Trimethylindan- 1-one	N-Ethyl-2,2- diisopropyl- butanamide	Cyclopropanecar- boxylic acid (2-isopropyl- 5-methyl- cyclohexyl)- amide	Magnolol	2-(Methylthio)- ethyl acetate	3-(Methylthio)- propyl mercapto- acetate
Category	4550	4551	4552	4553	4554	4555	4556	4557	4558	4559	4560	4561
Baked goods		0/0.1	0/0.1	0/0.1	1/5		0.005/0.03					1/5
Beverages (nonalcoholic)		0/0.1	0/0.1	0/0.1	1/5	0.5/5	0.01/0.03				1/5	1/10
Beverages (alcoholic)		0/0.1	0/0.1	0/0.1	2/10	25/100						
Breakfast cereal		0/0.1	0/0.1	0/0.1	1/5							
Cheese					1/10				2/6			
Chewing gum		0/0.1	0/0.1	0/0.1	5/20	500/1,000	0.005/0.02	3,000/6,000		2,000/2,000		
Condiments/ relishes	100/300				1/10	50/500	0.01/0.1		4/10			
Confectionery frostings		0/0.1	0/0.1	0/0.1	1/5	25/500	0.03/0.05	1,000/1,500				
Egg products									4/10			
Fats/oils	100/300	0/0.1	0/0.1	0/0.1	0/0.1				2/8			
Fish products						100/500			2/8		0.01/0.2	
Frozen dairy		0/0.1	0/0.1	0/0.1	1/5		0.005/0.02					
Fruit ices		0/0.1	0/0.1	0/0.1	0/0.1		0.01/0.02				2/10	
Gelatins/ puddings		0/0.1	0/0.1	0/0.1	1/5						2/10	
Granulated sugar												
Gravies	100/300	0/0.1							4/10			
Hard candy		0/0.1	0/0.1	0/0.1	2/5	12/500	0.005/0.01	1,000/1,500		2,000/2,000		
Imitation dairy												
Instant coffee/tea												1/10
Jams/jellies		0/0.1	0/0.1	0/0.1	0/0.1		0.03/0.05					
Meat products		0/0.1	0/0.1	0/0.1	1/5	100/500	0.3/5		2/8		0.01/0.2	
Milk products		0/0.1	0/0.1	0/0.1	0/0.1							1/10
Nut products												
Other grains						100/500			2/8			
Processed fruits						100/500			2/8			
Processed vegetables					1/10				2/8			
Reconstituted Vegetables					1/10							
Seasonings/ flavors		2/10	2/10	2/10	2/100	500/1,000			10/20			
Snack foods	100/300				2/10	100/500			8/20			
Soft candy		0/0.1		0/0.1	2/5			1,000/1,500				
Soups	100/300				1/10	50/500	0.005/0.02		4/10		0.05/0.1	
Sugar substitutes						0.1/5						
Sweet sauces					1/5		0.03/0.05					

	Ethyl 2-hydroxy- ethyl sulfide	Ethyl 3-(methylthio)- cis-2-propenoate	Ethyl 3-(methylthio)- trans-2- propenoate	Ethyl 3-(methylthio)- 2-propenoate	4-Methyl-2- (methylthio- methyl)-2- hexenal	5-Methyl-2- (methylthio- methyl)-2- hexenal	4-Methyl-2- (methylthio- methyl)-2- pentenal	1-(3- (Methylthio)- butyryl)-2,6,6- trimethylcy- clohexene	2-Oxothiolane	Butyl <i>beta-</i> (methylthio)- acrylate	Ethyl 3-(ethylthio)- butyrate	Methyl octyl sulfide
Category	4562	4563	4564	4565	4566	4567	4568	4569	4570	4571	4572	4573
Baked goods									0.002/0.02		0.3/1	1/6
Beverages (nonalcoholic)	0.01/0.05	1/5	1/5	1/5					0.0003/0.003	0.001/0.003		0.2/2
Beverages (alcoholic)												0.2/2
Breakfast cereal												
Cheese												
Chewing gum									0.02/0.2		0.03/0.1	
Condiments/ relishes	0.05/0.3				0.05/0.5							0.1/5
Confectionery frostings		0.01/0.5	0.01/0.5	0.01/0.5				0.001/0.01		0.001/0.005		
Egg products												
Fats/oils									0.02/0.2			0.5/1.5
Fish products												1/5
Frozen dairy							0.001/0.005		0.0006/0.006			0.2/2
Fruitices		2/10	2/10	2/10				0.005/0.01			0.003/0.01	
Gelatins/ puddings		2/10	2/10	2/10				0.001/0.005		0.001/0.005		0.1/1
Granulated sugar												
Gravies												0.1/1
Hard candy	0.05/0.3								0.002/0.02			
Imitation dairy												0.01/0.1
Instant coffee/tea												
Jams/jellies												
Meat products												4/40
Milk products												
Nut products												
Other grains												1/5
Poultry Processed fruits												
Processed vegetables												1/5
Reconstituted vegetables												
Seasonings/ flavors	0.05/0.3					0.1/0.5						1/80
Snack foods	0.05/0.3				0.05/0.5	0.1/0.5						
Soft candy												0.2/2
Soups												1/80
Sugar substitutes												
Sweet sauces												

	Methyl 1-propenyl sulfide	Diisoamyl disulfide	bis(2- Methylphenyl) disulfide	Mixture of butyl propyl disulfide and propyl and butyl disulfide	Di-sec-butyl disulfide	Methyl 2-methylphenyl disulfide	Diisoamyl trisulfide	Dodecanethiol	2-Hydroxy- Ethanethiol	4-Mercapto- 4-methyl-2- hexanone	3-Mercapto- 3-methylbutyl isovalerate	3-Mercapto- hexanal
Category	4574	4575	4576	4577	4578	4579	4580	4581	4582	4583	4584	4585
Baked goods			0.1/10								0.1/5	
Beverages (nonalcoholic)								0.001/0.005	2/10		0.00001/5	0.01/0.05
Beverages (alcoholic)								0.001/0.005	2/10			0.01/0.05
Breakfast cereal			0.01/10								0.02/5	
Cheese		0.001/0.01					0.01/0.05					
Chewing gum								0.005/0.02				
Condiments/ relishes						0.001/0.01					0.0001/0.1	
Confectionery frostings			0.01/10									
Egg products												
Fats/oils					0.1/0.5							
Fish products		0.002/0.02										
Frozen dairy			0.01/10									
Fruitices											0.1/5	
Gelatins/ puddings			0.1/10									
Granulated sugar												
Gravies												
Hard candy								0.005/0.02	5/20		0.1/5	0.02/0.1
lmitation dairy												
Instant coffee/tea										0.001/0.005		
Jams/jellies				0.001/0.01								
Meat products					0.5/2.5		0.01/0.05					
Milk products	0.001/0.01										0.1/5	
Nut products											0.0001/0.001	
Other grains  Poultry											0.0001/0.001	
Processed fruits												
Processed vegetables												
Reconstituted vegetables												
Seasonings/ flavors			0.01/10		0.2/1							
Snack foods	0.05/0.1		0.01/10	0.001/0.01	0.1/0.5		0.001/0.01					
Soft candy												
Soups	0.01/0.1	0.05/0.5		0.001/0.01	0.1/0.5	0.001/0.01	0.01/0.05				0.1/5	
Sugar substitutes												
Sweet sauces			0.01/10								0.1/5	

# GRAS FLAVORING SUBSTANCES 24

	Methyl isobutene- thioate	3-Mercapto- propionic acid	2-Ethylhexyl 3-mercapto- propionate	Butanal dibenzyl thioacetal	Methional diethyl acetal	Ethyl linalyl ether	Myrcenyl methyl ether	Linalool oxide pyranoid	2-Hydroxy- 5-methyl- acetophenone	2-Phenyl- propanal propylene- glycol acetal	Cinnamaldehyde propylene- glycol acetal	Ethyl alpha- acetyl cinnamate
Category	4586	4587	4588	4589	4590	4591	4592	4593	4594	4595	4596	4597
Baked goods		0.001/5	0.2/2	0.5/10	0.02/0.1			1/10	0.1/0.5		5/30	
Beverages (nonalcoholic)	0.1/0.5					0.0002/0.001	0.1/0.5	2/20		0.01/0.05		0.1/0.5
Beverages (alcoholic)	0.1/0.5						0.2/1	2/20				
Breakfast cereal												
Cheese		0.001/5							0.05/0.3			
Chewing gum	0.2/2							5/50				0.8/2
Condiments/ relishes										0.1/1		
Confectionery frostings				0.5/10						0.01/0.05		0.03/0.1
Egg products												
Fats/Oils		0.001/5	2/10									
Fish products												
Frozen dairy		0.001/0.005						0.7/7	0.05/0.3			
Fruitices	0.03/0.5				0.02/0.08							
Gelatins/ puddings							0.2/1	2/10			1/10	
Granulated sugar												
Gravies												
Hard candy	0.2/1	0.001/0.005				0.002/0.01	0.5/2.5	20/100				
lmitation dairy									0.1/0.5	0.1/1		
Instant coffee/tea								2/10				
Jams/jellies											1/10	
Meat products												
Milk products									0.05/0.3			
Nut products												
Other grains												
Processed Control of the Processed							0.5/2.5					
Processed vegetables												
Reconstituted vegetables												
Seasonings/ flavors												
Snack foods	0.03/0.5	0.001/5	0.2/2							0.1/0.5		
Soft candy	2.03, 0.3	3.552,73	0.2, 2					2/20		0.1/0.5		
Soups				0.1/1	0.03/0.1						5/20	
Sugar substitutes												
Sweet sauces												
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	Ethyl 2-hydroxy- 3-phenylpro- pionate	3-(3,4- Methylene- dioxyphenyl)- 2-methyl- propanal	Trehalose, dihydrate <sup>1</sup>	Rebaudioside A	N-(2- Hydroxyethyl)- 2,3-dimethyl-2- isopropylbutan- amide	N-(1,1- Dimethyl-2- hydroxyethyl)- 2,2-diethylbu- tanamide	Dimenthyl glutarate	trans-3- Nonen-1-ol	4-Formyl-2- methoxyphenyl 2-hydroxypro- panoate	Guaiacol butyrate	Guaiacol isobutyrate	Guaiacol propionate
Category	4598	4599	4600	4601	4602	4603	4604	4605	4606	4607	4608	4609
Baked goods		2/4	20,000/50,000					0.4/0.6	10/20	0.2/5	0.2/5	0.2/5
Beverages (nonalcoholic)		10/50	20,000/35,000	20/30			20/50	0.2/0.4	5/10	0.1/5	0.1/5	0.1/5
Beverages (alcoholic)			1,000/10,000	20/30			20/60	0.6/10	10/20	0.2/5	0.2/5	0.2/5
Breakfast cereal			15,000/30,000	20/30				0.4/1	10/20	0.2/5	0.2/5	0.2/5
Cheese			3,000/50,000									
Chewing gum		100/500	20,000/35,000	200/200	5,000/10,000	3,000/6,000	600/1,600	1/2	5/10			
Condiments/ relishes	0.7/2		20,000/50,000									
Confectionery frostings		10/100	20,000/50,000		1,800/3,000	1,000/1,500	80/240	0.4/0.6	10/20	0.2/5	0.2/5	0.2/5
Egg products			15,000/40,000									
Fats/oils			15,000/40,000					1/2				
Fish products			15,000/50,000									
Frozen dairy			15,000/50,000	20/30				0.2/0.4	10/100	0.1/5	0.1/5	0.1/5
Fruit ices			10,000/50,000	20/30				0.2/0.4	10/20	0.1/5	0.1/5	0.1/5
Gelatins/ puddings	0.01/0.1	10/50	50,000/50,000	20/30				0.2/0.4	10/50	0.2/5	0.2/5	0.2/5
Granulated sugar												
Gravies			20,000/50,000					0.4/0.6				
Hard candy		1/4	50,000/50,000	20/30	1,800/3,000	1,000/1,500	120/280	0.4/0.6		0.2/5	0.2/5	0.2/5
Imitation dairy			20,000/50,000	20/30						0.2/5	0.2/5	0.2/5
Instant coffee/tea			10,000/30,000	20/30				0.2/0.4		0.4/10	0.4/10	0.4/10
Jams/jellies			50,000/50,000									
Meat products			15,000/50,000									
Milk products			20,000/50,000	20/30				0.4/0.8	10/50			
Nut products			20,000/50,000							0.3/10	0.3/10	0.3/10
Other grains			15,000/30,000									
Poultry			15,000/50,000									
Processed fruits			10,000/30,000	20/30								
Processed vegetables			35,000/50,000	20/30								
Reconstituted vegetables			15,000/30,000									
Seasonings/ flavors			20,000/50,000					20/30				
Snack foods			20,000/50,000				16/32	0.4/0.6				
Soft candy		1/3	50,000/50,000	20/30	1,800/3,000	1,000/1,500	100/240	0.4/0.6		0.2/5	0.2/5	0.2/5
Soups			20,000/50,000					0.4/0.6				
Sugar substitutes										0.1/5	0.1/5	0.1/5
Sweet sauces		1/2	50,000/50,000	20/30				0.4/0.6	10/20			

	Ethyl 5-hydroxy- octanoate	lsopropyl- ideneglyceryl 5-hydroxy- decanoate	2-Ethyl-2- hexenal	Ethyl 2-hexenoate	Propyl sorbate	cis-2-Octenol	2-Hexyli- denehexanal	trans-2- Tridecenol	2-Phenoxyethyl propionate	Propyl 4- <i>tert</i> - butylphenyl- acetate	2-Phenoxy- ethanol	Phenyl butyrate
Category	4610	4611	4612	4613	4614	4615	4616	4617	4618	4619	4620	4621
Baked goods		4/8	0.003/0.005	0.5/3				0.05/5	0.2/5	5/50	4/8	
Beverages (nonalcoholic)	3/40		0.001/0.005		1/5				0.05/0.5		0.5/2	0.1/1
Beverages (alcoholic)	3/40								0.1/1		1/3	
Breakfast cereal												
Cheese										5/50		
Chewing gum	6/60		0.03/0.08		20/100							
Condiments/ relishes												
Confectionery frostings	5/60											
Egg products		2/4										
Fats/oils		20/50		0.5/3				0.05/5		5/50		
Fish products												
Frozen dairy		4/6							0.1/2		2/5	
Fruit ices	5/50								0.05/1		1/2	0.2/2
Gelatins/ puddings	5/40										1/3	0.2/2
Granulated sugar												
Gravies		2/4										
Hard candy	5/50	2/4			5/25			0.05/2	0.2/5	5/50	1/5	
Imitation dairy		20/30										
Instant coffee/tea			0.002/0.01									
Jams/jellies	6/50											
Meat products							0.002/0.01					
Milk products		15/30										
Nut products												
Other grains												
Poultry												
Processed fruits												
Processed vegetables												
Reconstituted Vegetables												
Seasonings/ flavors												
Snack foods		2/4		0.5/3			0.05/0.1	0.05/5		5/50		
Soft candy	7/100								0.2/5		1/5	
Soups						0.1/0.5	0.1/0.5					
Sugar substitutes												
Sweet sauces		<u> </u>					· ·	<u> </u>				

	Piperonal propyleneglycol acetal	Benzyl levulinate	4-Methylbenzyl alcohol	Phenylacet- aldehyde diethyl acetal	Benzyl nonanoate	Anisaldehyde propylene- glycol acetal	4-Methylbenzal- dehyde propyleneglycol acetal	Phenylacetal- dehyde propylene- glycol acetal	2-Ethylhexyl benzoate	2-Ethyl-3- methyl thiopyrazine	2-Ethoxy-3- isopropylpyr- azine	2-Ethoxy-3- ethylpyrazine
Category	4622	4623	4624	4625	4626	4627	4628	4629	4630	4631	4632	4633
Baked goods	2/10	3/50		0.1/1	0.1/5		1/2	0.1/5		0.005/0.1	0.0001/0.0005	0.02/0.1
Beverages (nonalcoholic)	1/8	0.3/5	0.01/0.1		0.1/5	0.2/5		0.01/1	0.01/0.1	0.001/0.01	0.00001/0.00005	
Beverages (alcoholic)		0.1/1	0.02/0.5									
Breakfast cereal												
Cheese												
Chewing gum	1/9	15/250								0.1/1		
Condiments/ relishes								0.2/2		0.02/0.1		
Confectionery frostings	0.02/0.1											
Egg products												
Fats/oils	0.1/1	1.5/50		0.1/1			1/2			0.005/0.1		
Fish products												
Frozen dairy		1/10			1/5	1/10			0.01/0.2	0.04/0.2		
Fruit ices	2.5/10	0.6/6	0.01/0.5									
Gelatins/ puddings	2/8	1/20			0.5/5				0.02/0.5			
Granulated sugar												
Gravies		1/20										0.01/0.1
Hard candy	1/8	1.5/50			0.1/5	1/20		0.05/1		0.005/0.1	0.003/0.02	
lmitation dairy	2/7											
Instant coffee/tea	2.5/10											
Jams/jellies												0.01/0.1
Meat products										0.04/0.2		0.01/0.1
Milk products												
Nut products											0.003/0.02	
Other grains											0.003/0.02	0.01/0.1
Poultry										0.04/0.2		0.01/0.07
Processed fruits												
Processed vegetables											0.003/0.02	0.01/0.1
Reconstituted Vegetables												
Seasonings/ flavors										0.04/0.2	0.003/0.02	
Snack foods	0.1/1	0.1/5		0.1/1	0.1/5		1/2					0.01/0.1
Soft candy	2/8	0.1/5			1/10							
Soups										0.02/0.1		0.01/0.1
Sugar substitutes												
Sweet sauces	2/9											

	Butyl <i>beta-</i> naphthyl ether	Isoamyl phenethyl ether	2-Acetyl-4- isopropenyl- pyridine	4-Acetyl-2- isopropenyl- pyridine	2-Acetyl-4- isopropyl- pyridine	2-Methoxy- pyridine	6-Methoxyqui- noline	2-Pentylthia- zole	2-Thienylmeth- anol	2-Acetyl-5- methylthio- phene	4-Methyl-3- thiazoline	3,4-Dimethyl- thiophene
Category	4634	4635	4636	4637	4638	4639	4640	4641	4642	4643	4644	4645
Baked goods							0.5/2	0.01/0.3		0.005/0.05	0.02/0.2	
Beverages (nonalcoholic)	1/10	0.5/2.5								0.001/0.01		
Beverages (alcoholic)	0.01/0.5	0.5/2.5										
Breakfast cereal											0.01/0.1	
Cheese												
Chewing gum		1/5	0.1/0.5	0.1/0.5	0.1/0.5						0.1/1	
Condiments/ relishes												
Confectionery frostings			0.05/0.3	0.05/0.3	0.05/0.3							
Egg products												
Fats/oils							0.5/2	0.01/0.3				
Fish products												
Frozen dairy												
Fruit ices	2/20											
Gelatins/ puddings	2/20					0.2/5						
Granulated sugar												
Gravies												
Hard candy	0.2/1	1/5	0.05/0.3	0.05/0.3	0.05/0.3						0.01/0.1	
Imitation dairy												
Instant coffee/tea						0.1/2			0.001/0.01	0.001/0.01		
Jams/jellies												
Meat products											0.02/0.2	
Milk products												
Nut products												
Other grains												
Processed fruits												
Processed vegetables												
Reconstituted Vegetables												
Seasonings/ flavors												
Snack foods							0.5/2	0.01/0.3	0.005/0.1			0.005/0.01
Soft candy			0.1/0.5	0.1/0.5	0.1/0.5							
Soups									0.001/0.01		0.02/0.2	0.01/0.05
Sugar substitutes												
Sweet sauces						0.2/5				0.003/0.1		

	1-(2-Thienyl) ethanethiol	4,5-Dimethyl-2- isobutylthiazole	Cyclotene butyrate	3-(Methylthio)- propylamine	4-Methyl- <i>cis</i> - 2-pentene	1-Nonene	1,3,5,7- Undecate- traene	Ethyl alpha- ethyl-beta- methyl-beta- phenylglycidate	Methyl <i>beta</i> - phenylglycidate	d-8-p- Menthene- 1,2-epoxide	L-8-p- Menthene- 1,2-epoxide	2,3- Epoxyoctanal
Category	4646	4647	4648	4649	4650	4651	4652	4653	4654	4655	4656	4657
Baked goods	0.001/0.005		0.5/4									0.1/1
Beverages (nonalcoholic)	0.0001/0.001	0.001/0.001	0.2/2				0.001/0.02	0.1/5	0.1/1	0.03/0.5	0.1/0.5	0.001/0.1
Beverages (alcoholic)									0.1/1		0.2/1	0.001/0.1
Breakfast cereal												
Cheese												0.1/1
Chewing gum								5/50			1/5	0.001/0.1
Condiments/ relishes					0.02/0.1	0.02/0.1				0.5/5		0.1/1
Confectionery frostings												
Egg products												0.1/1
Fats/oils												0.1/1
Fish products				2/5								
Frozen dairy							0.001/0.05		0.2/5			0.01/0.5
Fruit ices												
Gelatins/ puddings							0.003/0.05	0.3/5			0.2/1	
Granulated sugar												
Gravies												
Hard candy	0.001/0.005	0.005/0.05					0.003/0.05	1/20	2/20		0.5/2.5	
Imitation dairy												
Instant coffee/tea												0.1/1
Jams/jellies												
Meat products			1/8									0.1/1
Milk products									0.5/5	0.05/0.5		0.1/1
Nut products												
Other grains												
Poultry Processed fruits			1/8									
Processed vegetables												
Reconstituted vegetables												
Seasonings/ flavors	0.001/0.005	0.002/0.01	2/15		0.02/0.1	0.02/0.1						1/10
Snack foods	0.001/0.005			0.1/3	0.02/0.1	0.02/0.1						0.1/1
Soft candy												
Soups			1/8	1/5								0.1/1
Sugar substitutes												
Sweet sauces												0.1/1

	2,3- Epoxy- heptanal	2,3- Epoxydecanal	Hydroxy(4- hydroxy-3- methoxyphenyl) acetic acid	4-Hydroxy-4- (3-hydroxy-1- butenyl)-3,5,5- trimethyl-2- cyclohexen- 1-one	(+/-)- 2,6,10,10- Tetramethyl-1- oxaspiro[4.5] deca-2,6-dien- 8-one	4-(2-Butenyl- idene)-3,5,5- trimethyl-2- cyclohexen- 1-one	Digeranyl ether	1-(4-Hydroxy-3- methoxyphenyl) decan-3-one	αlphα- Bisabolol
Category	4658	4659	4660	4661	4662	4663	4664	4665	4666
Baked goods	0.1/1	0.1/1	10/20						4/20
Beverages (nonalcoholic)	0.001/0.1	0.001/0.1	5/10	1/10	2/20	1/5	15/30	10/50	10/30
Beverages (alcoholic)		0.001/0.1	10/20				30/60	20/100	10/30
Breakfast cereal			10/20						10/30
Cheese	0.1/1	0.1/1							
Chewing gum			5/10					300/800	50/500
Condiments/ relishes	0.1/1	0.1/1							
Confectionery frostings			10/20				70/100		20/100
Egg products		0.1/1							
Fats/oils	0.1/1							80/250	10/50
Fish products	0.1/1	0.1/1							
Frozen dairy			10/100					50/150	8/50
Fruitices			10/20				50/100		8/50
Gelatins/ puddings			20/50				50/100	50/150	8/50
Granulated sugar									
Gravies									
Hard candy			5/10				70/100	50/150	20/100
lmitation dairy			10/20						10/30
Instant coffee/tea	0.1/1	0.1/1		1/10	2/20	1/5			10/50
Jams/jellies									
Meat products	0.1/1	0.1/1							
Milk products	0.1/1	0.1/1	10/50					50/150	10/30
Nut products									
Other grains									
Poultry Processed									
fruits									10/30
Processed vegetables									
Reconstituted vegetables									
Seasonings/ flavors	1/10							100/250	20/100
Snack foods	0.1/1							20/50	
Soft candy							50/100	80/200	20/100
Soups	0.1/1	0.1/1						20/100	8/50
Sugar substitutes									
Sweet sauces	0.1/1	0.1/1	10/20						

TABLE 3. Updated Average Usual Use Levels/Average Maximum Use Levels

Average usual use levels (ppm)/average maximum use levels (ppm) for flavoring substances

previously recognized as FEMA GRAS. Superscript 'a' represents a new use level.

	Citral	Parsley oil	Jambu oleoresin	N-Gluconyl ethanolamine	N-Lactoyl ethanolamine	cis-3-Nonen- 1-ol
	FEMA No. 2303	2836	3783	4254	4256	4412
GRAS Publication	3	3	16	23	23	23
Category						
Baked goods	133/178	19/24		50°/200°	50°/200°	0.4ª/0.6ª
Beverages (nonalcoholic)	17/28	1/2	30°/60°	50°/200°	50°/200°	0.2°/1
Beverages (alcoholic)	3/6	1/2	25/60ª	50ª/200ª	50°/200°	0.6ª/1
Breakfast cereal			30ª/60ª	50ª/200ª	50ª/200ª	0.4ª/1ª
Cheese	0/0.2			50ª/200ª	50ª/200ª	
Chewing gum	7,000ª/10,000ª	8,000°/12,500°	1,000°/3,000°	50ª/200ª	50ª/200ª	1ª/2
Condiments/ relishes	10/10	45/64	10/30	50a/200a	50a/200ª	
Confectionery frostings			70ª/150ª	50ª/200ª	50a/200ª	0.4ª/0.6ª
Egg products				50ª/200ª	50ª/200ª	
Fats/oils				50ª/200ª	50ª/200ª	1ª/2ª
Fish products			10/30	50°/200°	50ª/200ª	
Frozen dairy	22/34	0.9/1	25ª/50ª	50°/200°	50ª/200ª	0.2ª/1
Fruit ices			25°/50°	50°/200°	50ª/200ª	0.2ª/0.4ª
Gelatins/ puddings	174/210	7/10	30ª/60ª	50°/200°	50°/200°	0.2ª/0.4ª
Granulated sugar				50°/200°	50ª/200ª	
Gravies	0.5/0.8	2/6		50°/200°	50ª/200ª	0.4ª/0.6ª
Hard candy	950°/1,000°	1,000°/1,000°	230°/350°	50°/200°	50ª/200ª	0.4ª/2
Imitation dairy				50°/200°	50°/200°	
Instant coffee/tea			25ª/50ª	50°/200°	50°/200°	0.2°/0.4°
Jams/jellies			25ª/50ª	50ª/200ª	50ª/200ª	
Meat products	1/2	38/63		50°/200°	50ª/200ª	
Milk products				50°/200°	50°/200°	0.4ª/1
Nut products				50°/200°	50ª/200ª	
Other grains				50°/200°	50ª/200ª	
Poultry				50ª/200ª	50ª/200ª	
Processed fruits			5ª/20ª	50ª/200ª	50°/200°	
Processed vegetables		0.8/1	5/20	50ª/200ª	50°/200°	
Reconstituted vegetables			5/20	50ª/200ª	50ª/200ª	
Seasonings/ flavors			25ª/100	50ª/200ª	50°/200°	20ª/30ª
Snack foods			50°/100°	50ª/200ª	50ª/200ª	0.4ª/0.6ª
Soft candy	142/181	3/6	230ª/300ª	50ª/200ª	50ª/200ª	0.4ª/2
Soups		33/66	15ª/30ª	50ª/200ª	50°/200°	0.4ª/0.6ª
Sugar substitutes				50ª/200ª	50ª/200ª	
Sweet sauces			10/30	50°/200°	50°/200°	0.4ª/0.6ª