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GRAS

FLAVORING SUBSTANCES 25

The 25th publication by the Expert Panel of the Flavor and Extract Manufacturers Association provides an update on recent progress in the consideration of flavoring ingredients generally recognized as safe under the Food Additives Amendment.

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More than half a century has passed since the first FEMA Expert Panel began a program to assess the safety of flavor ingredients for their intended use in food. Under the authority provided by the 1958 Food Additives Amendment to the Food, Drug and Cosmetic Act—Public Law No. 85-929, 72 Stat. 1784 (1958), codified at 21 U.S.C. Sec. 348 (1988)—the program's primary objective is to evaluate whether or not substances nominated by the flavor industry can be considered "generally recognized as safe" (GRAS) for their intended use as flavor ingredients. In existence since 1960, the FEMA GRAS program has become the longest-running and most widely recognized industry-sponsored GRAS assessment program.

The FEMA GRAS program began with the passage of the Food Additives Amendment, which defined a food additive as: "… any substance … which … may … [become] a component or … [affect] the characteristics of any food … if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures … to be safe under the conditions of its intended use."

This definition removed from consideration as food additives those substances deemed GRAS, therefore explicitly excluding them from mandatory premarket approval by the U.S. Food and Drug Administration (FDA). This allowed

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the FDA to dedicate resources to food additive issues of greater safety concern.

The GRAS 25 publication includes the results of the Expert Panel's review of 61 new GRAS flavoring substances (Tables 1, 2, and 3). In addition, based on poundage and use level data provided by the International Chewing Gum Association (ICGA), the Expert Panel determined that new use levels for 560 flavoring substances in the chewing gum category are consistent with their current GRAS status (Table 4).

In this publication, the Panel also critically reviews the results of chronic 2-year bioassays performed at the National Toxicology Program (NTP) for pyridine (FEMA No. 2966). Also included are changes in the GRAS status of two substances recently re-evaluated by the Expert Panel, an update on the GRAS status of common salts of GRAS substances, and an update on the current membership of the Panel.

ICGA Chewing Gum Survey and FEMA GRAS Re-evaluation

The ICGA (formerly the National Association of Chewing Gum Manufacturers) conducted surveys of the use of flavoring ingredients employed in chewing gum in 1972[1] and again in 1975. These surveys provided important information on how flavor ingredients were used in chewing gum; for instance, between 1972 and 1975, 252 additional flavoring substances were reported to be used in chewing gum. Although these surveys were part of an ongoing ICGA program to periodically review the use of flavors in chewing gum, this program was superseded by the FDA's interest in undertaking a comprehensive review of the patterns and volumes of use of food additives and GRAS substances used in food. The chewing gum surveys were thus incorporated into regular flavor poundage surveys performed by the U.S. flavor industry and sponsored by the FDA and the National Academy of Sciences. Although flavor ingredient poundage used in chewing gum was monitored approximately every 10 years as part of the larger flavor poundage surveys, there was no ongoing program to monitor the changes in use levels or the introduction of new flavor ingredients into chewing gum products during this time. Therefore,

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in 2000, the ICGA decided to perform a comprehensive survey of the addition of flavor ingredients to chewing gum products.

The 2000 ICGA flavor survey[2] was designed primarily to determine key statistics relevant to the total use of each flavor ingredient covered by the survey in the chewing gum industry in calendar year 2000, including:

1) Number of manufacturers and number of products in which the substance was used;
2) The average (arithmetic mean) concentration at which the substance was used in chewing gum;
3) The weighted mean concentration at which the substance was used;
4) The median concentration at which the substance was used;
5) The highest concentration at which the substance was used;
6) The total amount of the substance used in 2000 (calendar year), based on the weighted mean concentration of the substance and the volume of chewing gum disappearing into the marketplace.

The final report covered 768 FEMA GRAS flavoring substances for which data related to use in chewing gum were collected for the year 2000. The vast majority of those 768 flavoring substances are also FDA-approved food additives or FDA GRAS substances allowed for use in the U.S. at levels consistent with good manufacturing practice. In the total number reported in the ICGA Survey, numerous flavoring ingredients were determined to exhibit usual and/or maximum levels higher than those reported in the earlier surveys. The Expert Panel had previously recommended (Smith and Ford, 1993) that usual and maximum levels that may potentially result in significantly increased exposure be re-evaluated; therefore, ICGA submitted all substances with higher usual or higher maximum levels for review to ensure their new uses were consistent with current GRAS status.

While not all uses of flavoring substances in chewing gum were covered by the ICGA 2000 survey, ICGA estimated that more than 95% of the chewing gum products sold at that time in the United States were surveyed. The pattern of use of these substances will obviously vary from time to time as the availability and price of various flavoring substances fluctuates or manufacturers discontinue or modify existing products, or introduce new products.

Good Manufacturing Practice for Chewing Gum Flavoring

Compared to other food uses, a higher level of flavoring substance is required in gum in order to achieve acceptable flavoring properties. Since sufficient flavor must be available to maintain a palatable taste for periods of at least 20 minutes, a far higher concentration of flavoring substance is used in chewing gum compared to use in other food products. Chewing also stimulates an increased flow of saliva, thus requiring a more concentrated flavoring to compensate for dilution. Additionally, a piece of chewing gum weighs far less than an individual serving of most other food products[3]. Therefore, a proportionately higher concentration of flavoring substance must be used to achieve a given quantity of flavoring in chewing gum than in other food products[4].

Another key factor that determines flavor concentration is the retention of flavoring substance within the chewing gum base. The gum base retains a portion of the flavoring throughout the chewing period. »»

The rate and amount of release of a flavoring agent from a specific gum base during chewing, referred to as "chew-out," is also determined in part by the structure and physicochemical properties of the flavoring substance. Since saliva is aqueous, the water solubility of a substance may be related to the amount of chew-out, provided that the flavoring substance does not undergo chemical changes that affect these properties. ICGA developed a program to analyze chew-out data for 44 representative flavor ingredients that are used in chewing gum, and provided that information to the Panel. The Panel incorporated these data where relevant to refine intake estimates for the applicable flavor ingredients used in chewing gums that were re-evaluated for FEMA GRAS status.

Determination of Intake of Flavor Ingredients from Chewing Gum

In order to make meaningful comparison of the use and intake of flavoring substances from chewing gum with the use and intake of these substances in other foods, several additional factors were considered by the Expert Panel. A simple comparison of the concentrations (in ppm) of flavoring substances in chewing gum with the concentrations (in ppm) in other foods is misleading. More relevant information is obtained by comparing the weight of the substance consumed on a *per serving* basis or a *per day* basis. For chewing gum, a "serving" is a piece of gum chewed for about 20 minutes. If the stick is chewed for a lesser time, it is equivalent to part of a serving because a smaller portion of the flavoring substance is released during a shorter period.

As one example, consider a 2 g (2,000 mg) stick of gum that contains 0.8% (8,000 ppm) peppermint oil, which itself contains 2% menthofuran. The 2 g stick of gum would contain 16 mg of peppermint oil and 0.32 mg of menthofuran. Upon chewing for 20 minutes, only 10%, or 0.032 mg of the menthofuran, is chewed out. If the person chewing weighs 60 kg, the intake of menthofuran would be less than 0.0005 mg/kg body weight (0.5 µg/kg body weight). By comparison, if a 20 g portion of soft candy contained 100 ppm peppermint oil that contained 2% menthofuran, the intake of peppermint oil would be 2 mg, and the intake of menthofuran would be 0.04 mg/person or for a 60 kg body weight, 0.0006 mg/kg body weight (0.6 µg/kg body weight). Although both intakes are relatively small, intake of menthofuran (0.5 µg/kg body weight) from chewing a 2 g stick of gum containing 8,000 ppm peppermint oil for 20 minutes is roughly equivalent to the intake of menthofuran from consuming a 20 g portion of soft candy containing 100 ppm of the same peppermint oil.

FEMA GRAS Re-evaluation

The Panel re-evaluated all relevant metabolic and toxicity data for these flavor ingredients within the context of their increased use levels in chewing gum. The intake of flavoring substance from chewing gum—given its light weight per serving, flavor retention rates, but seemingly high added concentrations—may be roughly equivalent to the intake of these same substances at lower concentration in foods that are consumed over a shorter time period and have a much greater portion size. Therefore, in cases where the relevant data were available, the intake related to use of these flavor ingredients in chewing gum was evaluated in the context of the effects of portion size, level of chew-out, and other factors affecting the intake of the flavor ingredient. Based on their review of the intake data, and the relevant metabolic and toxicity data for these substances, the FEMA Expert Panel determined that the new or higher use levels in chewing gum for the 560 flavoring ingredients listed in Table 4 are consistent with their current GRAS status.

Safety Assessment of Pyridine (FEMA No. 2966)

At ppm levels, the aroma of pyridine is described as warm, burnt, and smoky (Arctander, 1969). Based upon a reported annual volume of pyridine of 54 kg in the United States (Gavin et al., 2008), the daily per capita intake ("eaters only")[5] of pyridine from use as a flavor ingredient is calculated to be 7 µg/person/day. Pyridine has been

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isolated in the volatile components from cooked beef (sukiyaki) in Japan (Shibamoto et al., 1981); fried chicken in the U.S. (Tang et al., 1983); fried bacon (Ho et al., 1983); Beaufort cheese (Dumont and Adda, 1978); black tea aroma (Vitzthum et al., 1975); and coffee aroma (Aeschbacher et al., 1989). An 8 oz cup of fresh brewed coffee may contain up to 5 µg of pyridine. Concentrations in cocoa (0.5 ppm), coffee (37–49 ppm), and shrimp (4.1–9.9 ppm) represent principal food sources of pyridine (Nijssen et al., 2010). Based on quantitative natural occurrence data, the intake of pyridine from consumption of all traditional foods exceeds its intake as an added flavor ingredient by a factor of at least 100 (Stofberg and Kirschman, 1985; Stofberg and Grundschober, 1987).

In animals, pyridine is metabolized primarily by two biotransformation routes: oxidation at the nitrogen atom to give pyridine N-oxide and methylation of the nitrogen atom to yield the quaternary ammonium ion, N-methylpyridinium. Both polar metabolites are excreted in the urine (D'Souza et al., 1980; Damani et al., 1982). To a lesser extent, ring oxidation may occur to give 2- and 4-pyridone and 3-hydroxypyridine. In vitro experiments with human and rat microsomal and cytosolic liver fractions, and human microsomal and cytosolic kidney and lung fractions, show the formation of these three ring-oxidized metabolites (Wilke et al., 1989). In vivo studies in rats demonstrate that CYP2E1 is induced by pyridine and is responsible for formation of pyridine N-oxide (Kim et al., 1988; Kaul and Novak, 1987). Other pyridine-induced isoforms include rat renal CYP1A1 and CYP1A2 (Kim et al., 1995), rat hepatic CYP2B1/2B2 (Kim et al., 1993), and rabbit liver CYP2B1/2B2 (Kim et al., 1991).

In two separate 90-day studies, groups of 10 male and 10 female F344/N or 10 male Wistar rats were provided drinking water containing pyridine at concentrations of 0, 50, 100, 250, 500, or 1,000 ppm (equivalent to average daily doses of 5, 10, 25, 55, or 90 mg pyridine/kg body weight) (NTP, 2000). For the F344/N rats, in addition to increased mortality (2 females at 1,000 ppm), dehydration and decreased body weights were reported at the two highest concentrations. On day 5, erythrocytosis was reported in males at concentrations of 100 ppm and greater. This observation is consistent with dehydration, which can cause relative erythrocytosis due to decreased blood volume and hemoconcentration (Jain, 1986). On day 20, the erythrocytosis was replaced by a developing normocytic, normochromic, non-responsive anemia, demonstrated by decreased hematocrit values, hemoglobin

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concentrations, and erythrocyte counts relative to controls in males and females exposed to concentrations of 250 ppm or greater. At study termination, evidence of anemia persisted in the 500 and 1,000 ppm males and all exposed groups of females. At the two highest concentrations, there was evidence of hepatocellular injury and/or altered hepatic function (increased serum alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations). Liver weights of males and females exposed to 250 ppm or greater were significantly greater than controls. The incidences of hepatic centrilobular degeneration, hypertrophy, chronic inflammation, and pigmentation were generally increased in 500 and 1,000 ppm males and females relative to controls. In the kidney, the incidences of granular casts and hyaline degeneration (hyaline droplets) were significantly increased in 1,000 ppm males and slightly increased in 500 ppm males; these lesions suggested alpha-2u-globulin-type nephropathy. Additionally, there were increased incidences and/or severities of protein casts, chronic inflammation, mineralization, and regeneration primarily in 500 and 1,000 ppm males. Based on the appearance of erythrocytosis in males at 100 ppm, the NOAEL (no observed adverse effect level) was concluded to be 50 ppm or approximately 5 mg/kg body weight per day.

Responses (lower mean body weights, dehydration, and hepatic injury) in male Wistar rats provided pyridine in drinking water were similar to those in F344/N rats and occurred in a similar concentration range, and the NOAEL in Wistar rats was at a concentration of 100 ppm, or approximately 10 mg/kg body weight per day. Groups of 10 male and 10 female B6C3F1 mice were exposed to the same concentrations of pyridine as used in the 90-day rat study. Based on increased liver weights relative to controls in males exposed to 100 ppm or greater, the NOAEL was concluded to be 50 ppm or approximately 5 mg/kg body weight per day.

In a 2-year bioassay performed by the National Toxicology Program (NTP, 2000), groups of 50 B6C3F1 mice of both sexes were exposed to pyridine in drinking water at concentrations calculated to provide an average daily intake of 0, 35, 65, or 110 mg/kg body weight for males and 15, 25, or 70 mg/kg body weight for females. Based on the results of the 2-year drinking water study in B6C3F1 mice, the NTP reached the following conclusion: "There was *clear evidence of carcinogenic activity* of pyridine in male and female B6C3F1 mice based on increased incidences of malignant hepatocellular neoplasms."

Hepatocellular adenomas occurred at an increased incidence in males (29/50 in controls, 40/50 ($p = 0.003$), 34/49, and 39/50 ($p = 0.011$) in low-, mid-, and high-dose groups, respectively. The incidence of hepatocellular carcinomas in

males was 15/50 in controls, 35/50 in the low-, 41/49 in the mid-, and 40/50 in the high-dose group, respectively ($p < 0.001$, pairwise comparisons for all treated groups). The incidence of hepatoblastomas in males was 2/50, 18/50, 22/49, and 15/50 ($p < 0.001$, pairwise comparisons for all treated groups) in control, low-, mid-, and high-dose groups, respectively. In female mice, the incidence of hepatocellular carcinomas was increased in a dose-related manner: 13/49 in controls, 23/50, 33/50 ($p = 0.014$), and 41/50 ($p < 0.001$) in the low- mid-, and high-dose groups, respectively. The incidence of hepatoblastomas was also dose-dependent and significantly increased: 1/49 in controls, 2/50, 9/50 ($p = 0.007$), and 16/50 ($p < 0.001$) in the low-, mid-, and high-dose groups, respectively (NTP, 2000).

The statistical evidence of increased incidence of liver neoplasms must be evaluated in the context of strain and species-specific effects recently elucidated in the B6C3F1 mouse (Turosov, 2002). Shortly after publication of the 2-year bioassay with pyridine, the NTP reported an unexpected 5-fold increase in the incidence of spontaneous hepatoblastomas in control B6C3F1 mice during the period 1994–2002. This was accompanied by an increase in the incidence of chemically induced hepatoblastomas in B6C3F1 mice in 2-year NTP studies compared to the previous 7 years. There was a positive association between an increased incidence of mice with hepatoblastoma and an increased incidence of mice with hepatocellular tumors. Although a variety of chemicals caused an increased incidence of mice with hepatoblastoma, there was no apparent association between a specific chemical structure and their capacity to induce hepatoblastomas. Hepatoblastoma is a component of the spectrum of hepatocellular tumors that are identified separately in addition to hepatocellular adenoma and carcinoma in a study. Chemicals that induce hepatoblastomas and hepatocellular carcinomas are not necessarily more potent than chemicals that induce hepatocellular carcinomas alone. Because hepatoblastomas frequently arise within hepatocellular adenomas and hepatocellular carcinomas, the study authors (Turosov et al., 2002) concluded that it is reasonable to combine the incidence of mice with hepatoblastomas with the incidence of mice with hepatocellular adenomas and hepatocellular carcinomas in the overall evaluation for hazard classification.

The overall rates of tumor incidence for combined hepatocellular adenomas, carcinomas, and blastomas for male B6C3F1 mice exposed to pyridine was 38/50 (76%) in controls, 47/50 (94%) in the low-, 46/49 (94%) in the mid-, and 47/50 (94%) in the high-dose groups. The combined tumor incidence for female B6C3F1 mice was 41/49 (84%) in controls, 42/50 (84%) in the low-, 45/50 (90%) in the mid-, and 44/50 (88%) in the high-dose groups. Therefore, there are no statistically significant differences in tumor incidence between test and control groups of either sex of mice. The increase in spontaneous background incidence of liver neoplasms in male B6C3F1 mice in the 2-year NTP bioassay is now well recognized. This phenomenon has been reported in 2-year studies for other flavor ingredients (Smith et al., 2009; Adams et al., 2005). It is also generally well accepted that male and female B6C3F1 mouse liver tumors that arise in 2-year bioassays with various agents (e.g., chloroform; see Meek et al., 2003) can be the result of dose-related chronic toxicity and resulting regenerative cellular proliferation. In the absence of this chronic toxicity at exposure levels in humans, the occurrence of these tumors does not provide evidence that pyridine represents a significant risk for humans (Cohen et al., 2004).

There is substantial evidence that the appearance of male B6C3F1 mouse liver tumors is not relevant to a human risk assessment. First, there was no statistical evidence of an increased incidence of total hepatic tumors in male or female rats related to administration of pyridine. Second, all dose groups of male and female B6C3F1 mice suffered chronic hepatic toxicity prior to the development of liver adenomas, carcinomas, or blastomas, as evidenced by the results of the 90-day and 2-year studies. Hepatocellular tumors also occurred late in the life span of both male and female mice. From a biological perspective, the increase in the incidence of tumors in B6C3F1 mice reflects the impact of high-dose liver damage to an organ already prone to spontaneous development of liver

Expert Panel Member Changes

In May 2010, Phillip Portoghese of the University of Minnesota retired from the Panel. Portoghese spent more than a quarter-century in service to the Expert Panel and the flavor industry. His experience in biochemistry, medicinal chemistry, and metabolism provided the Panel with expertise that contributed significantly to the long-standing success of the Panel.

In October 2010, William Waddell of the University of Louisville retired from the Panel after more than a decade of service. With extensive experience in pharmacology, toxicology, medicine, and mechanisms of carcinogenicity, Waddell made numerous key contributions to the work of the Panel. Portoghese and Waddell are now recognized as Emeritus Members of the Panel.

In September 2010, Stephen Hecht, Professor of Cancer Prevention at the University of Minnesota, joined the Panel. His work focuses on the role of carcinogen metabolism and DNA binding in mechanisms of carcinogenesis.

In September 2010, Shoji Fukushima, Director at the Japan Bioassay Research Center, joined the Panel. Fukushima has published numerous articles with a research focus on the mechanisms of carcinogenesis.


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neoplasms (Smith et al., 2009; Haseman et al., 1986; Haseman, 1990).

Therefore, it can be concluded that the carcinogenic potential in this sensitive strain and sex of laboratory mouse is a secondary biological response to dose-dependent hepatotoxicity, and is not relevant to humans who consume pyridine at low nontoxic levels (<0.0005 mg/kg body weight per day) from intended use as a flavoring ingredient or as a constituent of food. The 90-day NOAEL of either 5 or 10 mg/kg body weight per day in Fisher F344/N or male Wistar rats, respectively, (NTP, 2000) is approximately 1,000 times the daily per capita intake ("eaters only") intake of 0.007 mg/kg body weight per day from use of pyridine as a flavor ingredient. Also, these levels of intake are at least four orders of magnitude lower than those used in the NTP bioassay that resulted in hepatic toxicity and neoplasms.

In the rat 2-year bioassay, groups of 50 F344/N rats of both sexes were exposed to pyridine in the drinking water at concentrations calculated to provide an average daily intake of 0, 7, 14, or 33 mg/kg body weight per day. In a second strain of rats, groups of male Wistar rats were maintained on drinking water containing pyridine at concentrations calculated to provide an average daily intake of 0, 8, 17, or 36 mg/kg body weight per day.

Consistent with the 13-week studies, the target organs included the liver and kidney in male F344/N rats, the liver and testes in Wistar rats, and the liver in female F344/N rats. Although, in general, these liver lesions were more severe in Wistar rats than in F344/N rats, there was no evidence of an increase in the incidence of hepatocellular neoplasms in either sex or strain of treated rats compared to controls. The only evidence of neoplasms occurred in the kidney where there was an increased incidence of renal tubule adenomas in male F344/N rats [2/50 (4%) in the controls, 3/48 (4%) in the low-, 6/50 (12%) in the mid-, and 10/50 (20%) in the high-dose groups] in the 2-year bioassay based on evaluation of single and multiple sections combined. Based on these results, the NTP concluded: "Under the conditions of these 2-year drinking water studies, there was *some evidence of carcinogenic activity* of pyridine in male F344/N rats based on increased incidences of renal tubule neoplasms."

Although the NTP noted the presence of hyaline droplets, granular casts, and immunohistochemical evidence of alpha 2u-globulin nephropathy, the droplets and casts were clearly less severe than for other alpha 2u-globulin nephropathy inducers and there were no linear foci of mineralization within the renal medulla in this study, a change normally characteristic of alpha 2u-globulin-associated nephropathy. Based primarily on these observations, the NTP suggested that the renal neoplastic response in the male F344/N rat kidney was not attributable to alpha 2u-globulin nephropathy.

Although the incidence and severity of renal tubular neoplasms associated with the formation of hyaline droplets is evident in treated males, the lack of any evidence of renal tubular adenomas and carcinomas in female F344 rats and male Wistar rats and the lack of renal changes in mice clearly establishes that the carcinogenic response is sex-, strain-, and species-specific. One carcinoma was recorded in male F344/N rats, and that result is not considered to be treatment related in that it occurred only in the low-dose group. Renal tubule hyperplasia was slightly increased in male F344/N rats [9/50 (18%) in the controls, 7/48 (15%) in the low-, 11/50 (22%) in the mid-, and 15/50 (30%) in the high-dose groups]. The hyperplastic and the benign tumorigenic response (adenomas only) in male F344/N rats are weak compared to that for other alpha 2u-globulin inducers. Although the proliferative response in the male F344/N rats is slight and there is a lack of known mineralization characteristic of alpha 2u-globulin nephropathy, the immunohistochemical evidence from the 13-week study

at higher concentrations cannot be dismissed. Pyridine is non-genotoxic based on mainly negative results in both in vitro and in vivo assays (Pai et al., 1978; NTP, 2000; MacGregor et al., 2000; Harper et al., 1984; Kawachi et al., 1980; Warren et al., 1981; Riebe et al., 1982; Florin et al., 1980; Haworth et al., 1983; Abe and Sasaki, 1977; Ishidate and Odashima, 1977), so the mode of action for induction of the renal tumors is non-genotoxic and dependent on dose-related increase in proliferation. The specific mode of action for these pyridine-induced renal tumors remains to be established.

The other carcinogenic effect reported by NTP was an increased incidence of mononuclear cell-leukemia in female F344/N rats. They noted that incidences of mononuclear cell leukemia in female rats were slightly but significantly increased in the 200 and 400 ppm groups compared to controls [12/50 (24%) in controls, 16/50 (32%) in the low-, 22/50 (44%) in the mid-, and 23/50 (46%) in the high-dose groups], and that the incidence in the 400 ppm group exceeded the historical control range. The mean historical incidence in 2-year drinking water studies with untreated control groups is 30.9% (± 10.0%) with a range of 16–44%. In males, there was no statistically significant difference in the incidence of mononuclear cell leukemia, but the rates were all higher than in females (0 ppm, 29/50; 100 ppm, 32/50; 200 ppm, 26/50; 400 ppm, 27/50). There was no increased incidence of leukemia in male Wistar rats: this strain exhibits a low spontaneous incidence of this type of tumor. In all animals with this neoplasm, neoplastic cells were found in the spleen and usually also in the liver. Infiltrations in the lung, bone marrow, lymph nodes, adrenal gland, and kidney were also common. Incidences of mononuclear cell leukemia in male rats were similar to those in controls and in the same range as for females at the two higher dose levels (0 ppm, 29/50; 100 ppm, 32/50; 200 ppm, 26/50; 400 ppm, 27/50). Based on the marginal increase in leukemia in females at 200 and 400 ppm, the NTP concluded that: "There was *equivocal evidence of carcinogenic activity* of pyridine in female F344/N rats based on increased incidences of mononuclear cell leukemia."

More than 20 years ago, members of NTP reported (Rao et al., 1990) that the incidence of mononuclear cell leukemia in female F344/N rats in drinking water studies had been steadily increasing. From a low of 2.1% in 1971, control rates had increased to over 30% in females. The trend is more pronounced in males, where rates had climbed from 7.9% to as high as 52% (Haseman and Rao, 1992). More recently, as a result of a workshop that focused on whether the choice of animal models used by the NTP should be changed (King-Herbert and Thayer, 2006), the NTP has now concluded that the Harlan Sprague-Dawley rat will replace the F344/N strain as the animal model in future bioassays (King-Herbert et al., 2010). In the NTP study on pyridine using F344/N rats, while statistically significant increases in the incidence of mononuclear cell neoplasms in female rats were reported, the biological significance of these tumors and their relevance to humans remains uncertain.

Pyridine was reaffirmed as GRAS (GRASr) in 2010 based upon its efficient detoxification in humans; its low level of flavor use; the lack of genotoxic and mutagenic potential; the safety factor calculated from results of subchronic studies (NTP, 2000) indicating a margin of safety of at least 1,000; the conclusion that the statistically significant findings in the NTP mouse bioassay, of an increased incidence of hepatocellular neoplasms in male and female B6C3F1 mice were secondary to pronounced hepatotoxicity at high dose levels; the conclusion that the increased incidence of renal neoplasms in male F344/N rats occurs via a dose-dependent non-genotoxic mode of action; and the conclusion that the increased incidence of mononuclear cell leukemia in female F344/N rats is likely species- and sex-specific, the biological significance of which remains uncertain. Based on these conclusions, the use of pyridine as a flavor ingredient is not considered to produce any significant risk to human health. This evaluation is supported by the occurrence of pyridine as a natural component of traditional foods resulting in concentrations in the diet producing a "natural intake" that is at least 100 times higher than that which occurs when pyridine is employed as a flavor ingredient.

ReGRAS of 2-Methyl-5-vinylpyrazine and 2-Hexyl-4-acetoxytetrahydrofuran

The substance 2-methyl-5-vinylpyrazine (formerly FEMA No. 3211) was removed from the GRAS list in 1984 (Oser et al., 1984). At that time, the substance was reevaluated by the panel and found to require additional data including toxicological testing for continuation of GRAS status. Additional metabolism data supporting side chain oxidation of the substance and toxicity data from a 90-day study on the structurally related substance 2-vinylpyridine were presented to the Panel in October 2009. Based upon an evaluation of these data, the Panel concluded that 2-methyl-5-vinylpyrazine is GRAS under conditions of intended use as a flavor ingredient. The Panel restored the GRAS status of 2-methyl-5-vinylpyrazine with its original FEMA GRAS number.

The substance 2-hexyl-4-acetoxytetrahydrofuran (formerly FEMA No. 2566) was removed from the GRAS list

Photo courtesy of Virginia Dare

in 1970 due to questions concerning certain isomeric components. In May 2010, clarification of chemical identity and purity was submitted to the Panel together with data supporting the hydrolysis of the ester. The Panel concluded that its FEMA GRAS status should be restored with its original FEMA GRAS number.

Panel Statement on Salt Forms of FEMA GRAS Substances

The FEMA Expert Panel concludes that the neutral, hydrated, and salt forms of GRAS substances that are physiologically equivalent are assigned the same GRAS number. Such salt forms include the chlorides, sulfates, carbonates, bicarbonates, and phosphates of quaternary ammonium and sulfonium salts. The same GRAS number would also be applied to the sodium, potassium, calcium, ferrous, ferric, ammonium, and quaternary ammonium salts derived from FEMA GRAS amines, carboxylates, sulfonates, sulfamates, or sulfates, provided the level of intake of the respective mineral in the salt is sufficiently low compared to dietary intake of these minerals. **FT**

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NOTES

[1] For a description of previous surveys conducted by the NACGM, see "Introduction to NACGM Flavor Survey Final Compilation of Data," Aug. 1, 1972, Exhibit 20 to "A Comprehensive Survey of Industry on the Use of Food Chemicals Generally Recognized as Safe (GRAS)," Subcommittee on Review of the GRAS list—Phase II, Committee on Food Protection, Food and Nutrition Board, Division of Biology and Agriculture, National Research Council (National Academy of Sciences, September, 1972).

[2] Full details related to the methodology and results of the survey, as well as data related to retention/release of flavor ingredients from chewing gum matrices, are expected to be reported elsewhere.

[3] A stick of ordinary slab chewing gum weighs about 2 g, and a piece of bubblegum weighs about 5 g. The flavor ordinarily represents 0.5%–1.5% of the product, but in some instances ranges up to 3.0% or even higher.

[4] It should be noted in passing that the very same factors which require a much higher concentration of flavoring in chewing gum than in other foods also substantially reduce the potential toxicity of the use of these higher levels.

[5] Intake (μg/person/day) calculated as follows: (((annual volume, kg) x (1×10^9 μg/kg))/(population x survey correction factor x 365 days)), where population (10%, "eaters only") = 28×10^6 for the U.S.; where correction factor = 0.8 represents the assumption that only 80% of the flavor volume was reported in the 2005 survey (Gavin et al., 2008). Intake (μg/kg body weight per day) calculated as follows: [(μg/person/day)/body weight], where body weight = 60 kg. Slight variations may occur from rounding off.

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TABLE 1. Primary Names & Synonyms

Primary names (in boldface) & Synonyms (in lightface)

FEMA NO.	SUBSTANCE PRIMARY NAME AND SYNONYMS
2566	**2-HEXYL-4-ACETOXYTETRAHYDROFURAN (RE-GRAS)** 3-Furanol, 5-hexyltetrahydroacetate
3211	**2-METHYL-5-VINYLPYRAZINE (RE-GRAS)** Pyrazine, 2-ethenyl-5-methyl-
4667	**2(4)-ETHYL-4(2),6-DIMETHYLDIHYDRO-1,3,5-DITHIAZINE (MIXTURE OF ISOMERS)** 2(4)-Ethyl-4(2),6-dimethyldihydro-1,3,5-dithiazinane Ethyl thialdine
4668	**(2*E*,6*E*/*Z*,8*E*)-*N*-(2-METHYLPROPYL)-2,6,8-DECATRIENAMIDE** Spilanthol *N*-Isobutyl-2*E*-decenamide Affinin
4669	**4-AMINO-5,6-DIMETHYLTHIENO[2,3-*D*]PYRIMIDIN-2(1*H*)-ONE** 4-Amino-5,6-dimethylthieno[2,3-*d*] pyrimidin-2(1*H*)-one hydrochloride
4670	**1,1-PROPANEDITHIOL** 1,1-Dimercaptopropane
4671	***Z*-5-OCTENYL ACETATE** *cis*-5-Octenyl acetate (5*Z*)-Octen-1-ol acetate
4672	**(*E*)-4-UNDECENAL** *trans*-Undec-4-enal 4*E*-Undecenal
4673	***DELTA*-HEXADECALACTONE** Tetrahydro-6-undecyl-2*H*-pyran-2-one 6-Undecyltetrahydropyran-2-one *delta*-Hexadecanolide *delta*-Palmitolactone 5-Hexadecanolide 5-Hydroxyhexadecanoic acid *delta* lactone 6-Undecyltetrahydro-2*H*-pyran-2-one
4674	**TRILOBATIN** Prunin dihydrochalcone Phloretin 4′-glucoside 1-Propanone, 1-[4-(*beta*-*D*-glucopyranosyloxy)- 2,6-dihydroxyphenyl]-3-(4-hydroxyphenyl)-
4675	***L*-ISOLEUCINE** (S)-Isoleucine (2S,3S)-2-Amino-3-methylpentanoic acid [S-(R*,R*)]-2-Amino-3-methylpentanoic acid
4676	**1-(2-FURFURYLTHIO)PROPANONE** 1-(Furan-2-ylmethylsulfanyl)propan-2-one 2-Propanone, 1-[(2-furanylmethyl)thio]- (Furfurylthio)acetone 1-[(2-Furylmethyl)sulfanyl]acetone
4677	**(±)-4-METHYL-2-PROPYL-1,3-OXATHIANE** 1,3-Oxathiane, 4-methyl-2-propyl-
4678	***N*-(2-METHYLCYCLOHEXYL)-2,3,4,5,6-PENTAFLUOROBENZAMIDE** PFMC Benzamide
4679	**ARACHIDONIC ACID ENRICHED OIL** AREO Arasco
4680	**5-ISOPROPYL-2,6-DIETHYL-2-METHYLTETRAHYDRO-2*H*-PYRAN** 2,6-Diethyl-2-methyl-5-(propan-2-yl)tetrahydro-2*H*-pyran 2*H*-Pyran, 2,6-diethyltetrahydro-2-methyl-5-(1-methylethyl)-
4681	**(1R,2S,5R)-*N*-(4-METHOXYPHENYL)-5-METHYL-2-(1-METHYLETHYL)CYCLOHEXANECARBOXAMIDE** *N*-(4-Methoxyphenyl)-*p*-menthanecarboxamide (1R,2S,5R)-*N*-(4-Methoxyphenyl)-5-methyl-2- (1-methylethyl)cyclohexanecarboxamide

FEMA NO.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4682	**OCTAHYDRO-4,8*A*-DIMETHYL-4*A*(2*H*)-NAPHTHOL** Geosmin Octahydro-4,8*a*-dimethyl-4*a*(2*H*)-naphthol 4,8*a*-Dimethyloctahydronaphthalen-4*a*(2*H*)-ol 4*a*(2*H*)-Naphthalenol, octahydro-4,8*a*-dimethyl- 1,10-Dimethyl-9-decalol
4683	**2-METHYL-4,5-DIHYDROFURAN-3-THIOL** 3-Furanthiol, 4,5-dihydro-2-methyl- 2-Methyl-4,5-dihydrofuran-3-thiol 3-Mercapto-2-methyl-4,5-dihydrofuran 4,5-Dihydro-2-methyl-3-mercaptofuran
4684	**(2S,5R)-*N*-[4-(2-AMINO-2-OXOETHYL)PHENYL]-5-METHYL-2-(PROPAN-2-YL)CYCLOHEXANECARBOXAMIDE** Benzeneacetamide, 4-[[[(2S,5R)-5-methyl-2-(1- methylethyl)cyclohexyl]carbonyl]amino]-
4685	**(±)-6-OCTYLTETRAHYDRO-2*H*-PYRAN-2-ONE** 5-Tridecanolide 6-Octyltetrahydro-2*H*-pyran-2-one Tetrahydro-6-octyl-2*H*-pyran-2-one *delta*-Tridecalactone 5-Hydroxytridecanoic acid *delta* lactone *delta*-Octylvalerolactone Trideca-1,5-lactone
4686	**(±)-2-METHYLTETRAHYDROFURAN-3-THIOL ACETATE** 2-Methyltetrahydrofuran thioacetate 2-Methyl-3-thioacetoxytetrahydrofuran Ethanethioic acid, S-(tetrahydro-2-methyl-3-furanyl)ester 2-Methyltetrahydrofuran-3-thiol acetate
4687	**(±)-3-HYDROXY-3-METHYL-2,4-NONANEDIONE** Lactadione
4688	**1,1-DIPROPOXYETHANE** Acetaldehyde, dipropyl acetal
4689	**CHRYSANTHEMUM EXTRACT** *Chrysanthemum morifolium*, ext.
4690	**HONEYSUCKLE EXTRACT** *Honeysuckle*, *Lonicera japonica*, ext.
4691	**YUZUNONE** 6,8*E*,10-Undecatrien-3-one
4692	***L*-METHIONYLGLYCINE**
4693	***N*-CYCLOPROPYL-5-METHYL-2-ISOPROPYLCYCLOHEXANECARBOXAMIDE** Cyclohexanecarboxamide, *N*-cyclopropyl- 5-methyl-2-(1-methylethyl)-
4694	**3-PENTANETHIOL** Pentane-3-thiol 3-Pentyl mercaptan
4695	**2-ETHYL-2,5-DIHYDRO-4-METHYLTHIAZOLE** 2-Ethyl-4-methyl-3-thiazoline
4696	**1-(METHYLDITHIO)-2-PROPANONE** Methyl 2-oxopropyl disulfide 1-(Methyldisulfanyl)acetone 1-Methyldisulfanylpropan-2-one
4697	**5-METHYLFURFURYLMERCAPTAN** (5-Methylfurfuryl)mercaptan 5-Methyl-2-furanmethanethiol (5-Methylfuran-2-yl)methanethiol
4698	**4-MERCAPTO-3-METHYL-2-BUTANOL** 4-Mercapto-3-methylbutan-2-ol 3-Methyl-4-sulfanyl-2-butanol 4-Thio-3-methyl-2-butanol
4699	**FERROUS *L*-LACTATE** *L*-2-Hydroxy-propanoic acid, iron (2+) salt dihydrate

FEMA NO.	SUBSTANCE PRIMARY NAME AND SYNONYMS
4700	***O-TRANS*-COUMARIC ACID** 2-Propenoic acid, 3-(2-hydroxyphenyl)-, (*E*)- Cinnamic acid, *o*-hydroxy-, (*E*)- (*E*)-2-Hydroxycinnamic acid
4701	**3-[(4-AMINO-2,2-DIOXIDO-1*H*-2,1,3-BENZOTHIADIAZIN-5-YL)OXY]-2,2-DIMETHYL-*N*-PROPYLPROPANAMIDE** 3-(4-Amino-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yloxy-2,2-dimethyl-*N*-propylpropanamide-2,2-dioxide 3-(1*H*-Benzo[*c*][1,2,6]thiadiazin-4-amine-2,2-dioxide)-5-yloxy-2,2-dimethyl-*N*-propylpropanamide
4702	**2(3),5-DIMETHYL-6,7-DIHYDRO-5*H*-CYCLOPENTAPYRAZINE**
4703	**CINNAMYL BENZOATE** 3-Phenyl-2-propenyl benzoate
4704	***BETA*-NAPHTHYL METHYL ETHER** 2-Methoxynaphthalene 2-Naphthol methyl ether 2-Naphthyl methyl ether
4705	**ROSEMARY OLEORESIN** *Rosemarinus officinalis* oleoresin
4706	**9-DECEN-2-ONE** Dec-9-en-2-one Methyl oct-7-enyl ketone
4707	**1-(METHYLTHIO)-3-OCTANONE** 1-Methylsulfanyloctan-3-one
4708	**3',7-DIHYDROXY-4'-METHOXYFLAVAN** (±)-3',7-Dihydroxy-4'-methoxyflavan 3,4-Dihydro-2-(3-hydroxy-4-methoxyphenyl)-2*H*-1-benzopyran-7-ol
4709	**GLUTAMYL-VALYL-GLYCINE** *L-gamma*-Glutamyl-*L*-valyl-glycine *N*-(*N*-*L-gamma*-Glutamyl-*L*-valyl)-glycine
4710	***L*-THREONINE** (S)-Threonine [R-(R*,S*)]-2-Amino-3-hydroxybutanoic acid
4711	**LUO HAN FRUIT CONCENTRATE** Luo han guo concentrate Luo han kuo concentrate *Siraitia grosvenorii* concentrate *Fructus momordicae* concentrate Buddha's Fruit concetrate Monk's Fruit concentrate Longevity Fruit concetrate *Rakanka* concentrate
4712	***L*-ALANYL-*L*-GLUTAMINE** Glutamine, *N*2-*L*-alanyl-
4713	**SUCROSE MONOPALMITATE** *alpha-D*-glucopyranoside, monohexadecanoate *beta-D*-fructofuranoside, monohexadecanoate

FEMA NO.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4714	**ETHYL 2-MERCAPTO-2-METHYLPROPIONATE** Ethyl 2-methyl-2-sulfanylpropanoate Ethyl 2-mercapto-2-methylpropanoate Propanoic acid, 2-mercapto-2-methyl-, ethyl ester
4715	**2-(3,4-DIHYDROXYPHENYL)-5,7-DIHYDROXY-4-CHROMANON** 4*H*-1-Benzopyran-4-one, 2-(3,4-dihydroxyphenyl)-2,3-dihydro-5,7-dihydroxy- (±)-Eriodictyol (±)-3',4',5,7-Tetrahydroxyflavanone
4716	***N*-[*N*-[3-(3-HYDROXY-4-METHOXYPHENYL)PROPYL]-*L-ALPHA*-ASPARTYL]-*L*-PHENYLALANINE 1-METHYLESTER, MONOHYDRATE** Advantame
4717	**SWEET BLACKBERRY LEAVES EXTRACT** Chinese Blackberry Extract *Rubus suavissimus S. Lee*, ext. *Rubus chingii Hu*, ext. *Rubus palmatus Thunb.*, ext.
4718	**2-[2-(*P*-MENTHYLOXY)ETHOXY]ETHANOL** 2-[(2-*p*-Menthoxy)ethoxy]ethanol 2-[2-(2-Isopropyl-5-methyl-cyclohexyloxy)ethoxy]-ethanol 2-[2-(*p*-Menthan-3-yloxy)ethoxy]ethanol
4719	**SUCCINIC ACID** Butanedioic acid 1,2-Ethanedicarboxylic acid
4720	**REBAUDIOSIDE C** Dulcoside B
4721	**1-(2-HYDROXYPHENYL)-3-(PYRIDIN-4-YL)PROPAN-1-ONE**
4722	**1-(2-HYDROXY-4-ISOBUTOXYPHENYL)-3-(PYRIDIN-2-YL)PROPAN-1-ONE**
4723	**1-(2-HYDROXY-4-METHOXYPHENYL)-3-(PYRIDIN-2-YL)PROPAN-1-ONE**
4724	***TRANS*-4-TERT-BUTYLCYCLOHEXANOL** *trans*-1-tert-Butylcyclohexan-4-ol *trans-p*-tert-Butylcyclohexanol
4725	**3-(1-((3,5-DIMETHYLISOXAZOL-4-YL)METHYL)-1*H*-PYRAZOL-4-YL)-1-(3-HYDROXYBENZYL)-IMIDAZOLIDINE-2,4-DIONE** 2,4-Imidazolidinedione, 3-[1-[(3,5-dimethyl-4-isoxazolyl)-methyl]-1*H*-pyrazol-4-yl]-1-[(3-hydroxyphenyl)methyl]-
4726	**3-(1-((3,5-DIMETHYLISOXAZOL-4-YL)METHYL)-1*H*-PYRAZOL-4-YL)-1-(3-HYDROXYBENZYL)-5,5-DIMETHYLIMIDAZOLIDINE-2,4-DIONE** 2,4-Imidazolidinedione, 3-[1-[(3,5-dimethyl-4-isoxazolyl)methyl]-1*H*-pyrazol-4-yl]-1-[(3-hydroxyphenyl)methyl]-5,5-dimethyl-
4727	**CLOVER HERB DISTILLATE** Yellow sweet clover distillate Sweet clover distillate *Melilotus officinalis* distillate

TABLE 2 Average Usual Use Levels/Average Maximum Use Levels

Average Usual Use Levels (ppm)/Average Maximum Use Levels (ppm) for new FEMA GRAS Flavoring Substances on which the FEMA Expert Panel based its judgments that the substances are generally recognized as safe (GRAS)

	2-Hexyl-4-acetoxytetrahydrofuran	2-Methyl-5-vinylpyrazine	2(4)-Ethyl-4(2),6-dimethyldihydro-1,3,5-dithiazine (mixture of isomers)	(2*E*,6*E*/*Z*,8*E*)-*N*-(2-Methylpropyl)-2,6,8-decatrienamide	4-Amino-5,6-dimethylthieno[2,3-d]pyrimidin-2(1H)-one	1,1-Propanedithiol	*Z*-5-Octenyl acetate	(*E*)-4-Undecenal	*delta*-Hexadecalactone	Trilobatin
CATEGORY	FEMA NO. 2566	3211	4667	4668	4669	4670	4671	4672	4673	4674
Baked Goods	0.3/3	4/9	0.5/1		5/10	0.01/0.05	8/10	0.05/0.1	10/50	
Beverages (Non-alcoholic)	0.1/1	0.1/2		15/30	7.5/15		6/8	0.05/0.08	10/50	100/100
Beverages (Alcoholic)		1/3		12.5/30	7.5/15			0.08/0.1		
Breakfast Cereal			0.5/1	15/30	10/20	0.01/0.05	8/10	0.05/0.08	5/25	100/100
Cheese			0.5/1			0.01/0.05			2/10	
Chewing Gum				100/250	10/50		10/12	0.08/0.1		
Condiments/Relishes			0.5/1	5/15		0.01/0.05			2/10	
Confectionery Frostings				35/75	10/25			0.05/0.08	10/50	
Egg Products										
Fats/Oils			1/2			0.02/0.08	9/11	0.08/0.1	10/50	
Fish Products				5/15					2/10	
Frozen Dairy	0.3/3	2/5		12.5/25	7.5/15		8/10		10/50	
Fruit Ices				12.5/25	7.5/15		8/10	0.05/0.08	2/10	
Gelatins/Puddings		1/3		12.5/20	5/10		8/10	0.05/0.08		
Granulated Sugar							8/10			
Gravies			0.5/1			0.01/0.05			10/50	
Hard Candy				115/175	10/25		8/10	0.08/0.1	50/250	
Imitation Dairy			0.5/1		7.5/15	0.02/0.08			10/50	
Instant Coffee/Tea							8/10	0.05/0.08		
Jams/Jellies				12.5/25	10/25		8/10	0.05/0.08		
Meat Products			1/2			0.02/0.08		0.05/0.08	2/10	
Milk Products			0.5/1		7.5/15	0.01/0.05	8/10		10/50	250/750
Nut Products										
Other Grains										
Poultry			0.5/1			0.02/0.08		0.05/0.08	2/10	
Processed Fruits				2.5/10			8/10			
Processed Vegetables			0.5/1			0.01/0.05		0.05/0.08		
Reconstituted Vegetables										
Seasonings/Flavors			1/10	12.5/25	5/15	0.08/0.1	8/10	0.05/0.08	50/250	
Snack Foods			1/2	25/50	5/15	0.02/0.08			20/100	
Soft Candy	0.3/3	4/9		115/150	10/25		8/10	0.05/0.08		
Soups			0.5/1	7.5/15		0.01/0.05	8/10		5/25	
Sugar Substitutes					300/600					
Sweet Sauces					10/25		8/10	0.05/0.08		

	L-Isoleucine	1-(2-Furfurylthio)-propanone	(±)-4-Methyl-2-propyl-1,3-oxathiane	*N*-(2-Methylcyclohexyl)-2,3,4,5,6-pentafluorobenzamide	Arachidonic acid enriched oil	5-Isopropyl-2,6-diethyl-2-methyltetrahydro-2*H*-pyran	(1R,2S,5R)-*N*-(4-Methoxyphenyl)-5-methyl-2-(1-methylethyl)-cyclohexanecarboxamide	Octahydro-4,8*a*-dimethyl-4*a*(2*H*)-naphthol	2-Methyl-4,5-dihydrofuran-3-thiol	(2S,5R)-*N*-[4-(2-Amino-2-oxoethyl)phenyl]-5-methyl-2-(propan-2-yl)-cyclohexanecarboxamide
CATEGORY	**4675**	**4676**	**4677**	**4678**	**4679**	**4680**	**4681**	**4682**	**4683**	**4684**
Baked Goods	50/50	1/3	0.4/1	10/20	1/10	5/25	1/5	0.1/4		10/50
Beverages (Non-alcoholic)	200/250	1/2	0.4/1	1/5		1/10	1/5	1/5		
Beverages (Alcoholic)	50/50	1/2	0.2/1			4/20	1/10	1/5		
Breakfast Cereal	50/50		0.1/1			1/10	1/5	0.1/1		
Cheese					5/50			0.1/1		400/800
Chewing Gum			0.3/1	10/20		500/2,000	100/500	1/2.5		
Condiments/ Relishes					1/10			0.1/1		25/100
Confectionery Frostings		2/5	0.3/1	1/5		2/20	1/10	1/5		
Egg Products						2/20	1/10	0.1/1		
Fats/Oils						2/20	1/10	0.1/1		
Fish Products								0.1/1		
Frozen Dairy				1/5		20/100	5/20	0.1/1		
Fruit Ices			0.1/1	1/5		10/50	2/20	1/5		
Gelatins/Puddings				1/5		10/50	2/20	1/5		
Granulated Sugar						10/50	2/20	0.1/1		
Gravies		2/5	0.1/1		10/50			0.1/1		25/100
Hard Candy		1/2	0.1/1	1/5		10/50	2/20	1/3		
Imitation Dairy					1/10	5/10	1/5	0.1/1		
Instant Coffee/Tea		2/5		1/5		2/10	1/5	0.1/1		20/100
Jams/Jellies			0.1/1	5/10		10/50	2/20	1/3		
Meat Products	50/50	2/5	0.1/1		10/50			0.1/1	0.3/3	
Milk Products	50/50			1/5	1/10	2/10	1/5	0.1/1	0.05/0.2	
Nut Products								0.1/1		
Other Grains								0.1/1		
Poultry		0.1/1			10/100			0.1/1		
Processed Fruits			0.2/1	1/5		2/10	1/5	0.1/1		
Processed Vegetables			0.2/1					0.1/1		
Reconstituted vegetables								0.1/1		
Seasonings/ Flavors			0.2/1		10/50	10/50		1/3	0.2/1	
Snack Foods		1/3	0.2/1		10/50			0.1/1	3/10	20/100
Soft Candy			0.1/1	1/5		3/50	1/20	1/3		
Soups	50/50	1/2			10/50	4/50	1/20	0.1/1	0.3/2	
Sugar Substitutes						3/50	1/20	0.1/1		
Sweet Sauces				1/5				0.1/1		

TABLE 2 *CONTINUED*- Average Usual Use Levels/Average Maximum Use Levels

Average Usual Use Levels (ppm)/Average Maximum Use Levels (ppm) for new FEMA GRAS Flavoring Substances on which the FEMA Expert Panel based its judgments that the substances are generally recognized as safe (GRAS)

	(±)-6-Octyltetrahydro-2*H*-pyran-2-one	(±)-2-Methyltetrahydrofuran-3-thiol acetate	(±)-3-Hydroxy-3-methyl-2,4-nonanedione	1,1-Dipropoxyethane	Chrysanthemum extract	Honeysuckle extract	Yuzunone	*L*-Methionylglycine	*N*-Cyclopropyl-5-methyl-2-isopropylcyclohexanecarboxamide	3-Pentanethiol
CATEGORY	4685	4686	4687	4688	4689	4690	4691	4692	4693	4694
Baked Goods	0.5/5	0.1/0.5	5/20				0.06/0.6	50/1,000		0.01/0.1
Beverages (Non-alcoholic)	0.1/2	0.01/0.03	1/3	24/50		100/200	0.002/0.015		10/40	
Beverages (Alcoholic)		0.02/0.05	5/20				0.004/0.03			
Breakfast Cereal		0.01/0.03	2/10			100/200				
Cheese		0.1/0.2	5/20					50/1,000		
Chewing Gum		0.01/0.03	10/20		400/400	100/200	0.2/2		1,200/4,000	
Condiments/Relishes		0.01/0.03			50/200		0.01/0.03			0.01/0.1
Confectionery Frostings		0.01/0.03	1/5		50/200	100/200	0.1/0.3		20/100	
Egg Products		0.01/0.03								
Fats/Oils		0.01/0.03	5/30				1/5			
Fish Products		0.01/0.03								
Frozen Dairy		0.01/0.03	1/5			100/200	0.005/0.05			
Fruit Ices		0.01/0.03	1/3			100/200	0.003/0.02			
Gelatins/Puddings		0.02/0.05	1/3			100/200	0.006/0.05			
Granulated Sugar		0.01/0.03				100/200				
Gravies		0.01/0.03			20/40			50/1,000		0.01/0.1
Hard Candy		0.01/0.03	1/5		70/200	100/200	0.01/0.025		100/400	
Imitation Dairy	1/10	0.01/0.03	5/30					50/1,000		
Instant Coffee/Tea		0.01/0.03	1/3							
Jams/Jellies		0.02/0.05	1/3			100/200	0.01/0.025		10/30	
Meat Products		0.02/0.05	2/5							0.01/0.1
Milk Products	0.5/5	0.01/0.04	5/30			100/200	0.06/0.2	50/1,000		
Nut Products		0.01/0.03				100/200				
Other Grains		0.01/0.03								
Poultry		0.02/0.05				100/200				0.01/0.1
Processed Fruits		0.01/0.03								
Processed Vegetables		0.01/0.03						50/1,000		0.02/0.1
Reconstituted Vegetables		0.01/0.03								
Seasonings/Flavors		0.01/0.03	100/2,000		50/200			50/1,000		0.01/0.1
Snack Foods		0.01/0.03	5/20		50/200	100/200	0.006/0.12	50/1,000		0.01/0.1
Soft Candy		0.01/0.03	1/5		50/200	100/200	0.015/0.2		100/300	
Soups		0.01/0.03	1/10		50/200		0.003/0.02	50/1,000		0.01/0.1
Sugar Substitutes		0.01/0.03				100/200				
Sweet Sauces		0.02/0.05	1/10		50/200	100/200	0.03/0.12			

	2-Ethyl-2,5-dihydro-4-methylthiazole	1-(Methyldithio)-2-propanone	5-Methylfurfurylmercaptan	4-Mercapto-3-methyl-2-butanol	Ferrous *L*-lactate	*o-trans*-Coumaric acid	3-[(4-Amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]-2,2-dimethyl-*N*-propylpropanamide	2(3),5-Dimethyl-6,7-dihydro-5*H*-cyclopentapyrazine	Cinnamyl benzoate	*beta*-Naphthyl methyl ether
CATEGORY	4695	4696	4697	4698	4699	4700	4701	4702	4703	4704
Baked Goods		0.5/1		0.2/0.5		20/30	10/22	10/15	15.2/24.3	13/17
Beverages (Non-alcoholic)	0.1/0.5		0.005/0.05			10/30		10/15	3.63/7.13	4/8
Beverages (Alcoholic)	0.1/0.5					10/30		10/15	2/4	0.1/0.3
Breakfast Cereal						20/30	15/22	10/15		
Cheese					10/100			10/15		
Chewing Gum	0.2/0.5					20/50	30/300	10/15		9/14
Condiments/ Relishes		0.5/1		0.2/0.5	20/200		3/22	10/15		
Confectionery Frostings						10/30	10/22	10/15		
Egg Products					10/100					
Fats/Oils					10/100			20/25		
Fish Products					10/100					
Frozen Dairy	0.1/0.5					10/30	5/22	10/15	5/10	8/10
Fruit Ices	0.1/0.5					10/30	5/22	10/15		
Gelatins/Puddings	0.1/0.5					10/30	5/22	12/18	10/20	9/11
Granulated Sugar								10/15		
Gravies	0.1/0.5	0.5/1		0.2/0.5	20/200			15/20		
Hard Candy	0.1/0.5					10/30	15/75	20/25		3/3
Imitation Dairy								10/15		
Instant Coffee/Tea			0.005/0.05			10/30		10/15		
Jams/Jellies							10/22	10/15		
Meat Products		0.5/1		0.2/0.5	20/200				2/5	
Milk Products						5/20	3/22	10/15		
Nut Products								10/15		
Other Grains								10/15		
Poultry		0.5/1		0.2/0.5	20/200					
Processed Fruits										
Processed Vegetables		0.5/1		0.2/0.5						
Reconstituted Vegetables								10/15		
Seasonings/ Flavors	0.1/0.5	0.5/1		0.2/0.5	20/200			10/15		
Snack Foods		0.5/1		0.2/0.5	20/200			10/15		
Soft Candy						10/30	15/75	10/15	9/18	12/14
Soups	0.1/0.5	0.5/1		0.2/0.5	20/200	10/20		10/15		
Sugar Substitutes						10/30		10/15		
Sweet Sauces	0.1/0.5						10/22	10/15		

TABLE 2 *CONTINUED*- Average Usual Use Levels/Average Maximum Use Levels

Average Usual Use Levels (ppm)/Average Maximum Use Levels (ppm) for new FEMA GRAS Flavoring Substances on which the FEMA Expert Panel based its judgments that the substances are generally recognized as safe (GRAS)

	Rosemary oleoresin	9-Decen-2-one	1-(Methylthio)-3-octanone	3',7-Dihydroxy-4'-methoxyflavan	Glutamyl-valyl-glycine	*L*-Threonine	Luo han fruit concentrate	*L*-Alanyl-*L*-glutamine	Sucrose monopalmitate	Ethyl 2-mercapto-2-methyl-propionate
CATEGORY	4705	4706	4707	4708	4709	4710	4711	4712	4713	4714
Baked Goods	20/2,000		0.1/5	50/300		50/200	40/60	1,400/3,000	4/100	0.1/0.5
Beverages (Non-alcoholic)	20/2,000	5/25		50/500		50/200	40/60	60/600	0.2/50	0.1/0.5
Beverages (Alcoholic)	20/2,000	10/50		100/500		50/200	40/60	60/600	0.2/50	0.1/0.5
Breakfast Cereal				50/400		50/200	40/80	600/3,000	0.1/100	0.1/0.5
Cheese			0.1/5	50/400		50/200		1,400/3,000	0.1/100	
Chewing Gum		30/150		50/600		50/200		100/500	0.5/50	0.1/0.5
Condiments/ Relishes			0.1/5			50/200	5/40	2,000/5,000	5/100	
Confectionery Frostings		30/150		50/300		50/200	40/80	300/500	0.5/50	0.1/0.5
Egg Products			0.1/5			50/200		1,000/2,000	0.1/50	
Fats/Oils			0.1/5	50/300		50/200		200/600	0.1/50	
Fish Products				50/300		50/200		1,000/2,500	0.1/100	
Frozen Dairy		5/15		50/300	20/50	50/200	5/80	1,400/3,000	0.1/30	0.1/0.5
Fruit Ices		5/15		50/400		50/200	5/40	200/600	0.1/50	0.1/0.5
Gelatins/Puddings				50/300		50/200	40/80	200/500	0.1/50	
Granulated Sugar				50/400		50/200				
Gravies			0.1/5	50/500		50/200		1,400/3,000	0.1/50	0.1/0.5
Hard Candy				50/500		50/200	40/80	200/600	0.1/5	0.1/0.5
Imitation Dairy				50/500		50/200	5/40	1,400/3,000	0.5/5	
Instant Coffee/Tea				50/400		50/200		300/600	0.1/50	0.1/0.5
Jams/Jellies				50/500		50/200	10/40	300/500	0.1/100	0.1/0.5
Meat Products	20/2,000		0.1/5	50/300		50/200		1,400/3,000	0.1/100	
Milk Products		10/30		50/400	15/45	50/200	40/80	1,400/3,000	0.5/200	0.1/0.5
Nut Products						50/200	5/40	300/1,000	0.1/100	
Other Grains						50/200		300/2,000	0.1/50	
Poultry			0.1/5			50/200		1,000/2,000	0.1/50	
Processed Fruits		10/30				50/200	5/40	60/300	0.1/5	0.1/0.5
Processed Vegetables			0.1/5			50/200		300/500	0.1/50	
Reconstituted Vegetables			0.1/5			50/200		200/400	0.1/50	
Seasonings/ Flavors	20/2,000		0.1/5	50/600		50,000/100,000	5/40	20,000/250,000	0.1/50	0.1/0.5
Snack Foods		10/50	0.1/5	50/500	30/60	50/200	5/40	2,000/5,000	0.1/50	
Soft Candy				50/300		50/200	40/80	200/600	0.1/50	0.1/0.5
Soups			0.1/5	50/300	20/50	50/200		1,000/5,000	0.1/200	0.1/0.5
Sugar Substitutes				50/300		50/200		200/1,000	0.1/10	
Sweet Sauces				50/400		50/200	5/40	200/500	0.5/50	0.1/0.5

	2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-chromanon	*N*-[*N*-[3-(3-Hydroxy-4-methoxyphenyl) propyl]-*L*-alpha-aspartyl]-*L*-phenylalanine 1-methylester, monohydrate	Sweet blackberry leaves extract	2-[2-(*p*-Menthyloxy)-ethoxy] ethanol	Succinic acid	Rebaudioside C	1-(2-Hydroxyphenyl)-3-(pyridin-4-yl) propan-1-one	1-(2-Hydroxy-4-isobutoxyphenyl)-3-(pyridin-2-yl) propan-1-one	1-(2-Hydroxy-4-methoxyphenyl)-3-(pyridin-2-yl)-propan-1-one	*trans*-4-tert-Butyl-cyclohexanol
CATEGORY	4715	4716	4717	4718	4719	4720	4721	4722	4723	4724
Baked Goods	20/100				60/200			1/2	2/25	
Beverages (Non-alcoholic)	20/150	1/2	330/425	1/10	30/100	100/250	5/35			20/50
Beverages (Alcoholic)	20/100			1/10	60/200					20/50
Breakfast Cereal	20/100		330/425		60/200	200/400	5/35			
Cheese					60/200				5/25	
Chewing Gum	50/250	40/50	330/425	10/100	60/200	1,000/1,000				
Condiments/ Relishes				1/10	60/200			2/5	2/25	20/100
Confectionery Frostings	20/100			10/100	60/200					50/200
Egg Products					60/200					
Fats/Oils				0.5/5	60/200					20/100
Fish Products					60/200			2/5	2/2	
Frozen Dairy	20/100	0.9/1	330/425	1/10	60/200		5/30			
Fruit Ices			330/425	1/10	60/200					
Gelatins/Puddings	20/100			0.5/5	60/200					
Granulated Sugar					60/200					
Gravies				0.5/5	60/200			5/30	5/25	20/100
Hard Candy	20/100			1/10	60/200					20/100
Imitation Dairy	20/100				60/200				5/25	
Instant Coffee/Tea	20/100		330/425	0.1/1	60/200					20/50
Jams/Jellies				1/10	60/200	50/300				
Meat Products					60/200			5/20	5/25	20/100
Milk Products	20/100	0.9/1	330/425		60/200		5/35			
Nut Products					60/200					
Other Grains					60/200					
Poultry					60/200			5/20	5/5	
Processed Fruits					60/200					20/50
Processed Vegetables					60/200					
Reconstituted vegetables					60/200					
Seasonings/ Flavors	50/200			1,000/10,000	100/1,000			5/10	5/50	20/100
Snack Foods	20/100			1/10	60/200			5/10	5/25	20/100
Soft Candy				1/10	60/200					20/100
Soups	20/100			1/10	60/200			5/20		
Sugar Substitutes	20/100		330/425	0.05/0.5	100/1,000				5/25	20/100
Sweet Sauces	20/100			5/50	60/200					

TABLE 2 *CONTINUED*- Average Usual Use Levels/Average Maximum Use Levels

Average Usual Use Levels (ppm)/Average Maximum Use Levels (ppm) for new FEMA GRAS Flavoring Substances on which the FEMA Expert Panel based its judgments that the substances are generally recognized as safe (GRAS)

	3-(1-((3,5-Dimethylisoxazol-4-yl)methyl)-1*H*-pyrazol-4-yl)-1-(3-hydroxybenzyl)-imidazolidine-2,4-dione	3-(1-((3,5-Dimethylisoxazol-4-yl)-methyl)-1H-pyrazol-4-yl)-1-(3-hydroxybenzyl)-5,5-dimethylimidazolidine-2,4-dione	Clover herb distillate
CATEGORY	4725	4726	4727
Baked Goods			0.5/2
Beverages (Non-alcoholic)	2/10	2/10	0.3/0.8
Beverages (Alcoholic)			0.5/2
Breakfast Cereal	20/60	20/60	0.5/2
Cheese			
Chewing Gum	300/1,200	300/1,200	
Condiments/ Relishes	20/60	20/60	
Confectionery Frostings	20/60	20/60	0.5/2
Egg Products			
Fats/Oils			
Fish Products			
Frozen Dairy	20/60	20/60	0.4/2
Fruit Ices	20/60	20/60	
Gelatins/Puddings	20/60	20/60	0.4/2
Granulated Sugar			
Gravies			
Hard Candy	75/300	75/300	
Imitation Dairy	2/10	2/10	0.4/1.6
Instant Coffee/Tea	2/10	2/10	0.3/1
Jams/Jellies			0.4/1
Meat Products			
Milk Products	2/10	2/10	0.4/1.6
Nut Products			0.4/1.6
Other Grains			
Poultry			
Processed Fruits			
Processed Vegetables			
Reconstituted vegetables	20/60	20/60	
Seasonings/ Flavors	25/100	25/100	0.2/1
Snack Foods	20/60	20/60	0.5/2
Soft Candy	75/300	75/300	0.6/2
Soups	2/10	2/10	
Sugar Substitutes	2/20	2/20	
Sweet Sauces			0.3/0.8

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.

	Capiscum oleoresin	Sodium acetate	*L*-Glutamic acid	Glycine	Ethyl-2-isopropyl-5-methylcyclo-hexane-carboxamide
FEMA NO.	**2234**	**3024**	**3285**	**3287**	**3455**
GRAS PUBLICATION	**3**	**3**	**5**	**5**	**9**
CATEGORY					
Baked Goods	50/85	15/15	1,400[a]/3,000[a]	50/150	
Beverages(Non-alcoholic)	90/105	1.5/1.5	400/600[a]	250[a]/1,000	10/10
Beverages (Alcoholic)	800/900	1.5/1.5	60[a]/600[a]		10/10
Breakfast Cereal	25[a]/50[a]	0.01/60	600[a]/3,000[a]		
Cheese			1,400[a]/3,000[a]		
Chewing Gum	450[a]/500[a]		100[a]/500[a]		1,400[a]/2,000[a]
Condiments/Relishes	250/330		2,000[a]/5,000[a]	150/150	
Confectionery Frostings	20[a]/50[a]		300[a]/500[a]		10/10
Egg Products			1,000[a]/2,000[a]		
Fats/Oils	100[a]/125[a]	1/5	200[a]/600[a]		
Fish Products			1,000[a]/2,500[a]		
Frozen Dairy	25[a]/28[a]	15/15	1,400[a]/3,000		10/10
Fruit Ices		15/15	200[a]/600[a]		10/10
Gelatins/Puddings	18/20		200[a]/500[a]		10/10
Granulated Sugar					
Gravies	49/50[a]		1,400[a]/3,000[a]		
Hard Candy	100[a]/150[a]	200/200	200[a]/600[a]	25/150	100/150[a]
Imitation Dairy	15[a]/25[a]		1,400[a]/3,000[a]		
Instant Coffee/Tea	10[a]/15[a]		300[a]/600[a]		
Jams/Jellies	15[a]/25[a]	0.32/0.32	300[a]/500[a]	50/150	10/10
Meat Products	75/145	1,500[a]/2,500[a]	1,400[a]/3,000[a]	150/150	
Milk Products	15[a]/25[a]		1,400[a]/3,000[a]		
Nut Products	50[a]/100[a]	15,000[a]/ 30,000[a]	300[a]/1,000[a]		
Other Grains	25[a]/40[a]	6/6	300[a]/2,000[a]		
Poultry			1,000[a]/2,000[a]		
Processed Fruits	15[a]/50[a]		60[a]/300[a]		
Processed Vegetables	20[a]/25[a]		300[a]/500[a]		
Reconstituted Vegetables			200[a]/400[a]		
Seasonings/Flavors	100[a]/200[a]	1,500[a]/3,000[a]	20,000[a]/250,000[a]		
Snack Foods	50[a]/100[a]	15,000/30,000	2,000[a]/5,000[a]		66[a]/100[a]
Soft Candy	100[a]/200[a]	0.88/0.9	200[a]/600[a]	25/150	
Soups	25[a]/50[a]	0.1/0.5	1,000[a]/5,000[a]	150/150	
Sugar Substitutes			200[a]/1,000[a]		
Sweet Sauces	50[a]/75[a]		200[a]/500[a]		

TABLE 3 *CONTINUED*- 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.

	Vanillyl butyl ether	Neohesperidine dihydrochalcone	*L*-Alanine	*L*-Arginine	*L*-Lysine
FEMA NO.	**3796**	**3811**	**3818**	**3819**	**3847**
GRAS PUBLICATION	**16**	**17**	**18**	**18**	**18**
CATEGORY					
Baked Goods	5/20	5[a]/20[a]	75/375	1,400[a]/3,000[a]	1,400[a]/3,000[a]
Beverages(Non-alcoholic)	8[a]/20[a]	5/15[a]	400[a]/500[a]	60[a]/600[a]	60[a]/600[a]
Beverages (Alcoholic)	30[a]/80[a]	5/15[a]	50/150	60[a]/600[a]	60[a]/600[a]
Breakfast Cereal	60[a]/100[a]	8[a]/20[a]	50/150	600[a]/3,000[a]	600[a]/3,000[a]
Cheese	100[a]/200[a]	3/4	10/20	1,400[a]/3,000[a]	1,400[a]/3,000[a]
Chewing Gum	3,500[a]/4,200[a]	200/300[a]	5/10	100[a]/500[a]	100[a]/500[a]
Condiments/Relishes	40[a]/75[a]	2/3	20/100	2,000[a]/5,000[a]	2,000[a]/5,000[a]
Confectionery Frostings	70[a]/100[a]	3/3	25/100	300[a]/500[a]	300[a]/500[a]
Egg Products	5/10	2/3	50/250	1,000[a]/2,000[a]	1,000[a]/2,000[a]
Fats/Oils	200[a]/300[a]	4/4	10/30	200[a]/600[a]	200[a]/600[a]
Fish Products	200[a]/250[a]	2/3	50/250	1,000[a]/2,500[a]	1,000[a]/2,500[a]
Frozen Dairy	100[a]/150[a]	2/8[a]	60/200	1,400[a]/3,000[a]	1,400[a]/3,000[a]
Fruit Ices	35[a]/50[a]	2[a]/3[a]	10/20	200[a]/600[a]	200[a]/600[a]
Gelatins/Puddings	70[a]/100[a]	3/8[a]	50/150	200[a]/500[a]	200[a]/500[a]
Granulated Sugar	50[a]/100[a]		5/10	1/20	5/25
Gravies	10[a]/20[a]	3/4	200/1,000	1,400[a]/3,000[a]	1,400[a]/3,000[a]
Hard Candy	400[a]/700[a]	5/15	50/200	200[a]/600[a]	200[a]/600[a]
Imitation Dairy	90[a]/110[a]	3/10[a]	50/150	1,400[a]/3,000[a]	1,400[a]/3,000[a]
Instant Coffee/Tea	15[a]/30[a]	3[a]/6[a]	100/500	300[a]/600[a]	300[a]/600[a]
Jams/Jellies	35[a]/50[a]	2/3	5/10	300[a]/500[a]	300[a]/500[a]
Meat Products	10[a]/20[a]	2/3	100/500	1,400[a]/3,000[a]	1,400[a]/3,000[a]
Milk Products	25[a]/50[a]	3/10[a]	50/150	1,400[a]/3,000[a]	1,400[a]/3,000[a]
Nut Products	200[a]/500[a]	3/4	75/225	300[a]/1,000[a]	300[a]/1,000[a]
Other Grains	60[a]/100[a]	3/4	10/20	300[a]/2,000[a]	300[a]/2,000[a]
Poultry	100[a]/250[a]	2/3	100/500	1,000/2,000[a]	1,000[a]/2,000[a]
Processed Fruits	5[a]/25[a]	2/3	10/30	60[a]/300[a]	60[a]/300[a]
Processed Vegetables	5/25[a]	2/3	5/10	300[a]/500[a]	300[a]/500[a]
Reconstituted Vegetables	5/10	2/3	5/10	200[a]/400[a]	200[a]/400[a]
Seasonings/Flavors	10[a]/20[a]	3/4	2,000/4,000	20,000[a]/250,000[a]	20,000[a]/250,000[a]
Snack Foods	25[a]/65	3/3	100/200	2,000[a]/5,000[a]	2,000[a]/5,000[a]
Soft Candy	400[a]/500[a]	4[a]/10[a]	25/100	200[a]/600[a]	200[a]/600[a]
Soups	30[a]/45[a]	5/10	100/500	1,000[a]/5,000[a]	1,000[a]/5,000[a]
Sugar Substitutes	40[a]/55[a]	4/4	10/20	200[a]/1,000[a]	200[a]/1,000[a]
Sweet Sauces	65[a]/80[a]	2/3	25/100	200[a]/500[a]	200[a]/500[a]

	Sodium diacetate	*p*-Menthane-3,8-diol	*N*1-(2,4-Dimethoxybenzyl)-*N*2-(2-(pyridin-2-yl)ethyl)-oxalamide	*gamma*-Octadecalactone	*delta*-Octadecalactone
FEMA NO.	**3900**	**4053**	**4233**	**4446**	**4447**
GRAS PUBLICATION	**18**	**21**	**22**	**24**	**24**
CATEGORY					
Baked Goods		100[a]/120[a]	1/2	5/20[a]	0.5/10[a]
Beverages(Non-alcoholic)		48[a]/50[a]	1[a]/2[a]	1[a]/10[a]	0.1/1
Beverages (Alcoholic)		40[a]/50[a]			0.1/1
Breakfast Cereal		20[a]/50[a]	5[a]/10[a]		
Cheese		50[a]/75[a]	1/3	5/10	
Chewing Gum		1,500[a]/2,000[a]			0.5/3
Condiments/Relishes		50[a]/100[a]	2/4		
Confectionery Frostings		200[a]/350[a]			
Egg Products			1[a]/2[a]		
Fats/Oils		100[a]/500[a]	2/4	5/10	
Fish Products			1/3		
Frozen Dairy		5/25		5[a]/20[a]	0.1/10[a]
Fruit Ices		5/25			
Gelatins/Puddings		150[a]/200[a]			
Granulated Sugar		5[a]/25[a]			
Gravies		35[a]/40[a]	2/4		0.1/3
Hard Candy		500[a]/800[a]			
Imitation Dairy		75[a]/100[a]			
Instant Coffee/Tea		25[a]/50[a]			
Jams/Jellies		150[a]/175[a]			
Meat Products	1,500[a]/ 2,500[a]		1/3		
Milk Products		75[a]/100[a]		5/10	0.1/10[a]
Nut Products	15,000/30,000	15[a]/50	1[a]/2[a]		
Other Grains			1[a]/2[a]		
Poultry	1,500[a]/2,500[a]		1/3		
Processed Fruits		20[a]/150[a]			
Processed Vegetables		20[a]/75[a]	1/3		
Reconstituted Vegetables		20[a]/25[a]	1[a]/2[a]		
Seasonings/Flavors	15,000[a]/30,000[a]	15[a]/30[a]	5/10		
Snack Foods	15,000/30,000	15[a]/30[a]	5/10	5/20	2[a]/20[a]
Soft Candy		500[a]/750[a]			
Soups		15[a]/25[a]	2/4		0.1/1
Sugar Substitutes					
Sweet Sauces		25[a]/300[a]			

TABLE 4 Updated Average Usual Use Levels/Average Maximum Use Levels in Chewing Gum

Updated average usual use levels (ppm)/average maximum use levels (ppm) in chewing gum for flavoring substances previously recognized as FEMA GRAS

FEMA NO.	PRIMARY NAME	ANTICIPATED USUAL USE LEVEL (PPM)	ANTICIPATED MAXIMUM USE LEVEL (PPM)
2003	ACETALDEHYDE	70	1,000
2004	PROPYL PHENETHYL ACETAL	50	70
2005	ACETANISOLE	150	1,060
2006	ACETIC ACID	400	5,000
2008	ACETOIN	25	110
2011	ADIPIC ACID	500	4,040
2019	ALLSPICE OLEORESIN (*PIMENTA OFFICINALIS LINDL.* (MYRTACEAE))	5	10
2021	ALLYL BUTYRATE	5	10
2025	ALLYL CYCLOHEXANEHEXANOATE	20	25
2033	ALLYL *ALPHA*-IONONE	1	1
2038	ALLYL PHENOXYACETATE	5	10
2045	ALLYL ISOVALERATE	5	10
2050	AMBRETTE ABSOLUTE OIL (*HIBISCUS ABELMOSCHUS* L. (MALVACEAE))	1	5
2054	AMMONIUM ISOVALERATE	300	2,700
2061	*ALPHA*-AMYLCINNAMALDEHYDE	360	460
2067	*ALPHA*-AMYLCINNAMYL ISOVALERATE	1	2
2074	AMYL HEXANOATE	35	1,000
2080	ISOAMYL OCTANOATE	1	100
2081	ISOAMYL PHENYLACETATE	100	215
2084	ISOAMYL SALICYLATE	85	240
2086	*TRANS*-ANETHOLE	880	6,680
2087	ANGELICA ROOT EXTRACT (*ANGELICA ARCHANGELICA* L. (APIACEAE))	60	60
2093	ANISE (*PIMPINELLA ANISUM* L. (APIACEAE))	1	5
2096	ANISE, STAR, OIL (*ILLICIUM VERUM HOOK, F.* (APIACEAE))	80	470
2097	ANISOLE	1	5
2099	ANISYL ALCOHOL	1	50
2100	ANISYL BUTYRATE	3	5
2101	ANISYL FORMATE	25	70
2108	ASAFOETIDA OIL (*FERULA ASAFOETIDA* L. (UMBELLIFERAE))	10	20
2114	BALSAM FIR, OIL – *ABIES BALSAMEA* (L.) MILL.(PINACEAE))	5	25
2115	BALSAM FIR, OLEORESIN – *ABIES BALSAMEA* (L.) MILL. (PINACEAE)	2	2
2118	BASIL (*OCIMUM BASILICUM* L. (LAMIACEAE))	5	15
2125	BAY OIL, SWEET (*LAURUS NOBILIS* L. (LAURACEAE))	10	10
2130	BENZALDEHYDE PROPYLENE GLYCOL ACETAL	4	50
2134	BENZOPHENONE	115	500
2136	BENZYL ACETOACETATE	220	1,160
2141	BENZYL ISOBUTYRATE	10	15
2150	BENZYL PROPIONATE	90	150
2151	BENZYL SALICYLATE	5	30
2152	BENZYL ISOVALERATE	1	5
2160	ISOBORNYL ACETATE	100	100
2167	BORONIA ABSOLUTE (*BORONIA MEGASTIGMA NEES* (RUTACEAE))	2	9
2177	ISOBUTYL ACETOACETATE	55	180
2178	BUTYL ALCOHOL	160	400
2179	ISOBUTYL ALCOHOL	50	500
2185	ISOBUTYL BENZOATE	15	35
2187	ISOBUTYL BUTYRATE	3	100
2188	BUTYL ISOBUTYRATE	5	10
2189	ISOBUTYL ISOBUTYRATE	1	2,000
2190	BUTYL BUTYRYLLACTATE	25	50
2197	ISOBUTYL FORMATE	60	125
2201	BUTYL HEXANOATE	1	3
2205	BUTYL LACTATE	10	10
2206	BUTYL LAURATE	0.3	0.5
2208	*ALPHA*-ISOBUTYLPHENETHYL ALCOHOL	1	8
2213	ISOBUTYL SALICYLATE	45	50
2215	BUTYL SULFIDE	1	5
2216	BUTYL 10-UNDECENOATE	0.1	1
2217	BUTYL VALERATE	500	1,300
2219	BUTYRALDEHYDE	4	6
2220	ISOBUTYRALDEHYDE	40	200
2221	BUTYRIC ACID	50	300
2222	ISOBUTYRIC ACID	12	100
2223	(TRI-)BUTYRIN	250	250
2228	CALCIUM ACETATE	0.2	0.5
2229	CAMPHENE	5	400
2230	*D*-CAMPHOR	160	500
2231	CAMPHOR, JAPANESE, WHITE, OIL (*CINNAMOMUM CAMPHORA* (L.) NEES ET EBERM.)	2	7
2233	CAPSICUM EXTRACT *CAPSICUM FRUTESCENS* L. *CAPSICUM ANNUUM* L.	50	125
2248	4-CARVOMENTHENOL	150	1,500
2251	CARVYL PROPIONATE	25	60
2255	CASCARILLA BARK, OIL – *CROTON CASCARILLA* BENN. AND *C. ELUTERIA* BENN.	1	1
2256	CASSIA (*CINNAMOMUM CASSIA* BLUME)(LAURACEAE)	175	1,000
2257	CASSIA BARK EXTRACT (*CINNAMOMUM CASSIA BLUME* (LAURACEAE))	5	10
2268	CASSIA BARK, EXTRACT – *CINNAMOMUM CASSIA* BLUME	1	10
2269	CELERY SEED EXTRACT (*APIUM GRAVEOLENS* L. (APIACEAE))	1	1

FEMA NO.	PRIMARY NAME	ANTICIPATED USUAL USE LEVEL (PPM)	ANTICIPATED MAXIMUM USE LEVEL (PPM)
2270	CELERY SEED EXTRACT SOLID (*APIUM GRAVEOLENS* L. (APIACEAE))	1	1
2272	CHAMOMILE FLOWER, ENGLISH, OIL (*ANTHEMIS NOBILIS* L. (COMPOSITAE))	1	1
2287	CINNAMALDEHYDE ETHYLENE GLYCOL ACETAL	2	300
2288	CINNAMIC ACID	60	300
2289	CINNAMON [*CINNAMOMUM ZEYANICUM* NEES; C. *LOUREIRII* BLUME; C. CASSIA BLUME] – CEYLON CINNAMON; CHINESE CINNAMON; SAIGON CINNAMON	1,000	1,000
2293	CINNAMYL ACETATE	160	1,000
2298	CINNAMYL CINNAMATE	20	400
2299	CINNAMYL FORMATE	1	150
2305	CITRAL DIMETHYL ACETAL	0.1	0.5
2306	CITRIC ACID	10,000	25,400
2308	CITRONELLA OIL	10	30
2310	CITRONELLOXYACETALDEHYDE	5	15
2313	CITRONELLYL ISOBUTYRATE	25	115
2314	CITRONELLYL FORMATE	100	210
2315	CITRONELLYL PHENYLACETATE	25	45
2316	CITRONELLYL PROPIONATE	5	10
2320	CLARY (*SALVIA SCLAREA* L. (LAMIACEAE))	1	1
2321	CLARY OIL (*SALVIA SCLAREA* L. (LAMIACEAE))	3	10
2322	CLOVE BUD, EXTRACT – *EUGENIA CARYOPHYLLATA* THUNB. [*EUGENIA AROMATICA* (L.) BAILL.]	50	80
2324	CLOVE BUD, OLEORESIN – *EUGENIA CAROPHYLLATA* THUNB. [*EUGENIA AROMATICA* (L.) BAILL.]	95	155
2333	CORIANDER (*CORIANDRUM SATIVUM* L. (UMBELLIFERAE))	1	1
2337	*P*-CRESOL	1	3
2339	CUBEB OIL (*PIPER CUBEBA* L. F. (PIPERACEAE))	15	20
2340	CUMIN (*CUMINUM CYMINUM* L. (UMBELLIFERAE))	35	40
2346	CURRANT BUDS BLACK ABSOLUTE (*RIBES NIGRUM* L. (GROSSULARIACEAE))	5	20
2349	CYCLOHEXYL ACETATE	1	1
2351	CYCLOHEXYL BUTYRATE	5	50
2352	CYCLOHEXYL CINNAMATE	1	25
2353	CYCLOHEXYL FORMATE	3	5
2355	CYCLOHEXYL ISOVALERATE	120	400
2357	DANDELION, FLUID EXTRACT – *TARAXACUM OFFICINALE* WEBER; *T. ERYTHROSPERMUM* ANDRZ.	5	30
2358	DANDELION ROOT, EXTRACT SOLID – *TARAXACUM OFFICINALE* WEBER; *T. ERYTHROSPERMUM* ANDRZ.	1	5

FEMA NO.	PRIMARY NAME	ANTICIPATED USUAL USE LEVEL (PPM)	ANTICIPATED MAXIMUM USE LEVEL (PPM)
2360	*GAMMA*-DECALACTONE	50	225
2361	*DELTA*-DECALACTONE	15	100
2363	DECANAL DIMETHYL ACETAL	0.5	2
2366	2-DECENAL	5	10
2369	DECYL PROPIONATE	35	80
2374	DIETHYL MALATE	10	20
2376	DIETHYL SEBACATE	675	1,270
2377	DIETHYL SUCCINATE	350	2,950
2380	DIHYDROCARVYL ACETATE	50	500
2381	DIHYDROCOUMARIN	20	250
2382	DILL (*ANETHUM GRAVEOLENS* (APIACEAE))	1	10
2384	DILL SEED, INDIAN – *ANETHUM SOWA* ROXB. (*PEUCEDANUM GRAVEOLENS* BENTH. ET HOOK.; *A. GRAVEOLENS* L.)	1	10
2388	*ALPHA,ALPHA*-DIMETHYLBENZYL ISOBUTYRATE	30	500
2389	2,6-DIMETHYL-5-HEPTENAL	240	5,000
2394	*ALPHA,ALPHA*-DIMETHYLPHENETHYL BUTYRATE	10	500
2396	DIMETHYL SUCCINATE	50	300
2399	DITTANY OF CRETE (*ORIGANUM DICTAMNUS* L.)	10	42
2400	*GAMMA*-DODECALACTONE	40	100
2401	*DELTA*-DODECALACTONE	10	500
2407	ELEMI, GUM – *CANARIUM COMMUNE* L. OR C. *LUZONICUM* (MIQ.) A. GRAY	1	3
2408	ELEMI, OIL – *CANARIUM COMMUNE* L. OR C. *LUZONICUM* (MIQ.) A. GRAY	5	50
2412	ESTRAGON OIL (*ARTEMISIA DRACUNCULUS* L.(COMPOSITAE))	5	20
2413	*P*-ETHOXYBENZALDEHYDE	290	960
2415	ETHYL ACETOACETATE	170	1,500
2418	ETHYL ACRYLATE	100	500
2420	ETHYL P-ANISATE	3	10
2423	ETHYL BENZOYLACETATE	240	240
2426	2-ETHYLBUTYRALDEHYDE	1,000	5,000
2429	2-ETHYLBUTYRIC ACID	50	1,000
2431	ETHYL CYCLOHEXANEPROPIONATE	2	5
2432	ETHYL DECANOATE	35	600
2435	ETHYL 3(2-FURYL)PROPANOATE	1	5
2436	4-ETHYLGUAIACOL	5	15
2438	2-ETHYL-2-HEPTENAL	80	500
2442	ETHYL LEVULINATE	75	500
2448	ETHYL 2-NONYNOATE	5	10
2449	ETHYL OCTANOATE	30	500
2450	ETHYL OLEATE	1	10
2451	ETHYL PALMITATE	0.1	0.1
2452	ETHYL PHENYLACETATE	1	10
2453	ETHYL 4-PHENYLBUTYRATE	10	15

TABLE 4 *CONTINUED*- Updated Average Usual Use Levels/Average Maximum Use Levels in Chewing Gum

Updated average usual use levels (ppm)/average maximum use levels (ppm) in chewing gum for flavoring substances previously recognized as FEMA GRAS

FEMA NO.	PRIMARY NAME	ANTICIPATED USUAL USE LEVEL (PPM)	ANTICIPATED MAXIMUM USE LEVEL (PPM)
2455	ETHYL 3-PHENYLPROPIONATE	530	1,300
2458	ETHYL SALICYLATE	570	2,000
2459	ETHYL SORBATE	10	1,000
2460	ETHYL TIGLATE	40	250
2465	EUCALYPTOL	1,380	15,000
2474	ISOEUGENYL FORMATE	5	10
2475	EUGENYL METHYL ETHER	40	250
2476	ISOEUGENYL METHYL ETHER	150	190
2477	ISOEUGENYL PHENYLACETATE	1	1
2478	FARNESOL	1	500
2479	*D*-FENCHONE	10	100
2480	FENCHYL ALCOHOL	50	500
2481	FENNEL, COMMON(*FOENICULUM VULGARE* MILL. (APIACEAE))	5	10
2482	FENNEL, SWEET [*FOENICULUM VULGARE* MILL. VAR. *DULCE* (DC.) ALEF.] – FINOCHIO; FLORENCE FENNEL	15	20
2484	FENUGREEK (*TRIGONELLA FOENUM-GRAECUM* L. (FABACEAE))	226	500
2486	FENUGREEK OLEORESIN (*TRIGONELLA FOENUMGRAECUM* L. (FABACEAE))	300	600
2487	FORMIC ACID	450	650
2488	FUMARIC ACID	2,100	6,350
2490	FURFURYL ACETATE	95	375
2491	FURFURYL ALCOHOL	40	60
2492	2-FURFURYLIDENE BUTYRALDEHYDE	1	5
2493	FURFURYL MERCAPTAN	5	10
2501	GALBANUM, OIL – *FERULA GALBANIFLUA* BOISS. ET BUHSE AND OTHER *FERULA* SPP.	1	1
2505	GENET, EXTRACT [*SPARTIUM JUNCEUM* L.]-BROOM, EXTRACT	1	10
2506	GENTIAN ROOT EXTRACT (*GENTIANA LUTEA* L. (GENTIANACEAE))	10	70
2513	GERANYL ISOBUTYRATE	5	10
2515	GERANYL HEXANOATE	5	10
2522	GINGER OIL	35	190
2523	GINGER OLEORESIN (*ZINGIBER OFFICINALE* ROSC. (ZINGIBERACEAE))	10	25
2529	GRAINS OF PARADISE (*AFRAMOMUM MELEGUETA* (ROSC.) K. SCHUM. (ZINGIBERACEAE))	760	765
2531	GUAIAC GUM, EXTRACT – *GUAIACUM OFFICINALE* L.; G. *SANCTUM* L.	1	1
2533	GUAIAC WOOD, EXTRACT – *GUAIACUM OFFICINALE* L.; *G. SANCTUM* L.; *BULNESIA SARMIENTI* LORENTZ	10	120
2538	HAW BARK BLACK EXTRACT (*VIBURNUM PRUNIFOLIUM* L.(CAPRIFOLIACEAE))	1	1
2539	*GAMMA*-HEPTALACTONE	1	5
2543	2,3-HEPTANEDIONE	2	5
2556	*GAMMA*-HEXALACTONE	50	400
2557	HEXANAL	15	1,000
2558	2,3-HEXANEDIONE	140	420
2559	HEXANOIC ACID	100	1,000
2560	HEXEN-2-AL	65	1,000
2561	*CIS*-3-HEXENAL	5	100
2564	2-HEXEN-1-YL ACETATE (E)	100	1,000
2565	HEXYL ACETATE	150	1,300
2568	HEXYL BUTYRATE	100	5,000
2569	*ALPHA*-HEXYLCINNAMALDEHYDE	5	10
2571	HEXYL 2-FUROATE	90	235
2572	HEXYL HEXANOATE	320	500
2575	HEXYL OCTANOATE	0.5	1
2576	HEXYL PROPIONATE	1	2
2582	HORSEMINT LEAVES, EXTRACT – *MONARDA* SPP.	10	43
2584	HYDROXYCITRONELLAL DIETHYL ACETAL	1	5
2586	HYDROXYCITRONELLOL	25	50
2587	5-HYDROXY-4-OCTANONE	30	500
2593	INDOLE	40	350
2597	*ALPHA*-IRONE	2	5
2601	JASMINE SPIRITUS (*JASMINUM GRANDIFLORUM* L.(OLEACEAE))	1	9
2604	JUNIPER OIL (*JUNIPERUS COMMUNIS* L. (CUPRESSACEAE))	1	1
2607	KOLA NUT, EXTRACT – *COLA ACUMINATA* SCHOTT ET ENDL.	7	50
2611	LACTIC ACID	290	2,160
2614	LAURIC ACID	2	5
2616	LAURYL ACETATE	50	100
2622	LAVENDER, OIL – *LAVANDULA OFFICINALIS* CHAIX	3	5
2630	LICORICE ROOT (*GLYCYRRHIZA GLABRA* L. (LEGUMINOSAE))	30	3,000
2640	LINALYL ISOBUTYRATE	5	100
2645	LINALYL PROPIONATE	20	100
2646	LINALYL ISOVALERATE	1	100
2649	LOVAGE (*LEVISTICUM OFFICINALE* KOCH (UMBELLIFERAE))	5	32
2650	LOVAGE EXTRACT (*LEVISTICUM OFFICINALE* KOCH (UMBELLIFERAE))	10	100
2652	MACE (*MYRISTICA FRAGRANS* HOUTT. (MYRISTICACEAE))	2	9
2655	*L*-MALIC ACID	6,000	25,000
2660	MARJORAM, POT – *ORIGANUM VULGARE* L.	70	70
2666	(+)-NEOISOMENTHOL	500	2,000
2667	MENTHONE	1,000	6,000
2668	MENTHYL ACETATE (ISOMER UNSPECIFIED)	500	2,000
2671	2-METHOXY-4-METHYLPHENOL	15	25

FEMA No.	PRIMARY NAME	ANTICIPATED USUAL USE LEVEL (PPM)	ANTICIPATED MAXIMUM USE LEVEL (PPM)
2672	4-(*P*-METHOXYPHENYL)-2-BUTANONE	50	500
2673	1-(*P*-METHOXYPHENYL)-1-PENTEN-3-ONE	1	2
2675	2-METHOXY-4-VINYLPHENOL	2	5
2676	METHYL ACETATE	2	100
2680	*O*-METHYLANISOLE	45	55
2688	*ALPHA*-METHYLBENZYL FORMATE	2	5
2690	METHYL *P-TERT*-BUTYLPHENYLACETATE	10	25
2692	3-METHYLBUTYRALDEHYDE	760	5,000
2695	2-METHYLBUTYRIC ACID	100	2,000
2698	METHYL CINNAMATE	100	780
2699	6-METHYLCOUMARIN	100	300
2700	METHYLCYCLOPENTENOLONE	690	3,560
2701	4-(3,4-METHYLENEDIOXYPHENYL)-2-BUTANONE	70	480
2702	5-METHYLFURFURAL	20	500
2703	METHYL 2-FUROATE	25	155
2704	2-METHYL-3(2-FURYL)ACROLEIN	15	500
2706	2-METHYLHEPTANOIC ACID	12	100
2708	METHYL HEXANOATE	105	1,000
2717	METHYL *O*-METHOXYBENZOATE	1	10
2725	METHYL 2-NONENOATE	25	1,000
2726	METHYL 2-NONYNOATE	375	1,000
2727	2-METHYLOCTANAL	150	300
2728	METHYL OCTANOATE	0.1	0.2
2731	4-METHYL-2-PENTANONE	5	10
2734	3-METHYL-4-PHENYL-3-BUTENE-2-ONE	900	6,650
2735	2-METHYL-4-PHENYL-2-BUTYL ACETATE	500	1,000
2740	4-METHYL-1-PHENYL-2-PENTANONE	475	1,300
2741	METHYL 3-PHENYLPROPIONATE	50	250
2747	3-(METHYLTHIO)PROPIONALDEHYDE	1	5
2750	METHYL 9-UNDECENOATE	1,800	5,500
2751	METHYL 2-UNDECYNOATE	5	10
2752	METHYL VALERATE	250	500
2754	2-METHYLVALERIC ACID	2	500
2755	MIMOSA ABSOLUTE (*ACACIA DECURRENS* WILLD. VAR. *DEALBATA* (LEGUMINOSAE))	1	3
2757	MOUNTAIN MAPLE EXTRACT SOLID (*ACER SPICATUM* LAM. (ACERACEAE))	100	165
2759	MUSK TONQUIN (*MOSCHUS MOSCHIFERUS* L. (MOSCHIDAE))	60	230
2763	MYRISTALDEHYDE	0.5	1
2764	MYRISTIC ACID	6	10
2769	NARINGEN EXTRACT (*CITRUS PARADISI* MACF. (RUTACEAE))	2	10

FEMA No.	PRIMARY NAME	ANTICIPATED USUAL USE LEVEL (PPM)	ANTICIPATED MAXIMUM USE LEVEL (PPM)
2772	NEROLIDOL (ISOMER UNSPECIFIED)	1	100
2773	NERYL ACETATE	35	500
2774	NERYL BUTYRATE	5	10
2775	NERYL ISOBUTYRATE	5	10
2776	NERYL FORMATE	15	30
2778	NERYL ISOVALERATE	41	45
2780	2,6-NONADIEN-1-OL	5	20
2783	1,3-NONANEDIOL ACETATE (MIXED ESTERS)	1	5
2785	2-NONANONE	16	20
2791	NONYL ISOVALERATE	1	2
2792	NUTMEG (*MYRISTICA FRAGRANS* HOUTT. (MYRISTICACEAE))	20	20
2794	OAK CHIPS EXTRACT (*QUERCUS ALBA* L. (FAGACEAE))	115	200
2795	OAK MOSS, ABSOLUTE – *EVERNIA PRUNASTRI* (L.) ACH., *E. FURFURACEA* (L.) MANN, AND OTHER LICHENS	1	1
2801	2-OCTANOL	10	100
2803	3-OCTANONE	5	10
2808	OCTYL ISOBUTYRATE	150	300
2810	OCTYL HEPTANOATE	1	3
2815	OLEIC ACID	1	100
2816	OLIBANUM, OIL [*BOSWELLIA CARTERI* BIRDW. AND OTHER *BOSWELLIA* SPP.]-FRANKINCENSE	6	30
2819	ORANGE FLOWERS (*CITRUS AURANTIUM* L. (RUTACEAE))	50	135
2831	PALMAROSA, OIL – *CYMBOPOGON MARTINI* (ROXB.) STAPF	8	11
2832	PALMITIC ACID	1	1
2833	PAPRIKA (*CAPSICUM ANNUUM* L. (SOLANACEAE))	50	500
2834	PAPRIKA OLEORESIN (*CAPSICUM ANNUUM* L. (SOLANACEAE))	2	800
2835	PARSLEY – *PETROSELINUM CRISPUM* (MILLER) NYMAN (*P. SATIVUM* HOFFM.)	2	100
2840	*OMEGA*-PENTADECALACTONE	1	5
2842	2-PENTANONE	15	15
2843	4-PENTENOIC ACID	9	27
2845	PEPPER, BLACK, OIL (*PIPER NIGRUM* L.(PIPERACEAE))	1	50
2846	PEPPER, BLACK, OLEORESIN (*PIPER NIGRUM* L.(PIPERACEAE))	50	410
2853	PETITGRAIN, LEMON, OIL (*CITRUS LIMON* L. BURM. F (RUTACEAE))	20	30
2854	PETITGRAIN MANDARIN OIL (*CITRUS RETICULATA BLANCO* VAR. MANDARIN (RUTACEAE))	1	1
2857	PHENETHYL ACETATE	10	30
2859	PHENYLETHYL ANTHRANILATE	5	10
2860	PHENETHYL BENZOATE	45	90

TABLE 4 *CONTINUED*- Updated Average Usual Use Levels/Average Maximum Use Levels in Chewing Gum

Updated average usual use levels (ppm)/average maximum use levels (ppm) in chewing gum for flavoring substances previously recognized as FEMA GRAS

FEMA NO.	PRIMARY NAME	ANTICIPATED USUAL USE LEVEL (PPM)	ANTICIPATED MAXIMUM USE LEVEL (PPM)
2861	PHENETHYL BUTYRATE	40	95
2863	PHENETHYL CINNAMATE	1	5
2870	PHENETHYL TIGLATE	10	10
2873	2-PHENOXYETHYL ISOBUTYRATE	15	30
2876	PHENYLACETALDEHYDE DIMETHYL ACETAL	1	2
2878	PHENYLACETIC ACID	10	150
2880	4-PHENYL-3-BUTEN-2-OL	1	2
2881	4-PHENYL-3-BUTEN-2-ONE	15	30
2883	1-PHENYL-3-METHYL-3-PENTANOL	15	100
2886	2-PHENYLPROPIONALDEHYDE	1	5
2894	3-PHENYLPROPYL CINNAMATE	20	250
2895	3-PHENYLPROPYL FORMATE	1,060	7,220
2896	3-PHENYLPROPYL HEXANOATE	2,450	2,460
2897	3-PHENYLPROPYL PROPIONATE	1	50
2899	3-PHENYLPROPYL ISOVALERATE	675	5,850
2902	*ALPHA*-PINENE	175	1,300
2904	PINE NEEDLE, DWARF, OIL [*PINUS MUGO* TURRE VAR. *PUMILIO* (HAENKE) ZENARI]—PINUS PUMILIO, OIL; PINE, MOUNTAIN, OIL	1	1
2905	PINE NEEDLE, OIL [*ABIES SIBIRICA* LEDEB.; *A. ALBA* MILL.; *A. SACHALINENSIS* MASTERS; *A. MAYRIANA* MIYABE AND KUDO]—SIBERIAN FIR, OIL	100	270
2910	*D*-PIPERITONE	40	350
2911	PIPERONAL	60	875
2912	PIPERONYL ACETATE	10	25
2913	PIPERONYL ISOBUTYRATE	1	200
2921	POTASSIUM SORBATE	10	20
2922	PROPENYLGUAETHOL	6,070	16,250
2923	PROPIONALDEHYDE	250	600
2924	PROPIONIC ACID	100	300
2926	ISOPROPYL ACETATE	180	310
2928	PROPYL ALCOHOL	160	200
2929	ISOPROPYL ALCOHOL	30	600
2930	*P*-PROPYLANISOLE	225	393
2931	PROPYL BENZOATE	10	35
2933	*P*-ISOPROPYLBENZYL ALCOHOL	1	35
2934	PROPYL BUTYRATE	3	6
2935	ISOPROPYL BUTYRATE	5	50
2937	ISOPROPYL ISOBUTYRATE	5	50
2939	ISOPROPYL CINNAMATE	20	30
2943	PROPYL FORMATE	1	2
2949	PROPYL HEXANOATE	15	25
2960	PROPYL ISOVALERATE	1	2
2961	ISOPROPYL ISOVALERATE	35	35
2962	ISOPULEGOL	1,000	1,000
2963	PULEGONE	75	350
2964	ISOPULEGONE	20	100
2965	ISOPULEGYL ACETATE	50	500
2968	PYROLIGNEOUS ACID, EXTRACT	0.005	0.01
2970	PYRUVIC ACID	10	30
2984	RHODINYL FORMATE	65	500
2990	ROSE HIPS, EXTRACT [*ROSA CANINA* L.; *R. GALLICA* L.; *R. CONDITA* SCOP.; *R. RUGOSA* THUNB.; AND OTHER *ROSA* SPP.] – HIPBERRIES, EXTRACT	1	1
2992	ROSEMARY OIL (*ROSEMARINUS OFFICINALIS* L. (LAMIACEAE))	1	100
2993	ROSE WATER, STRONGER – *ROSA CENTIFOLIA* L.	1	1
2995	RUE OIL (*RUTA GRAVEOLENS* L. (RUTACEAE))	1	1
2998	SAFFRON (*CROCUS SATIVUS* L. (IRIDACEAE))	50	55
2999	SAFFRON EXTRACT (*CROCUS SATIVUS* L. (IRIDACEAE))	1	1
3000	SAGE (*SALVIA OFFICINALIS* L. (LAMIACEAE))	10	350
3001	SAGE OIL (*SALVIA OFFICINALIS* L.(LAMIACEAE))	3	350
3002	SAGE OLEORESIN (*SALVIA OFFICINALIS* L.(LAMIACEAE))	10	350
3003	SAGE, SPANISH, OIL – *SALVIA LAVANDULAEFOLIA* VAHL.	6	50
3014	SAVORY, SUMMER, OLEORESIN (*SATUREJA HORTENSIS* L.)	430	990
3015	SAVORY, WINTER (*SATUREJA MONTANA* L.(LAMIACEAE))	1	30
3016	SAVORY WINTER OIL (*SATUREJA MONTANA* L.(LAMIACEAE))	1	30
3017	SAVORY, WINTER, OLEORESIN (*SATUREJA MONTANA* L.(LAMIACEAE))	2	10
3025	SODIUM BENZOATE	10	20
3026	SODIUM CITRATE	100	1,000
3030	SPEARMINT (*MENTHA SPICATA* L.(LAMIACEAE))	6,900	13,500
3031	SPEARMINT EXTRACT (*MENTHA SPICATA* L.(LAMIACEAE))	525	525
3035	STEARIC ACID	20	35
3037	STYRAX, EXTRACT – *LIQUIDAMBER ORIENTALIS* MILL.; *L. STYRACIFLUA* L.	10	150
3043	TARRAGON (*ARTEMISIA DRACUNCULUS* L.(ASTERACEAE))	1	100
3044	TARTARIC ACID (*D*-, *L*-, *DL*-, MESO-)	500	5,000
3055	TETRAHYDROFURFURYL ACETATE	10	15
3056	TETRAHYDROFURFURYL ALCOHOL	5	10
3058	TETRAHYDROFURFURYL PROPIONATE	5	10
3059	3,4,5,6-TETRAHYDROPSEUDOIONONE	5	10
3065	THYME, WHITE, OIL (*THYMUS VULGARIS* L.(LAMIACEAE))	1	50

FEMA NO.	PRIMARY NAME	ANTICIPATED USUAL USE LEVEL (PPM)	ANTICIPATED MAXIMUM USE LEVEL (PPM)
3066	THYMOL	5	2,500
3083	TRIETHYL CITRATE	225	950
3092	UNDECANAL	1	4
3093	2-UNDECANONE	20	35
3095	10-UNDECENAL	1,000	2,500
3097	UNDECYL ALCOHOL	100	1,000
3099	VALERIAN ROOT EXTRACT (*VALERIANA OFFICINALIS* L. (VALERIANACEAE))	2	250
3103	*GAMMA*-VALEROLACTONE	1	5
3106	VANILLA, OLEORESIN – *VANILLA PLANIFOLIA* ANDREWS OR *V. TAHITENSIS* J.W. MOORE	170	225
3109	VERATRALDEHYDE	30	30
3111	WALNUT HULL, EXTRACT – *JUGLANS NIGRA* L. OR *J. REGIA* L.	50	240
3124	ZINGERONE	170	500
3135	2-*TRANS*,4-*TRANS*-DECADIENAL	5	10
3136	2,3-DIETHYLPYRAZINE	100	185
3142	3,7-DIMETHYL-6-OCTENOIC ACID	710	2,200
3144	P,*ALPHA*-DIMETHYLSTYRENE	160	485
3148	ETHYL *TRANS*-2,*CIS*-4-DECADIENOATE	20	1,000
3151	2-ETHYL-1-HEXANOL	750	4,400
3152	3-ETHYL-2-HYDROXY-2-CYCLOPENTEN-1-ONE	2,700	7,500
3154	2-ETHYL-5-METHYLPYRAZINE	30	65
3159	FURFURYL METHYL ETHER	1	5
3161	FURFURYL ISOPROPYL SULFIDE	40	75
3162	FURFURYL THIOACETATE	10	50
3163	2-FURYL METHYL KETONE	1,600	4,770
3165	*TRANS*-2-HEPTENAL	5	10
3166	NOOTKATONE	15	50
3169	*TRANS*-2-HEXENOIC ACID	35	100
3170	3-HEXENOIC ACID	1.5	3
3171	*CIS*-3-HEXEN-1-YL ACETATE	100	10,000
3173	1-HYDROXY-2-BUTANONE	100	600
3174	4-HYDROXY-2,5-DIMETHYL-3(2*H*)-FURANONE	100	1,000
3175	*GAMMA*-IONONE	1	5
3176	*P*-MENTHAN-2-ONE	5,000	9,800
3177	*P*-MENTHA-8-THIOL-3-ONE	1	5
3180	2-MERCAPTOPROPIONIC ACID	1	5
3181	*O*-METHOXYCINNAMALDEHYDE	5	50
3183	2,5 OR 6-METHOXY-3-METHYLPYRAZINE (MIXTURE OF ISOMERS)	1	1
3189	2-METHYL-3-,5 OR 6-(FURFURYLTHIO)PYRAZINE (MIXTURE OF ISOMERS)	5	10
3190	5-METHYL-2,3-HEXANEDIONE	5	10
3191	2-METHYLHEXANOIC ACID	500	5,000

FEMA NO.	PRIMARY NAME	ANTICIPATED USUAL USE LEVEL (PPM)	ANTICIPATED MAXIMUM USE LEVEL (PPM)
3194	2-METHYL-2-PENTENAL	1	100
3195	2-METHYL-2-PENTENOIC ACID	2,500	10,000
3196	3-METHYL-2-(2-PENTENYL)-2-CYCLOPENTEN-1-ONE	200	500
3199	5-METHYL-2-PHENYL-2-HEXENAL	1	5
3200	4-METHYL-2-PHENYL-2-PENTENAL	1,300	2,575
3201	METHYL PROPYL DISULFIDE	100	300
3202	METHYL 2-PYRROLYL KETONE	1	1
3204	4-METHYL-5-THIAZOLEETHANOL	1	2
3208	(METHYLTHIO)METHYLPYRAZINE (MIXTURE OF ISOMERS)	10	15
3209	5-METHYL-2-THIOPHENECARBOXALDEHYDE	50	100
3212	2,4-NONADIENAL	5	10
3213	2-NONENAL	1,000	5,000
3214	*DELTA*-OCTALACTONE	10	500
3215	2-OCTENAL	500	5,000
3217	2,4-PENTADIENAL	415	1,200
3218	2-PENTENAL	10	15
3223	PHENOL	1	10
3224	2-PHENYL-2-BUTENAL	1	4
3226	1-PHENYL-1,2-PROPANEDIONE	1	5
3235	4,5,6,7-TETRAHYDRO-3,6-DIMETHYLBENZOFURAN	200	1,000
3236	TETRAHYDRO-4-METHYL-2-(2-METHYLPROPEN-1-YL)PYRAN	5	10
3237	2,3,5,6-TETRAMETHYLPYRAZINE	1	1
3238	2,2'-(THIODIMETHYLENE)-DIFURAN	1	5
3239	4-THUJANOL	20	1,000
3242	*P-ALPHA,ALPHA*-TRIMETHYLBENZYL ALCOHOL	190	1,300
3243	1-(2,6,6-TRIMETHYL-1-CYCLOHEXEN-1-YL)-2-BUTEN-1-ONE	10	100
3244	2,3,5-TRIMETHYLPYRAZINE	1	5
3247	10-UNDECENOIC ACID	1.5	3
3249	2,6-XYLENOL	2	5
3251	2-ACETYLPYRIDINE	1	1
3268	3,4-DIMETHYL-1,2-CYCLOPENTADIONE	15	30
3269	3,5-DIMETHYL-1,2-CYCLOPENTADIONE	10	15
3271	2,3-DIMETHYLPYRAZINE	1	1
3275	DIMETHYL TRISULFIDE	2	5
3286	GLYCERYL TRIPROPANOATE	1	5
3289	4-HEPTENAL	0.1	1
3291	4-HYDROXYBUTANOIC ACID LACTONE	60	270
3293	4-HYDROXY-3-PENTENOIC ACID LACTONE	1	5
3294	5-HYDROXYUNDECANOIC ACID LACTONE	25	500
3303	2-METHYL-1-BUTANETHIOL	3	5

TABLE 4 *CONTINUED*- Updated Average Usual Use Levels/Average Maximum Use Levels in Chewing Gum

Updated average usual use levels (ppm)/average maximum use levels (ppm) in chewing gum for flavoring substances previously recognized as FEMA GRAS

FEMA NO.	PRIMARY NAME	ANTICIPATED USUAL USE LEVEL (PPM)	ANTICIPATED MAXIMUM USE LEVEL (PPM)
3305	1-METHYL-2,3-CYCLOHEXADIONE	5	15
3306	5*H*-5-METHYL-6,7-DIHYDROCYCLOPENTA(B)PYRAZINE	80	100
3309	2-METHYLPYRAZINE	30	65
3310	METHYL THIOBUTYRATE	10	20
3311	METHYL 2-THIOFUROATE	10	50
3312	3-METHYLTHIOPROPYL ISOTHIOCYANATE	160	860
3316	2-PENTANOL	1,500	2,000
3317	2-PENTYLFURAN	1	5
3322	THIAMINE HYDROCHLORIDE	5	15
3324	3,5,5-TRIMETHYL-1-HEXANOL	1	100
3327	2-ACETYL-3,5(AND 6)-DIMETHYLPYRAZINE	1	1
3328	2-ACETYLTHIAZOLE	1	1
3331	BISABOLENE	40	40
3336	2,3-DIETHYL-5-METHYLPYRAZINE	10	15
3343	ETHYL 3-METHYLTHIOPROPIONATE	35	200
3347	FURFURYL THIOPROPIONATE	10	50
3353	*CIS*-3-HEXENYL FORMATE	3,500	7,000
3356	HYDROXYNONANOIC ACID, *DELTA*-LACTONE	75	200
3357	2-KETO-4-BUTANETHIOL	10	10
3359	2-METHYLBUTYL 2-METHYLBUTYRATE	15	2,000
3369	2-METHYLPROPYL 3-METHYLBUTYRATE	15	1,000
3376	4-(METHYLTHIO)-4-METHYL-2-PENTANONE	1	5
3377	NONA-2-*TRANS*-6-*CIS*-DIENAL	5	50
3378	2,6-NONADIENAL DIETHYL ACETAL	0.1	0.5
3380	9,12-OCTADECADIENOIC ACID (48%) AND 9,12,15-OCTADECATRIENOIC ACID (52%)	1	100
3382	1-PENTEN-3-ONE	5	10
3389	2,6,6-TRIMETHYLCYCLOHEXA-1,3-DIENYL METHANAL	5	5
3390	1,3,3-TRIMETHYL-2-NORBORNANYL ACETATE	80	500
3393	*N*-BUTYL 2-METHYLBUTYRATE	1	50
3394	3-ETHYLPYRIDINE	1	1
3397	*ALPHA*-FURFURYL PENTANOATE	30	40
3402	*CIS*-3-HEXENYL BUTYRATE	32	2,000
3403	*CIS*-3-HEXENYL HEXANOATE	1	100
3406	2-ISOPROPYL-5-METHYL-2-HEXENAL	550	1,700
3408	METHYL DIHYDROJASMONATE	35	180
3410	METHYL JASMONATE	1	50
3411	METHYL LINOLEATE (48%)/METHYL LINOLENATE (52%) MIXTURE	1	10
3415	3-(METHYLTHIO)PROPANOL	1	5
3417	3-PENTEN-2-ONE	5	10
3420	1-(2,6,6-TRIMETHYLCYCLOHEXA-1,3-DIENYL)-2-BUTEN-1-ONE	100	300
3421	2,6,6-TRIMETHYLCYCLOHEX-2-ENE-1,4-DIONE	1	5
3422	2,4-UNDECADIENAL	15	15
3424	3-ACETYLPYRIDINE	1	1
3427	2,4-DIMETHYLBENZALDEHYDE	1	2
3428	ETHYL 3-HYDROXYBUTYRATE	350	4,000
3433	2-METHOXY-3-(1-METHYLPROPYL)PYRAZINE	1	2
3435	1-METHYL-1-CYCLOPENTEN-3-ONE	75	75
3438	3-(METHYLTHIO)-1-HEXANOL	1	5
3442	2,6,10-TRIMETHYL-2,6,10-PENTADECATRIEN-14-ONE	5	50
3443	VALENCENE	20	1,000
3448	DICYCLOHEXYL DISULFIDE	1	5
3450	2,5-DIMETHYL-2,5-DIHYDROXY-1,4-DITHIANE	5	10
3454	5-ETHYL-2-HYDROXY-3-METHYLCYCLOPENT-2-EN-1-ONE	50	100
3457	HEXYL PHENYLACETATE	3	3
3459	2-HYDROXY-3,5,5-TRIMETHYL-2-CYCLOHEXENONE	3	5
3461	2-ISOPROPYLPHENOL	1	1
3463	4-METHYLPENTANOIC ACID	20	100
3465	*CIS*-6-NONEN-1-OL	0.6	2
3466	2-*TRANS*-6-*TRANS*-OCTADIENAL	5	10
3467	*CIS*-3-OCTEN-1-OL	10	500
3471	1,5,5,9-TETRAMETHYL-13-OXATRICYCLO(8.3.0.0(4,9)) TRIDECANE	1	5
3472	THIOGERANIOL	1	5
3486	ETHYL *TRANS*-2-BUTENOATE	2,800	4,200
3489	ETHYL 2-METHYL-4-PENTENOATE	200	520
3498	3-HEXENYL 3-METHYLBUTANOATE	650	5,000
3506	2-METHYLBUTYL 3-METHYLBUTANOATE	2	2,000
3527	3-ACETYL-2,5-DIMETHYLTHIOPHENE	1	1
3536	DIMETHYL DISULFIDE	1	5
3538	2,6-DIMETHYL-3-((2-METHYL-3-FURYL)THIO)-4-HEPTANONE	3	5
3539	3,7-DIMETHYL-1,3,6-OCTATRIENE	5	35
3554	5-ISOPROPYL-2-METHYLPYRAZINE	10	15
3557	*P*-MENTHA-1,8-DIEN-7-AL	5	100
3558	*P*-MENTHA-1,3-DIENE	25	115
3565	*P*-MENTH-8-EN-2-ONE	1,200	3,800
3577	3-METHYL-5-PROPYL-2-CYCLOHEXEN-1-ONE	5	10
3578	2-METHYL-4-PROPYL-1,3-OXATHIANE	5	10
3579	1,4-NONANEDIOL DIACETATE	1	5

FEMA NO.	PRIMARY NAME	ANTICIPATED USUAL USE LEVEL (PPM)	ANTICIPATED MAXIMUM USE LEVEL (PPM)
3584	1-PENTEN-3-OL	5	10
3590	*DELTA*-TETRADECALACTONE	2	5
3592	(2,2,3-TRIMETHYLCYCLOPENT-3-EN-1-YL)ACETALDEHYDE	40	50
3595	2,5-XYLENOL	11	25
3596	3,4-XYLENOL	1	1
3609	2-ACETYL-5-METHYLFURAN	930	3,900
3622	*DELTA*-1-(2,6,6-TRIMETHYL-3-CYCLOHEXEN-1-YL)-2-BUTEN-1-ONE	60	120
3625	*BETA*-IONOL	40	40
3634	4,5-DIMETHYL-3-HYDROXY-2,5-DIHYDROFURAN-2-ONE	1	5
3641	ETHYL *TRANS*-2-DECENOATE	450	1,000
3643	ETHYL *TRANS*-2-OCTENOATE	1,500	10,000
3657	CAMPHOLENE ACETATE	50	160
3658	1,4-CINEOLE	15	500
3661	NEROL OXIDE	5	10
3665	2,2-DIMETHYL-5-(1-METHYLPROPEN-1-YL) TETRAHYDROFURAN	20	70
3670	*TRANS*,*TRANS*-2,4-DODECADIENAL	5	10
3675	ETHYL *TRANS*-2-HEXENOATE	20	60
3680	2-ETHYL-4-METHYLTHIAZOLE	1	5
3689	*CIS*-3-HEXENYL *CIS*-3-HEXENOATE	10	100
3690	*CIS*-3-HEXENYL LACTATE	20	400
3692	HEXYL *TRANS*-2-HEXENOATE	0.1	0.1
3695	HYDROQUINONE MONOETHYL ETHER	90	200
3702	METHYLBENZYL ACETATE (MIXED O,M,P)	1	1
3710	METHYL 3-NONENOATE	11,200	20,100
3746	LINALOOL OXIDE	20	100
3750	OSMANTHUS ABSOLUTE (*OSMANTHUS FRAGRANS* LOUR.(OLEACEAE))	2	10
3784	3-*L*-MENTHOXYPROPANE-1,2-DIOL	300	4,000
3787	2-METHYL-3-TETRAHYDROFURANTHIOL	1,480	5,900
3821	*DELTA*-3-CARENE	55	155
3869	3-METHYL-2-OXOBUTANOIC ACID	500	11,400
4049	4-HYDROXY-3,5-DIMETHOXY BENZALDEHYDE	15	75