30 GRAS
30. **GRAS Flavoring Substances.** This list of substances will appear in the 30th publication authored by the Expert Panel of the Flavor and Extract Manufacturers Association on recent progress in the consideration of flavoring ingredients “generally recognized as safe” (GRAS) under conditions of their intended use in food flavorings in accordance with the 1958 Food Additives Amendment to the Federal Food, Drug and Cosmetic Act. For more information on FEMA GRAS see “About the FEMA GRAS Program” on the FEMA website.

**FEMA EXPERT PANEL.** Samuel M. Cohen, Ph.D, M.D., Chair of the FEMA Expert Panel, Professor, Dept. of Pathology and Microbiology, and Havlik-Wall Professor of Oncology, University of Nebraska Medical Center, Omaha, NE; Gerhard Eisenbrand, Ph.D. (Retired), Food Chemistry and Toxicology, University of Kaiserslautern, Kaiserslautern, Germany; Shoji Fukushima, M.D., Director, Japan Bioassay Research Center, Japan Industrial Safety and Health Association, Kanagawa, Japan; Nigel J. Gooderham, Ph.D., Professor of Molecular Toxicology and Senior College Consul, Dept. of Surgery and Cancer, Imperial College London, England; F. Peter Guengerich, Ph.D., Tadashi Inagami Professor of Biochemistry, Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, TN; Stephen S. Hecht, Ph.D., Wallin Professor of Cancer Prevention, Masonic Cancer Center and Dept. of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN; Ivonne M.C.M. Rietjens, Ph.D., Vice-Chair FEMA Expert Panel, Professor of Toxicology and Chair, Dept. of Toxicology, Wageningen; and Thomas J. Rosol, D.V.M., Ph.D., M.B.A., Ohio University, Athens, Ohio.

The Expert Panel of the Flavor and Extract Manufacturers Association of the United States (FEMA) has evaluated substances for GRAS status under their conditions of intended use as flavoring substances since the early 1960s. The regulations of the U.S. Food and Drug Administration (FDA), and U.S. law, require that determinations that flavor substances and other food ingredients are “generally recognized as safe” (GRAS) be done in such a way that all information related to GRAS determinations is publicly available. The FEMA Expert Panel has met this requirement by publishing the identity of all flavoring substances determined to be GRAS by the Panel, and submits all information related to the GRAS reviews on these substances to the FDA. The key findings related to the GRAS evaluations of these substances are available at the end of this document. The Expert Panel also publishes separate extensive reviews of scientific information on all FEMA GRAS flavoring substances in the peer-reviewed scientific literature on the safety of structurally-related groups of flavoring substances. These important actions assure that there is “general recognition” of the safety of these substances when used as flavors.

**DISCLAIMER:** The user of this list agrees that its use of this document and the information contained therein is at the user’s sole risk and that FEMA shall have no liability to any person for any loss or damage arising out of the use of this document. This document and the information contained herein is subject to change. It is the responsibility of the user to ensure the information is up to date.
The FEMA GRAS status of mintlactone (CAS No. 13341-72-5; FEMA No. 3764) under its conditions of intended use as a flavor ingredient was reviewed by the FEMA Expert Panel. After reviewing the available information relevant to the FEMA GRAS status of mintlactone, including recent studies, the Expert Panel concluded that additional data are required to support the continuation of its GRAS status. Such data should include OECD- and GLP-compliant in vitro and in vivo genotoxicity testing, and confirmation from the industry that the commercial substance will not degrade to mutagenic impurities. Until such data are available for review by the Expert Panel, the flavor ingredient mintlactone has been removed from the FEMA GRAS list.
<table>
<thead>
<tr>
<th>FEMA NO.</th>
<th>PRIMARY NAMES AND SYNONYMS</th>
<th>FEMA NO.</th>
<th>PRIMARY NAMES AND SYNONYMS</th>
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<tbody>
<tr>
<td>4943</td>
<td>Decanedioic acid</td>
<td>4959</td>
<td>9-Dodecen-12-olide</td>
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<td></td>
<td>1,8-Octanedicarboxylic acid</td>
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<td>Yuzu lactone</td>
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<td>1,10-Decanedioic acid</td>
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<td>Oxacyclotridec-10-en-2-one</td>
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<td>Sebacic acid</td>
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<td>1-Oxacyclotridec-10-en-2-one</td>
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<td></td>
<td>Decanedicarboxylic acid</td>
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<td>trans-alpha-Bergamotene</td>
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<td>4944</td>
<td>trans-2-Decanedicarboxylic acid</td>
<td>(E)-Dodec-2-enedioic acid</td>
<td>alpha-Bergamotene, trans-</td>
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<td></td>
<td>Dodec-2-enedioic acid</td>
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<td>2-Norpinene, 2,6-dimethyl-6-(4-methyl-3-pentenyl)-,</td>
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<tr>
<td></td>
<td>Traumatic acid</td>
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<td>trans-(-)</td>
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<tr>
<td></td>
<td>trans-Traumatic acid</td>
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<td>Bicyclo(3.1.1)hept-2-ene, 2,6-dimethyl-6-(4-methyl-3-pentenyl)-,</td>
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<td>4945</td>
<td>cis-8-Decenal</td>
<td></td>
<td>(1S,5S,6R)-</td>
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<td>8-Decenal, (8E)</td>
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<td>Bicyclo(3.1.1)hept-2-ene, 2,6-dimethyl-6-(4-methyl-3-pentenyl)-,</td>
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<tr>
<td></td>
<td>(8Z)-Dec-8-enal</td>
<td></td>
<td>(1S-1.alpha, 5.alpha, 6.alpha)-</td>
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<td>4946</td>
<td>2-Amino-2-deoxy-poly-D-glucosamine</td>
<td>Chitosan</td>
<td>alpha-trans-Bergamotene</td>
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<td></td>
<td></td>
<td>alpha-Bergamotene, (-)-trans-</td>
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<td></td>
<td></td>
<td>(-)-trans-alpha-Bergamotene</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(-)-exo-alpha-Bergamotene</td>
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<td>4947</td>
<td>Glucosylated stevia extract 40% with 14% Rebaudioside A</td>
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<td>4-Methyltrideca-2E,4-dienal</td>
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<tr>
<td>4948</td>
<td>2-Hexylpyridine</td>
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<td>Lepidium meyenii root extract</td>
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<td>2-(n-Hexyl)pyridine</td>
<td></td>
<td>Lepidium peruvianum root extract</td>
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<td>4949</td>
<td>Corynebacterium ammoniagenes fermentation product</td>
<td>Corynebacterium glutamicum cell free fermentation product</td>
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</tr>
<tr>
<td></td>
<td>C. ammoniagenes dried fermentation broth</td>
<td>C. glutamicum dried fermentation broth</td>
<td></td>
</tr>
<tr>
<td>4950</td>
<td>Stevia rebaudiana extract with Rebaudiosides AM and M</td>
<td></td>
<td>N-[1-{1-(4-Amino-2,2-dioxido-1H-benzoc[1,2,6]thiadiazin-5-yl)oxy}-2-methylpropan-2-yl]isonicotinamide</td>
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<td>4951</td>
<td>Glucosylated steviol glycosides 90% supraglucosylated rebaudioside A</td>
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<td>4-Methylheptan-3-one</td>
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<tr>
<td>4952</td>
<td>Glucosylated steviol glycosides 91% supraglucosylated rebaudioside D</td>
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<td>delta-Cadinene</td>
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<tr>
<td>4953</td>
<td>Glucosylated steviol glycosides 58% supraglucosylated stevioside</td>
<td></td>
<td>Cadina-1(10),4-diene</td>
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<tr>
<td>4954</td>
<td>Blue agave inulin (Agave tequilana)</td>
<td>Boehmeria nivea leaf extract</td>
<td>Stevia rebaudiana extract with Rebaudioside M ≥90%</td>
</tr>
<tr>
<td>4955</td>
<td>Emblica officinalis fruit extract</td>
<td>Phyllanthus emblica extract</td>
<td>Yerba mate extract (Ilex paraguariensis A. St.-Hil.)</td>
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<tr>
<td></td>
<td>Amla extract</td>
<td>Indian gooseberry extract</td>
<td>Mate absolute</td>
</tr>
<tr>
<td></td>
<td>Boehmeria nivea leaf extract</td>
<td>Ramie leaf extract</td>
<td>llex paraguariensis A. St.-Hil. extract</td>
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<tr>
<td>4956</td>
<td>Rebaudioside M 85%</td>
<td>Rebaudioside X 85%</td>
<td>2-Methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one</td>
</tr>
<tr>
<td>4957</td>
<td></td>
<td></td>
<td>beta-Farnesene</td>
</tr>
<tr>
<td>4958</td>
<td>4-Formyl-2-methoxyphenyl l-menthy glutarate</td>
<td>4-Formyl-2-methoxyphenyl-(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl pentanediolate</td>
<td>(E)-beta-Farnesene</td>
</tr>
<tr>
<td></td>
<td>4-Formyl-2-methoxyphenyl-(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl pentanediolate</td>
<td>Pentanedioc acid, 1-(4-formyl-2-methoxyphenyl)-5-[(1R,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl] ester</td>
<td>trans-beta-Farnesene</td>
</tr>
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<td></td>
<td>4-Formyl-2-methoxyphenyl-(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl pentanediolate</td>
<td>Pentanedioc acid, 1-(4-formyl-2-methoxyphenyl)-5-[(1R,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl] ester</td>
<td>(E)-beta-Farnesene</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>trans-beta-Farnesene</td>
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</table>

**TABLE 1 - Primary Names & Synonyms**

Primary names (in boldface) & Synonyms (in lightface).
### GRAS FLAVORING SUBSTANCES 30
### TABLE 1 Continued - Primary Names & Synonyms

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

<table>
<thead>
<tr>
<th>FEMA NO.</th>
<th>PRIMARY NAMES AND SYNONYMS</th>
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<tbody>
<tr>
<td>4972</td>
<td>Diethyl mercaptosuccinate</td>
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<tr>
<td>4973</td>
<td>3-Mercapto-3-methyl-1-pentyl acetate</td>
</tr>
<tr>
<td>4974</td>
<td>Germacrene D ≥85%</td>
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<tr>
<td>4975</td>
<td><em>Scutellaria baicalensis</em> root extract</td>
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<tr>
<td></td>
<td>Chinese skullcap extract</td>
</tr>
<tr>
<td></td>
<td>Baikal skullcap extract</td>
</tr>
<tr>
<td>4976</td>
<td>Lemon seed (<em>Citrus limon</em>) oil</td>
</tr>
<tr>
<td></td>
<td><em>Citrus limon</em> seed oil</td>
</tr>
<tr>
<td></td>
<td><em>Citrus medica limonum</em> seed oil</td>
</tr>
<tr>
<td></td>
<td><em>Citrus medica</em> seed oil</td>
</tr>
<tr>
<td>4977</td>
<td>10-Hydroxy-4,8-dimethyldec-4-enal</td>
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<tr>
<td></td>
<td>4-Decenal, 10-hydroxy-4,8-dimethyl-</td>
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<tr>
<td>4978</td>
<td>Rebaudioside B 95%</td>
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<tr>
<td>4979</td>
<td>2-(Furan-2-yl)-4,6-dimethyl-1,3,5-dithiazinane</td>
</tr>
<tr>
<td>4980</td>
<td>Mixture of (8Z,11Z)-heptadeca-8,11-dienal and (Z)-heptadec-8-enal</td>
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</table>
# 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).

<table>
<thead>
<tr>
<th>Category/FEMA No.</th>
<th>Decanedioic acid</th>
<th>trans-2-Dodecadienoic acid</th>
<th>cis-8-Decenal</th>
<th>2-Amino-2-deoxy-D-glucose</th>
<th>Glucosylated stevia extract</th>
<th>Rebapudide A</th>
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<tbody>
<tr>
<td>Baked Goods</td>
<td>40/200</td>
<td>40/200</td>
<td>0.004/0.2</td>
<td>1500/2000</td>
<td>50/60</td>
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<tr>
<td>Beverages Type I, Non-Alcoholic</td>
<td>20/50</td>
<td>15/50</td>
<td>0.0002/0.01</td>
<td>1500/2000</td>
<td>50/60</td>
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<tr>
<td>Beverages Type II, Alcoholic</td>
<td>15/30</td>
<td>15/50</td>
<td>0.0002/0.01</td>
<td>1500/2000</td>
<td>50/60</td>
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<tr>
<td>Breakfast Cereals</td>
<td>50/100</td>
<td>50/200</td>
<td>0.002/0.1</td>
<td>1500/2000</td>
<td>50/60</td>
<td></td>
</tr>
<tr>
<td>Cheeses</td>
<td>40/100</td>
<td>50/200</td>
<td>0.0004/0.02</td>
<td>1500/2000</td>
<td>50/60</td>
<td></td>
</tr>
<tr>
<td>Chewing Gum</td>
<td>100/300</td>
<td>100/500</td>
<td>0.004/0.2</td>
<td>1500/2000</td>
<td></td>
<td></td>
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<tr>
<td>Condiments and Relishes</td>
<td>30/100</td>
<td>30/200</td>
<td>0.002/0.1</td>
<td>1500/2000</td>
<td>50/60</td>
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<tr>
<td>Confections and Frostings</td>
<td>40/100</td>
<td>40/200</td>
<td>0.002/0.1</td>
<td>1500/2000</td>
<td>50/60</td>
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<tr>
<td>Egg Products</td>
<td>50/100</td>
<td>40/300</td>
<td>0.001/0.05</td>
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<tr>
<td>Fats and Oils</td>
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<td>40/100</td>
<td>0.004/0.2</td>
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<td>Fish Products</td>
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<td>0.001/0.05</td>
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<tr>
<td>Frozen Dairy</td>
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<td>0.0004/0.02</td>
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<td>50/60</td>
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<td>Fruit Ices</td>
<td>30/60</td>
<td>15/100</td>
<td>0.0004/0.02</td>
<td>1500/2000</td>
<td>50/60</td>
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<tr>
<td>Gelatins and Puddings</td>
<td>30/60</td>
<td>15/100</td>
<td>0.0004/0.02</td>
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<tr>
<td>Granulated Sugar</td>
<td>40/200</td>
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<td>0.001/0.05</td>
<td>1500/2000</td>
<td>50/60</td>
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<tr>
<td>Gravies</td>
<td>40/100</td>
<td>40/200</td>
<td>0.001/0.05</td>
<td>1500/2000</td>
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<td>Hard Candy</td>
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<td>50/300</td>
<td>0.001/0.05</td>
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<td>Imitation Dairy Products</td>
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<td>Jams and Jellies</td>
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<td>Processed Fruits</td>
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<td>50/60</td>
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<td>Processed Vegetables</td>
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<td>Reconstituted Vegetable Protein</td>
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<td>Sugar Substitutes</td>
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<td>Sweet Sauces</td>
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<td>40/100</td>
<td>0.001/0.05</td>
<td>1500/2000</td>
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### 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)

<table>
<thead>
<tr>
<th>Category/FEMA No.</th>
<th>2-Hexylpyridine</th>
<th>Corynebacterium ammoniagenes fermentation product</th>
<th>Stevia rebaudiana extract with Rebaudiosides A and M</th>
<th>Glucosylated rebaudioside A, supraglucosylated rebaudioside A</th>
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<td>Baked Goods</td>
<td>1/5</td>
<td>1000/7500</td>
<td>50/150</td>
<td>70/70</td>
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<td>Beverages Type I, Non-Alcoholic</td>
<td>1/5</td>
<td>50/50</td>
<td>70/70</td>
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<tr>
<td>Beverages Type II, Alcoholic</td>
<td>1/5</td>
<td>50/50</td>
<td>70/70</td>
<td></td>
</tr>
<tr>
<td>Breakfast Cereals</td>
<td></td>
<td>1000/5000</td>
<td>50/50</td>
<td>70/70</td>
</tr>
<tr>
<td>Cheeses</td>
<td>1/5</td>
<td>2000/7500</td>
<td>50/50</td>
<td>70/70</td>
</tr>
<tr>
<td>Chewing Gum</td>
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<td>50/50</td>
<td>70/70</td>
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<tr>
<td>Condiments and Relishes</td>
<td>1/5</td>
<td>3000/20000</td>
<td>50/50</td>
<td>70/70</td>
</tr>
<tr>
<td>Confections and Frostings</td>
<td></td>
<td></td>
<td>50/50</td>
<td>70/70</td>
</tr>
<tr>
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### 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)

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<th>Category/FEMA No.</th>
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<th>Glucosylated steviol glycosides 58% supraglucosylated stevioside</th>
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### 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)

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<td></td>
<td>100/100</td>
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<td>0.5/2</td>
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<td>0.3/0.3</td>
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<td></td>
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<td></td>
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<td>0.5/2</td>
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<td><strong>Granulated Sugar</strong></td>
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<td><strong>Gravies</strong></td>
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<td>1/5</td>
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<td>35/35</td>
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<td><strong>Hard Candy</strong></td>
<td>22/22</td>
<td>1/5</td>
<td>0.9/0.9</td>
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<td>35/35</td>
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<td><strong>Jams and Jellies</strong></td>
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### 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)

<table>
<thead>
<tr>
<th>Category/FEMA No.</th>
<th>2-Methyl-1-(2-((5-((p-tolyl)-1H-imidazol-2-yl)methyl)piperidin-1-yl)piperidin-1-yl)butan-2-one</th>
<th>beta-Farnesene</th>
<th>Diethyl mercaptotocadonate</th>
<th>3-Mercapto-3-methyl-1-pentyl acetate</th>
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<tbody>
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<td>1/10</td>
<td>0.001/0.05</td>
<td>0.0001/0.002</td>
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<td>5/20</td>
<td>0.1/1</td>
<td>0.0001/0.002</td>
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<tr>
<td>Beverages Type II, Alcoholic</td>
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<td>5/20</td>
<td>0.1/1</td>
<td>0.0001/0.002</td>
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<td>10/50</td>
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<td></td>
<td></td>
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<tr>
<td>Cheeses</td>
<td>400/1000</td>
<td>2/10</td>
<td></td>
<td>0.0005/0.005</td>
</tr>
<tr>
<td>Chewing Gum</td>
<td>100/300</td>
<td>30/90</td>
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<td>0.0005/0.01</td>
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<td>Condiments and Relishes</td>
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<td>1/10</td>
<td>0.0001/0.01</td>
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<td>0.0002/0.003</td>
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<td>Gelatins and Puddings</td>
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<td>1/10</td>
<td>0.0002/0.003</td>
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<td>0.0005/0.005</td>
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<td>0.0003/0.005</td>
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<td>0.001/0.01</td>
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<td>0.01/0.5</td>
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<td>0.001/0.05</td>
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<td>10/30</td>
<td>1/10</td>
<td>0.001/0.1</td>
</tr>
<tr>
<td>Soups</td>
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<td>5/20</td>
<td>1/10</td>
<td>0.0003/0.003</td>
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### TABLE 2 Continued - Average Usual Use Levels/Average Maximum Use Levels

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<th>Scutellaria baicalensis root extract</th>
<th>Lemon seed oil (Citrus limon)</th>
<th>10-Hydroxy-4,8-dimethyldec-4-enal</th>
<th>Rebaudioside B 95%</th>
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<td>Soups</td>
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### GRAS Flavoring Substances 30

**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)

<table>
<thead>
<tr>
<th>Category/FEMA No.</th>
<th>2-(Furan-2-yl)-4,6-dimethyl-1,3,5-thiazinane</th>
<th>Mixture of (8Z,11Z)-heptadeca-8,11-dienal and (Z)-heptadeca-9-enal</th>
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<tr>
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<td>0.02/0.05</td>
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<tr>
<td>Beverages Type II, Alcoholic</td>
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<td>0.02/0.05</td>
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<td>Breakfast Cereals</td>
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<tr>
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<td>Condiments and Relishes</td>
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<td>Soups</td>
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<tr>
<td>Sugar Substitutes</td>
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<td>Sweet Sauces</td>
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<td>Egg Products</td>
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<tr>
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<tr>
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<td>Seasonings and Flavors</td>
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<td>Soups</td>
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<td>Sugar Substitutes</td>
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<td>3-(4-Hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one</td>
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<tr>
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<tr>
<td>Sugar Substitutes</td>
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<td>Hard Candy</td>
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<td>Imitation Dairy Products</td>
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<tr>
<td>Instant Coffee and Tea</td>
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<td>Meat Products</td>
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<td>Soft Candy</td>
<td>1,500*/2,500*</td>
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<tr>
<td>Soups</td>
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<tr>
<td>Sugar Substitutes</td>
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<td>FEMA No.</td>
<td>FEMA Primary Name</td>
<td>The Identification Description as Reviewed by the FEMA Expert Panel</td>
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<tr>
<td>4947</td>
<td>Glycosylated stevia extract 40% with 14% Rebaudioside A</td>
<td>35-45% Glucosylated steviol glycosides; 11-17% Rebaudioside A; 8-15% Steviolide; Less than 3% all other individual steviol glycosides; Maltodextrin 23-45%</td>
</tr>
<tr>
<td>4949</td>
<td>Corynebacterium ammoniagenes fermentation product</td>
<td>20-25% Miscellaneous nitrogen-containing compounds; 2-5% Amino acids; 3-5% Minerals; &lt;7% Carbohydrates typically monosaccharides; 50-55% Dextrins</td>
</tr>
<tr>
<td>4950</td>
<td>Stevia rebaudiana extract with Rebaudiosides AM and M</td>
<td>Total steviol glycosides &gt;95%, inclusive of 60-75% Rebaudioside AM; 15-20% Rebaudioside M; Other individual rebaudiosides not further glucosylated present at ≤1% individually and 5-10% supraglucosylated rebaudiosides</td>
</tr>
<tr>
<td>4951</td>
<td>Glucosylated steviol glycosides 90% supraglucosylated rebaudioside A</td>
<td>Total steviol glycosides &gt;95%, inclusive of 90-94% supraglucosylated rebaudioside A; 1-3% Not further glucosylated rebaudioside A; Trace amounts of other supraglucosylated individual rebaudiosides; &lt;4% Dextrins</td>
</tr>
<tr>
<td>4952</td>
<td>Glucosylated steviol glycosides 91% supraglucosylated rebaudioside D</td>
<td>Total steviol glycosides &gt;95%, inclusive of 91-95% supraglucosylated rebaudioside D; 1-4% Supraglucosylated rebaudioside B; 2-4% Not further glucosylated rebaudioside D; Trace amounts of other supraglucosylated individual rebaudiosides; &lt;3% Dextrins</td>
</tr>
<tr>
<td>4953</td>
<td>Glucosylated steviol glycosides 58% supraglucosylated stevioside</td>
<td>Total steviol glycosides &gt;95%, inclusive of 58-61% supraglucosylated stevioside; 24-35% Supraglucosylated stevioside A, 12-16% Supraglucosylated stevioside C; 1-2% Supraglucosylated stevioside D; Trace amounts of other supraglucosylated individual rebaudiosides; &lt;4% Not further glucosylated stevioside; &lt;2% Other not further glucosylated steviolides, individually; &lt;3% Dextrins</td>
</tr>
<tr>
<td>4954</td>
<td>Blue agave inulin (Agave tequilana)</td>
<td>Derived from Agave tequilana, blue agave inulin (Agave tequilana) is measured as inulin &gt;90%; Mono- and disaccharides typically fructose, glucose and sucrose &lt;10%.</td>
</tr>
<tr>
<td>4955</td>
<td>Emblica officinalis fruit extract</td>
<td>Derived from the Emblica officinalis fruit, Emblica officinalis fruit extract is measured as no more than 20% phenols derivatives typically gallic acid and gallic acid esters; 7% Lactones typically mucic acid lactone and ascorbate; 3% Aliphatic carboxylic acids with additional oxygenated functional groups; 60% Carbohydrates and no more than 5% ash</td>
</tr>
<tr>
<td>4956</td>
<td>Boehmeria nivea leaf extract</td>
<td>Derived from the leaves of Boehmeria nivea, Boehmeria nivea leaf extract is an ethanolic extract and is measured as 45-60% carbohydrates, 8-15% protein and 5-10% fat.</td>
</tr>
<tr>
<td>4957</td>
<td>Rebaudioside M 85%</td>
<td>Total steviol glycosides &gt;95%, inclusive of Rebaudioside M ≥85%; Rebaudioside D 3-12% and other individual steviol glycosides not further glucosylated each less than 1%</td>
</tr>
<tr>
<td>4959</td>
<td>Lepidium meyenii root extract</td>
<td>Derived from the root of Lepidium meyenii or L. peruvianum, Lepidium meyenii root extract is measured as no more than 2% total macamides; 10-20% Soluble polysaccharides; 10-15% Simple carbohydrates suspended in 75% glycerol</td>
</tr>
<tr>
<td>4961</td>
<td>Pandan leaf (Pandanus amaryllifolius) distillate extract</td>
<td>Derived from the leaves of Pandanus amaryllifolius, pandan leaf (Pandanus amaryllifolius) distillate extract is measured as less than 0.05% pyrroline derivatives suspended in an appropriate food grade solvent</td>
</tr>
<tr>
<td>4962</td>
<td>Corynebacterium glutamicum cell free fermentation product</td>
<td>No more than 30% glutamic acid; Up to 10% simple carbohydrates; Less than 5% sum of other individual amino acids; No more than 60% dextrins</td>
</tr>
<tr>
<td>4968</td>
<td>Stevia rebaudiana extract with Rebaudioside M ≥90%</td>
<td>Total steviol glycosides &gt;95%, inclusive of Rebaudioside M ≥90%; Other rebaudiosides not further glucosylated present at ≤4% individually</td>
</tr>
<tr>
<td>4969</td>
<td>Yerba mate extract (Ilex paraguariensis A. St.-Hil.)</td>
<td>Derived from the roots of Ilex paraguariensis A. St.-Hil., yerba mate extract (Ilex paraguariensis A. St.-Hil.) is measured as ≥95% dicaffeoyltquinic acids, chlorogenic acid and its related positional and stereoisomer as well as other related caffeic and quinic acid derivatives; &lt;0.05% Caffeine</td>
</tr>
<tr>
<td>4975</td>
<td>Scutellaria baicalensis root extract</td>
<td>Derived from the root of Scutellaria baicalensis, Scutellaria baicalensis root extract is measured as a 1% solution in propylene glycol, with the flavonoids baicalin, baica- lein, wogonin and oroxylin A each present at &lt;1%</td>
</tr>
<tr>
<td>4976</td>
<td>Lemon seed (Citrus limon) oil</td>
<td>Derived from the seeds of Citrus limon, lemon seed (Citrus limon) oil is measured as total fat as triglycerides ≥95%, inclusive of approximately 40-45% of linoleic and linolenic acids, approximately 30-35% of oleic acid and 15-20% of palmitic and stearic acids; Total volatile content of approximately 5%, inclusive of &lt;2% each of: Saturated aliphatic, acyclic, linear primary alcohols, aldehydes, carboxylic acids and related esters; Aliphatic linear and branched-chain alpha, beta-unsaturated aldehydes and related alcohols acids and esters; Aliphatic and aromatic hydrocarbons</td>
</tr>
</tbody>
</table>
Since its initial publication of GRAS (Generally Recognized As Safe) determinations for flavor ingredients (Hall and Oser, 1965), the FEMA Expert Panel has made available information on its determinations, including conditions of intended use for individual flavor ingredients, and the scientific basis and information supporting these determinations. Included herein are the key findings for each of the new GRAS determinations included within GRAS 30. Comprehensive monographs of the information relevant to the evaluations are also published as part of the FEMA Expert Panel’s ongoing GRAS re-evaluation program (see Hallagan and Hall, 2009; Hallagan et al., 2020). For more information on the FEMA GRAS program, please see “About the FEMA GRAS Program” on femaflavor.org.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding decanedioic acid (CAS 111-20-6) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4943) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of aliphatic primary alcohols, aldehydes, carboxylic acids, acetal and esters containing additional oxygenated functional groups. (JECFA, 2000; SLR, B1D). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of decanedioic acid from use as a flavor ingredient to be 69 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The substance occurs naturally in beer, clover honey (Trifolium Repens), honey of leptospermum species (Manuka and Kanuka), leatherwood honey (Eucryphia Lucida), thistle honey (Carduus Nutans), thyme honey (Thymus vulgaris), willow honey (Salix species), wort, pork fat (Van Dongen and Donders, 2021). Based on the quantitative data, a consumption ratio of 12 could be calculated (Stofberg and Grundsocher, 1987). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that decanedioic acid will undergo beta-oxidative cleavage and complete metabolism to CO₂ via the fatty acid pathway and the citric acid cycle (Smith et al., 2018). No increases in the frequency of revertant colonies were observed in an Ames assay for decanedioic acid in Salmoneilla typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 as well as Escherichia coli strain WP2 uvrA in the presence and absence of S9 metabolic activation (Shimizu et al., 1985). In an Ames assay with the structurally related substance adipic acid (FEMA 2011), there were no increases in the frequency of revertant colonies in S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538, as well as E. coli strain WP2 uvrA either in the absence and presence of S9 metabolic activation (Kubo et al., 2002; Prival et al., 1991; Shimizu et al., 1985). In an OECD guideline 476- and GLP-compliant in vitro mammalian cell gene mutation assay for the same structural relative in V79 Chinese hamster lung cells, there were no significant increases in mutant frequency at the HPRT locus in the presence and absence of S9 metabolic activation (ECHA, 2009a). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional group therein, the Expert Panel did not identify specific concerns related to the genotoxicity of decanedioic acid (Gooderham et al., 2020). No reproductive or developmental toxicity effects were reported in female rats administered the structural relative adipic acid (FEMA 2011) by gavage at doses up to 288 mg/kg bw/day from gestation days 6-15 (Morgareidge, 1973). In developmental toxicity studies in female rats and female rabbits, the structural relative nonanedioic acid (CAS 123-99-9) was provided in the diet at levels of 140 and 200 mg/kg bw/day, respectively, through pregnancy. No reproductive or developmental effects were observed (Mingrone et al., 1983). In 90- and 180-day dietary studies, no toxicologically significant clinical observations were reported for male and female Wistar rats or male and female New Zealand rabbits provided the structural relative nonanedioic acid (CAS 123-99-9) in the diet at levels up to 140 and 280 mg/kg bw/day for rats or 200 mg/kg bw/day and 400 mg/kg bw/day for rabbits, respectively (Mingrone et al., 1983). In a 2-year dietary toxicity study, male and female albino rats were administered the structural relative adipic acid (FEMA 2011) at dietary levels of approximately 75, 750, 2250 and 3750 mg/kg bw/day (Horn et al., 1957). Body weight gains in the top two dose groups were significantly less during the rapid growth period. The no observed adverse effect level (NOAEL) was concluded by the Expert Panel to be 750 mg/kg bw/day based on the slight body weight reductions in the 2250 and 3750 mg/kg bw/day treatment groups. This NOAEL is greater than 650,000 times the daily per capita intake of decanedioic acid from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding trans-2-dodecenedioic acid (CAS 6402-36-4) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4944) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of aliphatic primary alcohols, aldehydes, carboxylic acids, acetal and esters containing additional oxygenated functional groups (JECFA, 2000; SLR, B1D). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of trans-2-dodecenedioic acid from use as a flavor ingredient to be 14 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. Trans-2-Dodecenedioic acid is anticipated to undergo beta-oxidative cleavage and complete metabolism to CO₂ via the fatty acid pathway and the citric acid cycle (Smith et al., 2018). No increases in the frequency of revertant colonies were observed for the structural relative, decanedioic acid (FEMA 2011) in an Ames assay conducted in S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 as well as E. coli strain WP2 uvrA either in the absence and presence of S9 metabolic activation (Shimizu et al., 1985). In an Ames assay with the structural relative adipic acid (FEMA 2011), there were no increases in the frequency of revertant colonies in S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538, as well as E. coli strain WP2 uvrA either in the absence and presence of S9 metabolic activation (Kubo et al., 2002; Prival et al., 1991; Shimizu et al., 1985). In an OECD guideline 476- and GLP-compliant in vitro mammalian cell gene mutation assay for the same structural relative in V79 Chinese hamster lung cells, there were no significant increases in mutant frequency at the HPRT locus in the presence and absence of S9 metabolic activation (Kubo et al., 2002; Prival et al., 1991; Shimizu et al., 1985). In an OECD guideline 476 and GLP-compliant in vitro mammalian cell gene mutation assay for the same structural relative in V79 Chinese hamster lung cells, there were no significant increases in mutant frequency at the HPRT locus in the presence and absence of S9 metabolic...
entering the fatty acid cycle where it is converted to acetyl-
where it is metabolized to yield CO₂ and water (Smith et al.,
structural relative produced no statistically significant
administration at doses up to 2000 mg/kg bw of the same
carboxylic acid. The cis (Bhatia et al., 2010; Sokolowski, 2007a). In an
TA1537 in the absence or presence of S9 metabolic activation
increases in the frequency of revertant colonies in
substance 10-undecenal (FEMA 3095), there were no
specified in Table 2. This substance was evaluated
characterized by the purity assay and supporting spectral data
considered the specification of the material to be adequately
µg/person/day) (Munro et al., 1996). The Expert Panel
concluded that the use of the substance as a flavor ingredient
relative 10-undecenal (FEMA 3095) in male and female
Sprague-Dawley Crl:CD® (SD) IGS BR rats resulted in a
NOAEL of 200 ppm, or approximately 14.3 mg/kg bw/day
(Liwska and Watson, 2012), which is greater than
120,000,000 times the anticipated daily per capita intake of
cis-8-decanal from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the
GRAS application and supporting information regarding cis-8-
decanal (CAS 174155-46-5) and concluded that the use of the
substance as a flavor ingredient is GRAS (FEMA 4945) (Smith
et al., 2005a) in the food categories and at the use levels
specified in Table 2. This substance was evaluated
individually within the context of the chemical group of
unsaturated linear and branched-chain aliphatic, non-
conjugated aldehydes, related primary alcohols, carboxylic
acids and esters (JECFA, 1999, 2012, 2020; SLR, M1). The
Expert Panel calculated the anticipated per capita intake
(“eaters only”) of cis-8-decanal from use as a flavor ingredient
to be 0.007 µg/person/day, which is below the threshold of
toxicological concern for structural class I (1800
µg/person/day) (Munro et al., 1996). The Expert Panel
considered the specification of the material to be adequately
characterized by the purity assay and supporting spectral data
provided for FEMA GRAS evaluation. cis-8-Decanal is
anticipated to be oxidized to the corresponding unsaturated
carboxylic acid. The cis double bond is isomerized to the trans
double bond by 3-hydroxyacyl-CoA epimerase before
entering the fatty acid cycle where it is converted to acetyl-
CoA. The acetyl-CoA product then enters the citric acid cycle
where it is metabolized to yield CO₂ and water (Smith et al.,
2018; Nelson and Cox, 2008). In an OECD 471 guideline and
GLP-compliant Ames assay with the structurally related
substance as a flavor ingredient is GRAS (FEMA 4946) (Smith
et al., 2005a) in the food categories and at the use levels specified in Table 2. This
substance was evaluated individually within the context of the
chemical group of aliphatic poly-hydroxy compounds and
derivatives (SLR, B1F). This material was evaluated within the
context of the procedure for the FEMA GRAS evaluation of
flavor ingredients produced through biotechnology processes
(Cohen et al., 2015). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of 2-amino-2-
deoxy-poly-D-glucosamine from use as a flavor ingredient to be 3459 µg/person/day, which is above the threshold of
toxicological concern for structural class I (1800
µg/person/day) (Munro et al., 1996). The substance occurs
naturally in white button mushrooms and baker's yeast
(Christodoulidou et al., 1996; Ghormade et al., 2017; Kannan
et al., 2010). Based on the quantitative data, a consumption
ratio of 737 could be calculated (Stofberg and Grundsother, 1987). The Expert Panel noted the assay of the material was
>91% of the named material with water as the secondary component (6-7%) and considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included
within the application and found it satisfactory with regard to
intended conditions of use for the flavor ingredient (Harman and Halligan, 2013). It is presumed that 2-amino-2-deoxy-
poly-D-glucosamine is not subject to digestion via human digestive enzymes and is not absorbed. The substance is expected to travel intact throughout the upper gastrointestinal tract to the colon, where the material would be subject to fermentation by the endogenous microbiota population. Microbial fermentation would result in the production of normal metabolites of fermentation that include the production of short-chain fatty acids, water, carbon dioxide and methane gas (Lattimer and Haub, 2010). No increases in the frequency of revertant colonies were observed in an Ames assay for 2-
amino-2-deoxy-poly-D-glucosamine conducted in S.
typhimurium strains TA98, TA100, TA102, TA1535
and TA1537 in the absence or presence of S9 metabolic activation
(Bhatia et al., 2010; Sokolowski, 2007a). In an in vivo
micronucleus assay in male and female NMRI mice, gavage administration at doses up to 2000 mg/kg bw of the same
structural relative produced no statistically significant
increases in the frequency of micronuclei (Bhatia et al., 2010;
Honavar, 2007). Similar results in the OECD 471 guideline and
GLP-compliant Ames assay and the OECD 474 guideline
and GLP-compliant in vivo mouse micronucleus test were
also reported for the structural relative trans-4-decen-1-ol
(FEMA 3264) (Bhatia et al 2010; Honavar, 2008; Sokolowski, 2007b). Based on these results, as well as the
structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not
identify specific concerns related to the genotoxicity of cis-
8-decanal (Gooderham et al., 2020). An OECD 408 guideline
and GLP-compliant 90-day dietary toxicity study for structural
relative 10-undecenal (FEMA 3095) in male and female
Sprague-Dawley Crl:CD® (SD) IGS BR rats resulted in a
NOAEL of 200 ppm, or approximately 14.3 mg/kg bw/day
(Liwska and Watson, 2012), which is greater than
120,000,000 times the anticipated daily per capita intake of
cis-8-decanal from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the
GRAS application and supporting information regarding 2-
amino-2-deoxy-poly-D-glucosamine (CAS 9012-76-4) and
concluded that the use of the substance as a flavor ingredient
is GRAS (FEMA 4946) (Smith et al., 2005a) in the food
categories and at the use levels specified in Table 2. This
substance was evaluated individually within the context of the
chemical group of aliphatic poly-hydroxy compounds and
derivatives (SLR, B1F). This material was evaluated within the
context of the procedure for the FEMA GRAS evaluation of
flavor ingredients produced through biotechnology processes
(Cohen et al., 2015). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of 2-amino-2-
deoxy-poly-D-glucosamine from use as a flavor ingredient to be 3459 µg/person/day, which is above the threshold of
toxicological concern for structural class I (1800
µg/person/day) (Munro et al., 1996). The substance occurs
naturally in white button mushrooms and baker's yeast
(Christodoulidou et al., 1996; Ghormade et al., 2017; Kannan
et al., 2010). Based on the quantitative data, a consumption
ratio of 737 could be calculated (Stofberg and Grundsother, 1987). The Expert Panel noted the assay of the material was
>91% of the named material with water as the secondary component (6-7%) and considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included
within the application and found it satisfactory with regard to
intended conditions of use for the flavor ingredient (Harman and Halligan, 2013). It is presumed that 2-amino-2-deoxy-
poly-D-glucosamine is not subject to digestion via human digestive enzymes and is not absorbed. The substance is expected to travel intact throughout the upper gastrointestinal tract to the colon, where the material would be subject to fermentation by the endogenous microbiota population. Microbial fermentation would result in the production of normal metabolites of fermentation that include the production of short-chain fatty acids, water, carbon dioxide and methane gas (Lattimer and Haub, 2010). No increases in the frequency of revertant colonies were observed in an Ames assay for 2-
amino-2-deoxy-poly-D-glucosamine conducted in S.
typhimurium strains TA98, TA100, TA102, TA1535
and TA1537 in the absence or presence of S9 metabolic activation
(Bhatia et al., 2010; Sokolowski, 2007a). In an in vivo
micronucleus assay in male and female NMRI mice, gavage administration at doses up to 2000 mg/kg bw of the same
structural relative produced no statistically significant
Ames assay in *S. typhimurium* strains TA97, TA98, TA100, and TA102, 2-amino-2-deoxy-poly-D-glucosamine oligomers did not increase the frequency of revertant colonies in either the absence or presence of S9 metabolic activation (Qin et al., 2006). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 2-amino-2-deoxy-poly-D-glucosamine (Gooderham et al., 2020). In a developmental toxicity study, 2-amino-2-deoxy-poly-D-glucosamine was administered at daily doses of 480 mg/kg bw/day for 4 days to B6C3F1 female mice that were induced to ovulate (Choi et al., 2002). Treatment increased the number of ovulated oocytes and normal oocytes, as well as the *in vivo* and *in vitro* fertilization rates, compared to controls in animals fed a high-fat diet. In a 28-day toxicity study, Wistar rats were administered lobster-derived chitosan (approximately 309 kDa, with a degree of deacetylation of 83%; this material was considered by the Expert Panel to be compositionally equivalent to 2-amino-2-deoxy-poly-D-glucosamine) by gavage at doses of 0, 100, 300, or 1000 mg/kg bw/day (Lagarto et al., 2015). A statistically significant increase in erythrocyte count was reported in males in the 300 and 1000 mg/kg bw/day groups and in males in the 1000 mg/kg bw/day group compared to controls. The authors concluded that the NOAEL was 1000 mg/kg bw/day, noting that the findings of increased erythrocyte count were considered unreliable due to the short-term duration of the study, and no correlated erythrocyte turnover was reported in the long-term study conducted in Sprague-Dawley rats by the National Toxicology Program (NTP). In a 6-month feeding study conducted by the NTP, male and female Sprague-Dawley rats were administered feed containing 0, 1, 3, or 9% 2-amino-2-deoxy-poly-D-glucosamine (approximately 81.6 kDa, with 86.5% deacetylation, considered by the Expert Panel to be low molecular weight chitosan), approximately 450, 1,500, or 5,200 mg/kg bw/day in males and 650, 1,800, or 6,000 mg/kg bw/day in females, respectively (NTP, 2017). The NTP concluded that dietary exposure to 2-amino-2-deoxy-poly-D-glucosamine for 6 months resulted in decreased fat digestion and depletion of some fat-soluble vitamins in male and female rats, and accordingly, reported that “the lowest observed effect level for chitosan was 1% (approximately equivalent to 450 mg/kg) in males and 9% (approximately equivalent to 6,000 mg/kg) in female rats.” The Panel reviewed the data and determined that the thymus weight change in the 9% females was a biologically relevant effect. Therefore, the Panel determined that the lowest observed effect level (LOEL) for female rats was 3% (approximately equivalent to 1,800 mg/kg bw/day). These effects are considered as indirect consequences of the recognized fat binding properties of 2-amino-2-deoxy-poly-D-glucosamine, resulting in excretion of dietary fat and reduced absorption of fat-soluble vitamins, and as such were not direct toxic effects of chitosan on organ systems. The effects of 2-amino-2-deoxy-poly-D-glucosamine on fat absorption are considered an expected finding and are not of nutritional or toxicological significance. In a 52-week dietary administration chronic toxicity study, F344 rats were fed the constituent N-acetyl-D-glucosamine at concentrations of 1.25%, 2.5% or 5% (approximately 580, 1,159 and 2,323 mg/kg bw/day in males and 647, 1,269 and 2,545 mg/kg bw/day in females, respectively) (Takahashi et al., 2009). Body weights were slightly but statistically significantly decreased in 5% males. The slight suppression of body weights was considered by the authors to relate to reductions in caloric intake due to the high levels of intake of the test article and not a direct toxic effect. The NOAEL was concluded to be 5% in the diet in both studies, equivalent to 2,323 and 2,545 mg/kg bw/day in males and females, respectively. In a carcinogenicity study, F344 rats were fed the structural relative N-acetyl-D-glucosamine at concentrations of 2.5%, or 5% in the diet for 104 weeks (approximately 964 and 1,935 mg/kg bw/day in male rats and 1,106 and 2,244 mg/kg bw/day in female rats, respectively) (Takahashi et al., 2009). The NOAEL was concluded to be 5% in the diet, equivalent to 1,935 and 2,244 mg/kg bw/day in males and females, respectively. The NOAEL of 1,935 mg/kg bw/day is greater than 33,000 times the anticipated daily *per capita* intake of 2-amino-2-deoxy-poly-D-glucosamine from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding glucosylated stevia extract powder 40% with 14% rebaudioside A (CAS 1225018-62-1) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4947) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated *per capita* intake (“eaters only”) of glucosylated stevia extract powder 40% rebaudioside A 14% from use as a flavor ingredient to be 415 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This material is derived from the leaves of *Stevia rebaudiana*. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). Metabolic data exist that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Cardoso et al., 1996; Gardana et al., 2003; Geuns et al., 2003; Geuns et al., 2007; Hutapea et al., 1997; Koyama et al., 2003a; Koyama et al., 2003b; Nakayama et al., 1986; Purkayastha et al., 2014; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha and Kwok, 2020; Renwick and Tarka, 2008; Roberts and Renwick, 2008; Roberts et al., 2016; Wheeler et al., 2008; Wingard, 1980). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in *in vitro* mutagenicity assays, *in vivo* studies do not provide evidence of genotoxic effects (Nakajima, 2000; Pezzuto et al., 1985, 1986; Rumelhard et al., 2016; Suttajit et al., 1993; Terai et al., 2002; Williams and Burdock, 2009). Based on the results for the various steviol glycosides, the Expert Panel did not identify specific concerns related to the potential genotoxicity of glucosylated stevia extract powder 40% rebaudioside A 14% (Gooderham et al., 2020). In a 108-week carcinogenicity study for stevioside, no carcinogenic effects were observed (Toyoda et al., 1997). In a 2-year feeding study, male and female F344 rats were administered the equivalent of 0, 50, 150 or 550 mg/kg bw/day of a Stevia extract comprised of 74% stevioside and 16% rebaudioside A (Yamada et al., 1985). The authors considered the NOAEL from this 2-year rat feeding study of a stevia extract to be equal to 550 mg/kg bw/day, or
approximately 89.5 mg/kg bw/day of rebaudioside A (Yamada et al., 1985), which are greater than 78,500 times or 12,700 times the anticipated daily per capita intake of glucosylated stevia extract powder 40% rebaudioside A 14% from use as a flavor ingredient, respectively.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 2-hexylpyridine (CAS 1129-69-7) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4949) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of nitrogen containing heterocyclic and heteroaromatic substances (JECFA, 2006, 2012; SLR, D3). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of 2-hexylpyridine from use as a flavor ingredient to be 0.3 µg/person/day, which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). This substance occurs naturally in roasted chicken, lamb, and mutton fats (Van Dongen and Donders, 2021), but only qualitative data is available, and thus no consumption ratio can be calculated. The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that 2-hexylpyridine will undergo metabolism via oxidation of the side chain, and these oxidized products can form glucuronide conjugates and be excreted or further oxidized to ultimately result in a carboxylic acid via beta-oxidation that would be conjugated with glycine and excreted in the urine (Hawksworth and Scheline, 1975). In an alternative metabolic pathway, oxidation of the pyridine nitrogen would occur, and the corresponding oxide would be expected to be eliminated in the urine (Gorrod and Damani, 1980; Jakoby et al., 1982; Nguyen et al., 1988). In an OECD 471 guideline and GLP-compliant Ames assay in S. typhimurium strains TA98, TA100, TA102, TA1535, and TA1537, 2-hexylpyridine did not increase the frequency of revertant colonies either in the absence or presence of S9 metabolic activation (Vashi, 2019a). The Expert Panel reviewed their prior assessment of the genotoxicity data for the structural relative pyridine (FEMA 2966) and determined it sufficient to indicate a lack of genotoxic concern for 2-hexylpyridine (Smith et al., 2011). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 2-hexylpyridine (Gooderham et al., 2020). As described in the Expert Panel’s prior assessment of the structural relative pyridine (FEMA 2966), a NOAEL of 5 mg/kg bw/day was determined from NTP studies conducted with F344/N rats and B6C3F1 mice of both sexes (NTP, 2000; Smith et al., 2011). This NOAEL is greater than 1,000,000 times the anticipated daily per capita intake of 2-hexylpyridine from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding Corynebacterium ammoniagenes fermentation product and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4949) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of Corynebacterium ammoniagenes fermentation product from use as a flavor ingredient to be 1255 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Halligan, 2013). Metabolic data exist for a representative member of the principal identified congenic groups that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Smith et al., 2018). In an OECD 471 guideline and GLP-compliant Ames assay in S. typhimurium strains TA98, TA100, TA1535 and TA1537 as well as the E. coli strain WP2 uvrA (pKM101), Corynebacterium ammoniagenes fermentation product did not increase the frequency of revertant colonies in either the presence or absence of S9 metabolic activation (Kim, 2016a). Corynebacterium ammoniagenes fermentation product did not induce chromosomal aberrations in an OECD 473 guideline- and GLP-compliant in vitro mammalian chromosomal aberration assay in Chinese hamster lung (CHL/IU) cells (Kim, 2016b). In a 28-day dose-range finding study in male and female Sprague-Dawley rats, oral gavage administration of Corynebacterium ammoniagenes fermentation product at doses of 1250, 2500, or 5000 mg/kg bw/day resulted in no treatment-related abnormalities in any group (Lee, 2016a). No adverse effects were observed in a 90-day study with male rats, 3-month dietary study with male rats, 6-month dietary study with male and female Sprague-Dawley rats, or a 2-year dietary study with male and female beagle dogs administered the constituent disodium 5’-inosinate (CAS 4961-65-0) (Hara et al., 1966; Rivett et al., 1973; Usui et al., 1971; Yonetani et al., 1973). Additionally, no adverse effects or abnormalities were observed in a one-year dietary study with male and female Sprague Dawley rats, a 95-week dietary study with male and female Sprague-Dawley rats, or a 2-year dietary study with male and female beagle dogs administered the constituent inosine 5’-monophosphate (disodium salt) (CAS 4691-65-0) (Rivett et al., 1972; Yonetani et al., 1973). In an OECD 408 guideline and GLP-compliant 90-day dietary study, Corynebacterium ammoniagenes fermentation product was administered at mean dietary daily intakes of 1250, 2500 or 5000 mg/kg bw/day in male and female CRL Sprague-Dawley rats (Lee, 2016b). The NOAEL was concluded to be 5000 mg/kg bw/day. The NOAEL of 5000 mg/kg bw/day is greater than 239,000 times the daily intake of glucosylated stevia extract powder 40% rebaudioside A 14% from use as a flavor ingredient.
substance as a flavor ingredient is GRAS (FEMA 4950) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of *Stevia rebaudiana* extract with rebaudiosides AM and M from use as a flavor ingredient to be 1384 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This material is derived from the leaves of *Stevia rebaudiana*. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Halligan, 2013).

Metabolic data exist that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Cardoso et al., 1996; Gardana et al., 2003; Geuns et al., 2003; Geuns et al., 2007; Hutapea et al., 1997; Koyama et al., 2003a; Koyama et al., 2003b; Nakayama et al., 1986; Purkayastha et al., 2014; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha et al., 2020; Renwick and Tarka, 2008; Roberts and Renwick, 2008; Roberts et al., 2016; Wheeler et al., 2008; Wingard, 1980). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in *in vitro* mutagenicity assays, *in vivo* studies do not provide evidence of genotoxic effects (Nakajima, 2000; Pezzuto et al., 1985, 1986; Rumelhard et al., 2016; Suttajit et al., 1993; Terai et al, 2002; Williams and Burdock, 2009). Based on the results for the various steviol glycosides, the Expert Panel did not identify specific concerns related to the potential genotoxicity of glucosylated steviol glycosides 90% supraglucosylated rebaudioside A (Goorderham et al., 2020). In a 108-week carcinogenicity study for stevioside, no carcinogenic effects were observed (Toyoda et al., 1997). In a 2-year feeding study, male and female rats were administered the equivalent of 0, 50, 150, or 550 mg/kg bw/day of a stevia extract comprised of 74% stevioside and 16% rebabudioside A. The authors considered the NOAEL from this 2-year rat feeding study of a stevia extract to be equal to 550 mg/kg bw/day, or approximately 89.5 mg/kg bw/day of rebabudioside A (Yamada et al., 1985), which is greater than 23,800 times or 3800 times, respectively, the anticipated daily per capita intake of glucosylated steviol glycosides 90% supraglucosylated rebaudioside from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding glucosylated steviol glycosides 91% supraglucosylated rebaudioside D and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4952) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of glucosylated steviol glycosides 91% supraglucosylated rebaudioside D from use as a flavor ingredient to be 692 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This material is derived from the leaves of *Stevia rebaudiana*. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel...
evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). Metabolic data exist that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Cardoso et al., 1996; Gardana et al., 2003; Geuns et al., 2003; Geuns et al., 2007; Hutapea et al., 1997; Koyama et al., 2003a; Koyama et al., 2003b; Nakayama et al., 1986; Purkayastha et al., 2014; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha and Kwok, 2020; Renwick and Tarka, 2008; Roberts and Renwick, 2008; Roberts et al., 2016; Wheeler et al., 2008; Wingard, 1980). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in in vitro mutagenicity assays, in vivo studies do not provide evidence of genotoxic effects (Nakajima, 2000; Pezzuto et al., 1985, 1986; Rumelhard et al., 2016; Suttajit et al., 1993; Terai et al., 2002; Williams and Burdock, 2009). Based on the results for the various steviol glycosides, the Expert Panel did not identify specific concerns related to the potential genotoxicity of glycosylated steviol glycosides 91% supraglucosylated rebaisdoid D (Gooderham et al., 2020). In a 108-week carcinogenicity study for steviolide, no carcinogenic effects were observed (Toyoda et al., 1997). In a 2-year feeding study, male and female rats were administered the equivalent of 0, 50, 150, or 550 mg/kg bw/day of a stevia extract comprised of 74% stevioside and 16% rebaudioside A. The authors considered the NOAEL from this 2-year rat feeding study of a stevia extract to be equal to 550 mg/kg bw/day, or approximately 89.5 mg/kg bw/day of rebaisdoid A (Yamada et al., 1985), which is greater than 15,800 times or 2,500 times, respectively, the anticipated daily per capita intake of glycosylated steviol glycosides 58% supraglucosylated stevioside from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding blue agave inulin (Agave tequilana) (CAS 9005-80-5) and concluded that use of the substance as a flavor adjuvant is GRAS (FEMA 4954) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated individually with the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of glycosylated steviol glycosides 58% supraglucosylated stevioside from use as a flavor ingredient to be 138 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). Blue agave inulin is isolated from Agave tequilana. However, no consumption ratio can be calculated. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. Inulin is classified as a source of dietary fiber, however, at the use levels specified in the GRAS application, its use as a flavor adjuvant is non-nutritive. The Expert Panel concluded that metabolic data exist for a representative member of the principle congeneric group that indicate, in the context of anticipated levels of intake, that the group would be expected to be metabolized primarily by well-established metabolic pathways to innocuous products (Lopez et al., 2003). No increases in the frequency of revertant colonies were observed in an Ames assay for inulin conducted in S. typhimurium strains TA98, TA100 and TA102 in the presence and absence of S9 metabolic activation (Márquez-Aguirre et al., 2013). However, this study does not conform to standardized test guidelines, as it did not include at least five S. typhimurium tester strains and was not conducted up to a maximum concentration of 5 mg/plate as recommended for non-toxic substances. In in vivo chromosomal aberration and micronucleus assays, groups of
male Hsd:ICR mice (4-5 weeks old) received intraperitoneal injections of two commercial blue agave fructans at concentrations of 143, 357.5 or 715 mg/kg bw (Gracia et al., 2013). In the chromosomal aberration test, the number of bone marrow cells with deletions, fragments, translocations or gaps was not significantly increased among the blue agave fructans treated animals compared to the negative controls. In the micronucleus assay, the mean frequency of micronucleated cells in femoral bone marrow was not significantly increased by treatment with the blue agave fructans at any concentration compared to the negative control counts. Given the chemical and physiological similarities of inulins [average degree of polymerization (DP)>10, range 2-60], oligofructose (average DP 4-5, range 2-8) and a commercial preparation of short-chain fructooligosaccharides (FOS), the toxicological studies conducted with FOS are considered to be predictive of the effects of inulin and oligofructose in demonstrating safety (Carabin and Flamm, 1998). No increases in the frequency of revertant colonies were observed in an Ames assay for FOS (average DP 3.5, range 2-4) conducted in S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538, as well as in E. coli strain WP2 uvrA either in the presence or absence of S9 metabolic activation (Clevenger et al., 1988), FOS were negative in a mouse lymphoma forward mutation assay in L5178Y tk +/- mouse lymphoma cells when tested up to 5000 µg/mL and when tested in an unscheduled DNA synthesis assay in HeLa cells up to 51,200 µg/mL (Clevenger et al., 1988). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of blue agave inulin (Agave tequiliana) (Gooderham et al., 2020). Administration of 20% short-chain FOS to pregnant female Wistar rats through the diet from gestation day 1-21 showed no adverse effects (Carabin and Flamm, 1999). Reduced body weight gain was seen in the treated females, though this was concluded to be due to reduced caloric value, decreased intake of food or increased diarrhea and/or soft stools in the second and third weeks of the study. Despite the reduction in body weights for treated pregnant females, the fetuses and newborn weights were not affected. In a separate study, no reproductive or developmental effects were reported for C57 BL/6J mice pretreated with a short-chain FOS-supplemented diet at a concentration of 4.75% from post-coital day 0 to 6 in an attempt to avoid the diarrhea observed in the previous study, and 5, 10, or 20% short-chain FOS from days 6-15 (Carabin and Flamm, 1999). In a chronic/carcinogenicity study, male and female Fischer 344 rats were administered diets containing FOS at concentrations of 0, 8,000, 20,000 or 50,000 ppm for 104 weeks (Clevenger et al., 1988). The authors concluded that FOS did not affect the incidence of tumors in F-344 rats and that FOS lacks carcinogenic potential. However, the Panel concluded that an increase in uric acid in the female 8,000 ppm group was a significant effect, and therefore determined the LOAEL to be 8,000 ppm, or 341 mg/kg bw/day. No adverse clinical effects were observed in an acute toxicity study when male Balb/c mice were administered single gavage doses of blue agave fructans at concentrations of 175, 500, 1750 and 5000 mg/kg bw, or when groups of male and female Hsd:ICR mice were administered by gavage one of two different blue agave preparations at concentrations from 17.5-5000 mg/kg bw (Gracia et al., 2013; Márquez-Aguirre et al., 2013). No evidence of toxicity was found when six to seven-week old male Wistar rats were fed a dietary mixture of FOS at 5% or 10% ad libitum for six weeks (Carabin and Flamm, 1999). No treatment-related toxicity was noted in a study where male Wistar rats were administered FOS by gavage daily at concentrations of 1500, 3000, or 4500 mg/kg bw/day for six weeks (Carabin and Flamm, 1999). The authors assigned a NOAEL of 4500 mg/kg bw/day which is greater than 1,900,000 times the anticipated daily per capita intake of blue agave inulin (Agave tequiliana) from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding Emblica officinalis fruit extract (CAS 90028-28-7) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4955) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of Emblica officinalis fruit extract from use as a flavor ingredient to be 346 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). Emblica officinalis is known as Indian Gooseberry, the fruits of which are edible. However, no qualitative data are available and thus no consumption ratio can be calculated. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. For a closely related botanical extract of Emblica officinalis, no mutagenic potential was reported an Ames assay in S. typhimurium strains TA98, TA100, TA1535 and TA1537 and E. coli WP2 uvrA tested with concentrations of 5-5000 µg/plate in the presence and absence of S9 metabolic activation (FDA, 2013). In a chronic toxicity study, groups of Sprague-Dawley rats were administered Emblica officinalis fruit extract that was standardized to 20% gallic acid by aqueous gavage at concentrations of 300, 600, and 1200 mg/kg bw/day for 270 consecutive days (Jaijoy et al., 2010). A recovery group of male and female rats received 1200 mg/kg bw/day of Emblica officinalis fruit extract and were maintained for an additional 28 days without treatment to assess the reversibility of any potential effects. There was a significant decrease in body weights and body weight gains for all of the test group rats on day 270, however, the recovery group at termination showed body weighs comparable to controls. The Expert Panel noted that if the decrease in body weights is not biologically relevant. The NOAEL of 1200 mg/kg bw/day is greater than 208,000 times the anticipated daily per capita intake of Emblica officinalis fruit extract from use as a flavor ingredient, and if the LOAEL of 300 mg/kg bw/day is used, it is greater than 52,000 times the daily per capita intake of Emblica officinalis fruit extract from use as a flavor ingredient.
dietary studies in Wistar rats when administered the substance at 200 mg/kg bw of the constituent compound choline chloride (FEMA 4500) by oral gavage, or when administered 200 mg/kg bw of the constituent compound betaine monohydrate (FEMA 4223) was negative at dose levels up to 2,000 mg/kg bw (Asquith et al., 1996b). In an in vitro human lymphocyte assay the constituent compound betaine monohydrate (FEMA 4223) was not clastogenic at concentrations up to 10,000 µg/mL (Asquith et al., 1996c). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of Boehmeria nivea leaf extract (Gooderham et al., 2020). No signs of developmental toxicity were observed when rats and rabbits were fed diets containing the constituent compound nonanedioic acid (CAS 123-99-9) at concentrations of either 140 or 200 mg/kg bw/day respectively throughout pregnancy (Mingrone et al., 1983). No toxicologically significant clinical observations were detected in congruent 90- and 180-day dietary studies in Wistar rats when administered the constituent compound nonanedioic acid (CAS 123-99-9) at concentration of 140 and 280 mg/kg bw/day, nor when New Zealand rabbits were administered the same compound at concentrations of 200 and 400 mg/kg bw/day (Mingrone et al., 1983). In a GLP 28-day, single-dose study, no adverse effects were found between treated groups or their respective controls when male and female Balb/c mice were administered 200 mg/kg bw of the constituent compound choline chloride (FEMA 4500) by oral gavage, or when administered 200 mg/kg bw of choline chloride every alternate day via intraperitoneal injection (Mehta et al., 2009). In a series of three studies conducted to evaluate the sub-acute and sub-chronic effects of the constituent compound betaine (FEMA 4223), rats were administered the substance at concentrations of 0, 1147, 2298, or 5771 mg/kg bw/day in the feed. Groups of male and female Sprague-Dawley rats were fed the diets in a dose range-finding study (14 days), a sub-chronic study (90-93 days), and a reversibility study (28 days). No treatment-related toxicity was reported, and follow-up 28 and 90-day studies were conducted to investigate the levels at which triglyceride accumulation appeared in the livers of female Sprague-Dawley rats were administered betaine (FEMA 4223) at concentrations of 0, 718, 1071, 1428, or 7143 mg/kg bw/day in the feed. No significant treatment-related adverse effects were observed (Hayes et al., 2003).

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding rebaudioside M 85% (CAS 1220616-44-3) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4957) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of rebaudioside M 85% from use as a flavor ingredient to be 761 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1998). The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). Metabolic data exist that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products or to be excreted as such (Smith et al., 2018). In an OECD 471 guideline and GLP-compliant Ames assay in S. typhimurium strains TA1537, TA1535, TA98, TA100 and TA102, Boehmeria nivea leaf extract did not increase the frequency of revertant colonies in either the presence or absence of S9 metabolic activation (Tekale, 2018b). In an Ames assay in S. typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 the constituent compound, betaine monohydrate (FEMA 4223), did not increase the frequency of revertant colonies in the absence or presence of S9 metabolic activation (Asquith et al., 1989a). An in vivo mouse micronucleus study with the constituent compound betaine monohydrate (FEMA 4223) was negative at dose levels up to 2,000 mg/kg bw (Asquith et al., 1996b). In an in vivo mouse micronucleus study with the constituent compound betaine monohydrate (FEMA 4223) was negative at dose levels up to 2,000 mg/kg bw (Asquith et al., 1996b). In an in vitro human lymphocyte assay the constituent compound betaine monohydrate (FEMA 4223) was not clastogenic at concentrations up to 10,000 µg/mL (Asquith et al., 1996c). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of Boehmeria nivea leaf extract (Gooderham et al., 2020). No signs of developmental toxicity were observed when rats and rabbits were fed diets containing the constituent compound nonanedioic acid (CAS 123-99-9) at concentrations of either 140 or 200 mg/kg bw/day respectively throughout pregnancy (Mingrone et al., 1983). No toxicologically significant clinical observations were detected in congruent 90- and 180-day dietary studies in Wistar rats when administered the constituent compound nonanedioic acid (CAS 123-99-9) at concentration of 140 and 280 mg/kg bw/day, nor when New Zealand rabbits were administered the same compound at concentrations of 200 and 400 mg/kg bw/day (Mingrone et al., 1983). In a GLP 28-day, single-dose study, no adverse effects were found between treated groups or their respective controls when male and female Balb/c mice were administered 200 mg/kg bw of the constituent compound choline chloride (FEMA 4500) by oral gavage, or when administered 200 mg/kg bw of choline chloride every alternate day via intraperitoneal injection (Mehta et al., 2009). In a series of three studies conducted to evaluate the sub-acute and sub-chronic effects of the constituent compound betaine (FEMA 4223), rats were administered the substance at concentrations of 0, 1147, 2298, or 5771 mg/kg bw/day in the feed. Groups of male and female Sprague-Dawley rats were fed the diets in a dose range-finding study (14 days), a sub-chronic study (90-93 days), and a reversibility study (28 days). No treatment-related toxicity was reported, and follow-up 28 and 90-day studies were conducted to investigate the levels at which triglyceride accumulation appeared in the livers of
incubation method (Fujishima, 2019). The structural relative TA1535, TA1537 and E. coli strain WP2uvrA using the pre-menthyl glutarate in S. typhimurium results were observed in the Ames assays for the structurally and pre-incubation methodologies (Haddouk, 2003). Negative E. coli TA100, TA102 and mutation assay in S. typhimurium strains TA98, TA100, TA102, TA104, TA1535, TA1537 and E. coli strain WP2uvrA using the preliminary incubation method (Fujishima, 2019). The structural relative I-monomethyl glutarate (FEMA 4006) was not mutagenic in an OECD 471 guideline and GLP-compliant bacterial reverse mutation assay in S. typhimurium TA1535, TA1537, TA98, TA100, TA102 and E. coli WP2 uvrA using plate incorporation and pre-incubation methodologies (Haddouk, 2003). Negative results were observed in the Ames assays for the structurally related substance, vanillin (FEMA 3107), in S. typhimurium strains TA92, TA94, TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, and TA2637 using the plate incorporation and pre-incubation methodologies (De Flora et al., 1994; Florin et al., 1980; Ishidate et al., 1984; Jones, 1986; Kasamaki et al., 1982; Lawlor, 1991; Marzin, 1979a; Mortelmans et al., 1986; Nagabhushan and Bhide, 1985; Pool and Lin, 1982; Rapson et al., 1980). For the same structural relative, mixed positive and negative results were observed in in vitro sister chromatid exchange, chromosomal aberration and micronucleus induction assays conducted in Chinese hamster cells and human lymphocytes, human lymphocytes, and human cell lines, respectively (Jansson et al., 1986; Jansson and Zech, 1997; Sanjal et al., 1987; Sasaki et al., 1987). Vanillin (FEMA 3107) was negative in an unscheduled DNA synthesis assay in rat hepatocytes (Heck et al., 1989) and was negative in bone marrow micronucleus assays in female OF1 mice, male BDF1 mice, and in male MS/Ae mice (Inouye et al., 1988; Marzin, 1979b; Sutou et al., 1999). The structurally related substance, menthof (FEMA 2665), was uniformly negative for mutagenic activity in standard Ames studies conducted in several S. typhimurium strains with and without metabolic activation (Andersen and Jensen, 1984; Gomes-Carneiro et al., 1998; Ishidate et al., 1984; Kirkland et al., 2016; Nohmi et al., 1985; Zeiger et al., 1988). Potential genotoxicity was observed in an alkaline elution rat hepatocyte assay, but no sister chromatid exchanges in Chinese hamster ovary (CHO) cells, human lymphocytes or human embryonic lung cells, nor were chromosome aberrations observed in Chinese hamster lung fibroblasts, CHO cells or human lymphocytes (Ishidate et al., 1984; Ivett et al., 1989; Matsuoka et al., 1998; Murthy et al., 1991). Menthol was non-mutagenic in LS178Y mouse lymphoma forward mutation assays, in an in vitro comet assay, in in vivo single and repeated dose oral gavage studies, in in vivo alkaline comet assays, and was negative in a bone marrow micronucleus assay in B6C3F1 mice (Kiffe et al., 2003; Myhr et al., 1991; Olivo, 2016; Shelby et al., 1993; Tennant et al., 1987; Uno et al., 2015). The structural relative glutaric acid was negative in an Ames assay in S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538, in a mouse lymphoma assay conducted in L5178Y/TK cells, and in a bone marrow micronucleus assay in CD-1 mice (Fiune et al., 2012). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 4-formyl-2-methoxyphenyl I-methyl glutarate (Gooderham et al., 2020). In an OECD 407 guideline and GLP-compliant 28-day repeat-dose toxicity study in Sprague Dawley rats, oral administration of a 60-65%/30-35% mixture of the structural relatives I-monomethyl glutarate (FEMA 4006) and dimethyl glutarate (FEMA 4604) resulted in a NOAEL of 248 mg/kg bw/day, which is 2,480,000 times the anticipated daily per capita intake of 4-formyl-2-methoxyphenyl I-methyl glutarate from use as a flavor ingredient (Dhansa, 2008). Potential short-term and long-term toxicity was evaluated in a series of repeat-dose toxicity studies with vanillin administered to rats (FEMA 3107) (Hagan et al., 1967; Mancebo et al., 2003; OECD SIDS, 2002). Based on a review of these studies, the Expert Panel determined a conservative NOAEL for the structural relative vanillin (FEMA 3107) to be 150 mg/kg bw/day, which is greater than 1,200,000 times the anticipated per capita intake of 4-formyl-2-methoxyphenyl I-methyl glutarate from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 9-dodecen-12-olide (CAS 301310-73-6; 79894-05-6) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4959) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of aliphatic, alicyclic, alicyclic-fused and aromatic-fused ring lactones (Adams et al., 1998; JECFA, 1998, 2011; SLR, B1C). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of 9-dodecen-12-olide from use as a flavor ingredient to be 0.1 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of 9-dodecen-12-olide from use as a flavor ingredient to be 0.1 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). This material is known to be found in Yuzu, a citrus fruit native to Japan; however, quantitative data are unavailable and therefore a consumption ratio cannot be calculated (Van Dongen and Donders, 2021). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that the lactone ring of 9-dodecen-12-olide will undergo hydrolysis followed by conjugation and excretion of the resulting hydroxyoxycarboxylic acid derivative, or beta-oxidation of the hydroxy acid to yield short chain polar metabolites that are excreted either unchanged or in conjugated form (Smith et al., 2018). No increases in the frequency of reverse mutations were observed in an Ames assay with 9-dodecen-12-olide in S. typhimurium strains TA100 and TA98 in the presence and absence of S9 metabolic activation (Kino, 2019). The structural relative isoambrettolide (FEMA 4145) was non-
mutagenic in an OECD 471 guideline and GLP-compliant Ames assays in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 using the pre-incubation and plate incorporation methods (Forichon, 1997; Poth, 2003). No increases in the frequency of reverse mutations were observed in an OECD 471 guideline and GLP-compliant Ames assay with the structural relative, oxacyclohexadecen-2-one in *S. typhimurium* strain TA1535, TA1537, TA98, TA100, and TA102 using both the plate incorporation and pre-incubation methodologies in the absence and presence of S9 metabolic activation (Sokolowski, 2005). In an OECD 473 guideline and GLP-compliant *in vitro* chromosomal aberration study in human lymphocytes, oxacyclohexadecen-2-one did not induce increases in structural chromosomal aberrations (Schulz, 2005). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 9-dodecen-12-olide (Gooderham et al., 2020). In an OECD 407 guideline and GLP-compliant 28-day study in Sprague-Dawley rats, oral administration of the structural relative oxacyclohexadec(10)-en-2-one resulted in a NOAEL of 1000 mg/kg bw/day (ECHA, 2018a). In an OECD 407 guideline and GLP-compliant 28-day study in Crl:CD®BR rats, administration of the structural relative oxacyclohexadecen-2-one, the Expert Panel concluded the NOAEL to be 1000 mg/kg bw/day (Leuschner, 2005). In an OECD 408 guideline and GLP-compliant 90-day oral toxicity study in Sprague-Dawley Crl:CD®BR rats, administration of the structural relative oxacyclohexadecen-2-one via carboxymethylcellulose gavage resulted in a NOAEL of 1000 mg/kg bw/day, which is 500,000,000 times the anticipated daily *per capita* intake of 9-dodecen-12-olide from use as a flavor ingredient (Thomas, 1998). In an OECD 421 guideline and GLP-compliant reproductive and developmental toxicity study in Sprague-Dawley rats, the administration of the structural relative isoamrobatellidole (ECHA 4145) resulted in a NOAEL of 1000 mg/kg bw/day, which is 500,000,000 times the anticipated daily *per capita* intake of 9-dodecen-12-olide from use as a flavor ingredient (ECHA, 2018b).

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 4-methyltrideca-2E,4-dienal (CAS 2369713-22-2) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4961) in the food categories and at the use levels specified in Table 2. The substance was evaluated individually within the context of the chemical group of aliphatic linear and branched-chain *alpha*, *beta*-unsaturated aldehydes and related alcohols acids and esters (Adams et al., 2008; JECFA, 2009, 2012; SLR, M1). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of 4-methyltrideca-2E,4-dienal from use as a flavor ingredient to be 0.003 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is anticipated that 4-methyltrideca-2E,4-dienal will undergo oxidation to 4-methyltrideca-2E,4-dienoic acid, which then undergo *beta*-oxidation and complete metabolism to CO₂ and H₂O. In an alternative pathway, conjugation of the aldehyde with glutathione and subsequent excretion as the mercapturic acid derivative can occur (Smith et al., 2018). The Expert Panel reviewed the extensive literature available for 2,4-alkadienals, including assays conducted by the National Toxicology
The Expert Panel did not identify specific concerns related to the genotoxicity of 4-methyltrideca-2,4-dienal (FEMA 3429), the Expert Panel noted clear carcinogenic effects including increased incidences of forestomach epithelial hyperplasia (NTP, 2003). However, the Expert Panel determined that the effects were due to the high bolus doses administered in the studies, and the strong irritating nature of 2,4-hexadienal. A subchronic toxicity study of the structural relative trans,trans-2,4-hexadienal (FEMA 3429) administered to F344/N rats at doses of 7.5, 15, 30, 60, or 120 mg/kg bw/day by gavage 5 days per week for a total of 70 doses over 14 weeks, no mortalities were observed in this study (NTP, 2003). Significant reductions in final mean bodyweights and bodyweight gains were observed in male rats at doses of 30 mg/kg bw/day and above. No other signs of clinical toxicity were observed in treated animals at any dose with the exception of increased salivation in males and females at 30 or 120 mg/kg bw/day during week 4, and only in 120 mg/kg bw/day groups at later times. Increased incidences of mild-to-moderate forestomach epithelial hyperplasia were reported in both males and females at 120 mg/kg bw/day, accompanied by forestomach-localized tissue degeneration and active chronic inflammation. Increased incidences of olfactory epithelial atrophy, osteofibrosis, and excessive exudate of the nose were also reported in males at 120 mg/kg bw/day. There were no biologically significant changes in organ weights at any dose level. Statistically significant but sporadic and non-dose dependent variations in hematological and clinical chemistry parameters were reported but were not considered related to treatment. Based on these findings, the NOEL was determined to be 15 and 60 mg/kg bw/day for male and female rats, respectively. This NOEL is 300,000,000 times the anticipated daily per capita intake of 4-methyltrideca-2,4-dienal from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding Pandan leaf (Pandanus amaryllifolius) distillate extract (CAS 1175005-60-3) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4963) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated per capita intake ("eaters only") of Pandanus amaryllifolius distillate extract from use as a flavor ingredient.
to be 0.7 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This material is derived from the pandan leaf, which has traditionally been used for cooking in southeast Asia as a flavoring in rice cooking, sweets, and beverages. However, quantitative data are not available and a consumption ratio could not be calculated. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. Metabolic data exist for a representative member of the principal identified congenic groups that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Smith et al., 2018). The Expert Panel reviewed the key constituents of Pandan leaf (Pandanus amaryllifolius) distillate extract and noted that the congenic group intakes were below the respective thresholds of toxicological concern. Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of Pandan leaf (Pandanus amaryllifolius) distillate extract (Gooderham et al., 2020).

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding Corynebacterium glutamicum cell free fermentation product and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4964) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated per capita intake ("eaters only") of Corynebacterium glutamicum cell free fermentation product to be 1255 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. Metabolic data exist for a representative member of the principal identified congenic groups that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Smith et al., 2018). No evidence of mutagenicity was observed in an OECD 471 guideline and GLP-compliant Ames assay with Corynebacterium glutamicum cell free fermentation product in S. typhimurium strains TA98, TA100, TA1535 and TA1537 as well as E. coli WP2uvrA (pKM101) using the pre- incubation method either in the presence or absence of S9 metabolic activation (Kim, 2019a). No induction of chromosomal aberrations was observed in Chinese Hamster Lung (CHL/IU) cells in an OECD 473 guideline and GLP-compliant in vitro chromosomal aberration assay with Corynebacterium glutamicum cell free fermentation product (Kim, 2019b). In an OECD 474 guideline and GLP-compliant in vivo micronucleus assay conducted in male ICR mice with Corynebacterium glutamicum cell free fermentation product, no evidence of genotoxicity was observed (Kim, 2019c). No evidence of genotoxicity was observed when the structural relative monosodium L-glutamate monohydrate (FEMA 2756) was tested in an OECD 471 guideline and GLP-compliant Ames assay, GLP-compliant in vitro chromosomal aberration assay with CHL/IU cells, OECD 490 guideline and GLP-compliant in vitro mouse lymphoma assay conducted in TK +/− L5178Y cells, OECD 487 guideline and GLP-compliant in vitro micronucleus assay in human peripheral blood lymphocytes, or an OECD 474 guideline and GLP-compliant in vivo micronucleus assay (Takumi et al., 2019). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of Corynebacterium glutamicum cell free fermentation product (Gooderham et al., 2020). No evidence of toxicity was observed when male and female Sprague Dawley rats were administered Corynebacterium glutamicum cell free fermentation product in an OECD 407 guideline-compliant 28-day toxicity study and an OECD 408 guideline and GLP-compliant 90-day toxicity study at concentrations up to 5000 mg/kg bw/day (Moon, 2019a, b). The Expert Panel determined the most conservative NOAEL for Corynebacterium glutamicum cell free fermentation product to be 5000 mg/kg bw/day, which is greater than 238,000 times anticipated daily per capita intake of Corynebacterium glutamicum cell free fermentation product from use as a flavor ingredient. In a chronic toxicity study of the structural relative monosodium glutamate (FEMA 2756) at dietary levels up to 4000 mg/kg bw/day in Charles River rats, increased incidence and earlier onset of spontaneous subepithelial basophilic deposits in the renal pelvis of treated rats were observed. In female rats, there was an increase in the incidence of focal mineralization beneath the epithelium of the renal pelvis at all intake levels for the duration of the study. However, this incidence was also higher in control female rats compared to control males by 104 weeks and it was considered a spontaneous occurrence within the historical control incidence rates and unrelated to the administration of the test material (Owen et al., 1978). In another chronic toxicity study, no evidence of carcinogenicity was observed when Fisher 344 rats were administered the structural relative monosodium glutamate (FEMA 2756) in the diet at concentrations up to 1982 mg/kg bw/day in males and 2311 mg/kg bw/day in females for 104 weeks (Shibata et al., 1995). The NOAEL of 1982 mg/kg bw/day for the structural relative monosodium glutamate (FEMA 2756) was greater than 94,000 times the anticipated daily per capita intake of Corynebacterium glutamicum cell free fermentation product from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding N-1-[(4-amino-2,2-dioxido-1H-benzo[c][1,2,6]thiadiazin-5-y]oxy)-2-methylpropan-2-ylisonicotinamide (CAS 1622458-32-5) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4965) (Smith et al., 2005a) in the food categories and at the use levels specified Table 2. The substance was evaluated individually within the context of the chemical group of aliphatic and aromatic amines and related amides (JECFA, 2006, 2008, 2011, 2012, 2017; SLR, A7, C21). The Expert Panel calculated the anticipated per capita intake ("eaters only") of N-1-[(4-amino-2,2-dioxido-1H-benzo[c][1,2,6]thiadiazin-5-y]oxy)-2-methylpropan-2-ylisonicotinamide from use as a flavor ingredient to be 277
µg/person/day, which is above the threshold of toxicological concern (TTC) for structural class III (90 µg/person/day) (Munro et al., 1996). This material is not known to occur in nature and thus no consumption ratio can be calculated. The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Halligan, 2013). In vitro rat and human microsomal incubations of N-1-(4-amino-2,2-dioxido-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2-methylpropan-2-yl)isonicotinamide showed minor amounts of hydroxylated metabolites (Chen and Castillo, 2011; Guia, 2011). In vivo pharmacokinetic, bioavailability and metabolism studies in Sprague-Dawley rats indicated that N-1-(4-amino-2,2-dioxido-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2-methylpropan-2-yl)isonicotinamide is poorly bioavailable, poorly absorbed by the intestinal tract and undergoes limited amounts of metabolic transformation prior to excretion, which occurs predominately in the feces (Levy, 2019; Metabolism Study, 2019a, b, c). N-1-(4-amino-2,2-dioxido-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2-methylpropan-2-yl)isonicotinamide and its secondary component N-1-(4-amino-2,2-dioxido-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2-methylpropan-2-yl)pivalamide were non-mutagenic when tested in Ames assays with S. typhimurium TA98 and TA100 only (Samsam, 2012), and when tested with those strains plus TA1535, TA1537 as well as E. coli WP2uvrA either in the presence or absence of S9 metabolic activation (Dakoulas, 2019a, b). The structural relative N-1-(4-amino-2,2-dioxido-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2-methylpropan-2-yl)isonicotinamide (FEMA 4899) was non-mutagenic in a series of in vitro genotoxicity assays (Karanewsky et al., 2017). The structural relative 3-[4-amino-2,2-dioxido-1H-2,1,3-benzothiadiazin-5-yl]oxy]-2,2-dimethyl-N-propylpropanamide (FEMA 4701) similarly showed no evidence of mutagenicity, including no increases in the frequency of revertant colonies or chromosomal aberrations, non-mutagenic in vitro and in an OECD 474 guideline and GLP-compliant in vivo mammalian erythrocyte micronucleus test (Arthur et al., 2015). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of N-1-(4-amino-2,2-dioxido-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2-methylpropan-2-yl)isonicotinamide (FEMA 4899) to pregnant female Sprague Dawley rats by gavage resulted in a NOAEL of 200,000 times greater than the anticipated daily per capita intake of N-1-(4-amino-2,2-dioxido-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2-methylpropan-2-yl)isonicotinamide from use as a flavor ingredient (Karanewsky et al., 2017). Apart from significantly increased pituitary gland weights relative to body and brain weights, no other significant treatment-related effects were observed in a 28-day dietary toxicity study in male and female Sprague Dawley rats administered the structural relative 3-[(4-amino-2,2-dioxido-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2,2-dimethyl-N-propylpropanamide (FEMA 4701) at levels of 0, 10, 30 and 100 mg/kg bw/day. In a follow-up 90-day dietary toxicity study of the same structural relative administered to male and female Sprague Dawley rats at levels of 0, 5, 10 or 20 mg/kg bw/day, no significant adverse effects or significant differences were observed in ACTH (adrenocorticotropic hormone), TSH (thyroid stimulating hormone), cortico-sterone, LH (luteinizing hormone) and FSH (follice stimulating hormone) levels were observed. A NOAEL of 20 mg/kg bw/day was established for the structural relative FEMA 4701 (Arthur et al., 2015), which is 4,000 times greater the anticipated daily per capita intake of N-1-(4-amino-2,2-dioxido-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2-methylpropan-2-yl)isonicotinamide from use as a flavor ingredient. Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 4-methylheptan-3-one (CAS 6137-11-7) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4966) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of saturated and unsaturated aliphatic acyclic secondary alcohols, ketones and related esters (JECFA, 1999, 2003, 2017; SLR, A1). The Expert Panel calculated the anticipated per capita intake ("eaters only") of 4-methylheptan-3-one from use as a flavor ingredient to be 7 µg/person/day, which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). This material is known to occur in black chokeberry (Aronia melanocarpa), roasted Malaysian tropical almond nuts (Terminalia catappa) and guava fruit (Psidium guajava L.) (Idstein and Schreier, 1985; Kraujalyte et al., 2013; Lasekan and Abbas, 2010). However, due to limited quantitative data, a consumption ratio could not be calculated. The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that 4-methylheptan-3-one will be reduced to the corresponding secondary alcohol, followed by glucuronide or sulfate conjugation and urinary elimination (Kamil et al., 1953; Smith et al., 2018). Alternatively, at higher exposure levels, 4-methylheptan-3-one is expected to undergo α-oxidation or β-oxidation in the hepatocyte endoplasmic reticulum to the corresponding hydroxymethyl ketones and subsequently to the corresponding ketocarboxylic acids (α-oxidation) or diketones (β-oxidation). The carboxylic acids are expected to be conjugated with glucuronic acid and eliminated in the urine. Of the possible metabolites, omega-1 oxidation is expected to yield 4-methylheptan-2,5-dione, a gamma-diketone and a metabolite of toxicological concern based on
available literature (Couri and Milks, 1982; Lehning et al., 2000; O’Donoghue et al., 1984; Opanashuk et al., 2001; Topping et al., 1994). In addition, oxidation of the terminal carbon oxidation proximal to the carbonyl group of the candidate substance is expected to yield 4-methyl-3-heptan-2-one from use as a flavor ingredient. Neurotoxicity observed at higher doses (O’Donoghue et al., 1984). In an OECD 471 guideline and GLP-compliant Ames assay conducted in S. typhimurium strains TA98, TA100, TA1535 and TA1537 as well as E. coli strain WP2uvrA (pKM101), 4-methylheptan-3-one was non-mutagenic in the presence and absence of S9 metabolic activation at concentrations up to 1000 µg/plate (Spruth, 2019). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 4-methylheptan-3-one (Gooderham et al., 2020). In an OECD 414 guideline and GLP-compliant developmental toxicity study, sperm positive female Hsd. Han: WIST rats were administered the structural relative 5-methylheptan-3-one by oral gavage at doses of 0, 80, 300 and 750 mg/kg bw/day during gestation days 5-19 (ECHHA, 2016). Clinical signs of toxicity, treatment-related decreases in feed consumption accompanied by decreased bodyweight and bodyweight gain, lower fetal- and placental weight, higher relative placental weight, reduced fetal body weights, fetal skeletal malformations in some fetuses and increased incidence of skeletal variations due to delayed ossification attributed to maternal toxicity, were reported in the high-dose. The NOAEL for maternal and developmental toxicity was determined to be 300 mg/kg bw/day. In a 14-week toxicity study, the administration of the structural relative 3-heptanone (FEMA 2545) was administered to male rats by gavage at doses of 0, 179, 357, 714, 1428 or 2657 mg/kg bw/day for five days per week. resulted in a NOEL of 179 mg/kg bw/day due to evidence of neurotoxicity and central nervous system depression or narcosis at higher doses (O’Donoghue et al., 1984). In a 120-day drinking water study, female Wistar rats were treated with the structural relative 3-heptanone (FEMA 2545) at concentrations of 30 mg/kg bw/day, and at concentrations of 32 or 38 mg/kg bw/day in two preliminary studies. Increased kidney weights relative to bodyweight were observed, though these changes in organ weights were not accompanied with other histopathological changes (Homans and Maronpot, 1977). In a GLP-compliant 90-day toxicity study, the administration of the structural relative 5-methylheptan-3-one (ethyl isoamyl ketone) to adult male Sprague-Dawley rats by gavage at dose levels of 59, 293 and 586 mg/kg bw/day for 5 days/week resulted in a NOAEL of 59 mg/kg bw/day based on neurotoxicity observed at higher doses (Topping, 1984). This NOAEL is 590,000 times greater than the anticipated daily per capita intake of 4-methylheptan-3-one from use as a flavor ingredient. Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 

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\text{delta-cadinene (CAS 483-76-1) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4987) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. The substance was evaluated individually within the context of the chemical group of aliphatic and aromatic hydrocarbons (Adams et al., 2011; JEFCF, 2006, 2015; SLR, A6). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of delta-cadinene from use as a flavor ingredient to be 15 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The material is known to occur in Mastic (Pistacia lentiscus), Citrus sinensis x Poncirus trifoliata – Troyer Citrange essential oil (γ-Cadinene), Basil essential oil, Rio Red grapefruit juice, Beta vulgaris essential oil, Propolis essential oil. Gnanphallum affine (cudweed) oil, Damiana essential oil, and Majorana essential oil (Alcaraz-Meléndez et al., 2004; Caccioni et al., 1998; Chaudhary et al., 2017; Fernandes et al., 2015; Van Dongen and Donders, 2021; Souleles, 1991; Zardi-Bergaoui et al., 2017; Zeng et al., 2011; Zheljazkov et al., 2008). However, a consumption ratio could not be calculated. The Expert Panel noted the assay of the material was 93-95% of the named material with other aliphatic and aromatic hydrocarbons as the secondary component (3%) and considered the specification of the material to be adequately characterized by the purity assays and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that delta-cadinene will undergo hydroxylation of alkyl ring substituents to yield hydroxylated species that may be further oxidized and excreted, either unchanged or in conjugated form as glucuronide and sulfate conjugates. Additionally, the alkene groups present may undergo epoxidation and subsequent conjugation with glutathione or hydrolysis (Smith et al., 2018). delta-Cadinene was non-mutagenic in an OECD 471 guideline and GLP-compliant Ames assay when tested up to 5 µl/plate (approximately 4 µg/plate based on the specific density of the substance) in E. coli strains TA98, TA100, TA1535 and TA1537 and E. coli WP2uvrA (pKM101) either in presence or absence of S9 metabolic activation (Schreib, 2020a). Similar results were observed when the structurally related substances valencene (FEMA 3443) and cadinene (non-isomer specific) were tested in the same strains at concentration up to 5000 µg/plate (Bhalji, 2016c; Bowles and Thompson, 2013). The same structural relatives did not result in significant increases in micronuclei frequency when tested in OECD 487 guideline and GLP-compliant in vitro micronuclear assays in human lymphocytes at concentrations up to 103 µg/mL (Bhalji, 2016a, 2017c). No evidence of mutagenicity was observed when the structural relative β-caryophyllene (FEMA 2252) was tested in a series of in vitro and in vivo genotoxicity assays (Di Sotto et al., 2010; Heck et al., 1989; Jagannath, 1984; Molina-Jasso et al., 2009; Sasaki et al., 1987; Seifried et al., 2000). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of delta-cadinene (Gooderham et al., 2020). No adverse effects were observed when female Swiss mice were administered the structural relative β-caryophyllene (FEMA 2252) at concentrations of 300 mg/kg bw/day or 2000 mg/kg.
Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding Stevia rebaudiana extract with rebaudioside M ≥90% and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4968) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of Stevia rebaudiana extract with rebaudioside M ≥90% from use as a flavor ingredient to be 1384 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The material is derived from the leaves of Stevia rebaudiana. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Halligan, 2013). Metabolic data exist that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Gómez-Juaristi et al., 2018; Marques and Farah, 2010; Moura de Oliveira et al., 2017). Yerba Mate extract (Ilex paraguariensis A. St.-Hil.) was non-mutagenic at concentrations up to 5000 µg/plate in an OECD 471 guideline and GLP-compliant five-strain Ames assay conducted in S. typhimurium strains TA1537, TA1535, TA100, TA98 as well as E. coli WP2uvrA either in the presence and absence of S9 metabolic activation (Heard, 2019a). The substance also did not result in an increase in the induction of micronuclei in TK6 cells in an OECD 487 guideline and GLP-compliant in vitro micronucleus assay (Heard, 2019b). In an OECD 474 and 489 guideline and GLP-compliant in vivo combined micronucleus and comet assay in male Sprague Dawley rats at concentrations up to 2000 mg/kg bw/day, no evidence of mutagenicity was observed (Moy, 2020). A related aqueous mate extract (Ilex paraguariensis) was non-mutagenic and non-cytotoxic in an Ames assay in S. typhimurium TA97 and TA98 at concentrations up to 80,000 µg/plate (Fonseca et al., 2000). In vitro and in vivo chromosome aberration assays with the same related aqueous mixture resulted in significant increases in the frequency of metaphases with chromosome aberrations at concentrations of 100-750 µg/mL in the absence of S9 metabolic activation in human lymphocytes but was negative when male and female Wistar rats were administered the same aqueous mate extract at 0, 1000, or 2000 mg/kg bw (Fonseca et al., 2000). In a teratogenicity study, the administration of the constituents chlorogenic acid and caffeic acid to pregnant Wistar rats at concentrations up to 5-500 mg/kg bw/day and 40-187.5 mg/kg bw/day, respectively, resulted in NOAELS of the highest concentrations (Chauge and Swinyard, 1976). The Expert Panel determined that the NOAELS established for chlorogenic acid and caffeic acid are 38,400 times greater and 14,000 times greater, respectively, than the anticipated daily per capita intake of Yerba Mate extract (Ilex paraguariensis A. St.-Hil.) from use as a flavoring with modifying properties. The administration of a related
preparation, dried mate extract (Ilex paraguariensis) dissolved in water and administered to male and female Rattus norvegicus Wistar var albinus rats at a concentration of 2000 mg/kg bw/day for 12 weeks did not induce toxic effects (de Andrade et al., 2012). In an eight-week dietary toxicity study, the related preparation of 250 mL of the aqueous extract of Ilex paraguariensis was provided to male Wistar rats (8/group) as their only source of drinking water. Edema of the kidney (mainly associated with increased diuresis) and slight blood congestion were observed in treated rats compared to the control group. Increased urogenesis, defined by the authors as visible intensive glomerular filtration, was observed in treated rats as evidenced by tissue staining with Alcian blue. Significantly reduced basal membrane polysaccharides within the glomeruli was observed in the morphometric analysis of the kidneys. Significantly decreased membrane thickness of the capillary tuft and significantly increased glomerular capsule size were observed in treated rats. The authors suggested that the increased urogenesis observed was associated with decreased proteoglycan content in the capillary tuft (Kuropka et al., 2021). In a three-week dietary toxicity study, decreased kidney and adrenal weights were observed in Sprague Dawley rats (5/group) provided approximately 500 mg/kg bw/day of the constituent chlorogenic acid compared to the negative control group (Eklund, 1975). Increased lung γ-tocopherol and pooled a- and γ-tocopherol levels as well as decreased lung lipids were observed in Sprague Dawley rats (8/group) provided approximately 100 mg/kg bw/day of the constituent chlorogenic acid compared to the negative control group in a 28-day dietary toxicity study (Frank et al., 2003). The Expert Panel reviewed the other key constituents of Yerba mate extract (Ilex paraguariensis A. St-Hil) and noted that the congeneric group intakes, with the exception of phenol and phenol derivatives, were below the respective thresholds of toxicological concern.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 2-methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one (CAS 2413115-68-9) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4970) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of aliphatic and aromatic hydrocarbons (Adams et al., 2011; Andrade et al., 2012). In an eight-week dietary toxicity study, decreased kidney and adrenal weights were observed in Sprague Dawley rats (5/group) provided approximately 500 mg/kg bw/day of the constituent chlorogenic acid compared to the negative control group in a 28-day dietary toxicity study (Frank et al., 2003). The Expert Panel reviewed the other key constituents of Yerba mate extract (Ilex paraguariensis A. St-Hil) and noted that the congeneric group intakes, with the exception of phenol and phenol derivatives, were below the respective thresholds of toxicological concern.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding beta-farnesene (CAS 18794-84-8) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4971) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of aliphatic and aromatic hydrocarbons (Adams et al., 2011; JECFA, 2006, 2015; SLR, A6). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of beta-farnesene from use as a flavor ingredient to be 21 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The substance occurs naturally in angelica (Angelica archangelica L.), asharti pepper (Piper guineense Schum and Thom), chamomile, citrus fruits, curry (Bergera koenigii L.), ginger (Zingiber spp), pepper (Piper nigrum L.), pistacia palatina (Pistacia terebinthus L.), thyme (Thymus species), Alpinia species; coriander seed (Coriandrum sativum L.), lemon balm (Melissa officinalis L.), marula (Sclerocarya birrea subsp. Caffra), Ocimum species, omija fruit (Schisandra chinensis Bailon), passion fruit (Passiflora spp), quince, marmelo (Cydonia oblonga Mill.), rum, walnut (Juglans species) and wine (Van Dongen and Donders, 2021). Based on the quantitative data, a consumption ratio of 5 could be calculated (Stolfberg and Grundschober, 1987). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). It is presumed that 2-methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one will be hydroxylated, followed by the subsequent conjugation of some hydroxylated groups primarily with glucuronic acid to conjugated products (Laue and Hostettler, 2019a). In an Ames microplate assay conducted in S. typhimurium TA98 and TA100, 2-methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one did not significantly increase the number of revertants at concentrations up to 2.5 µg/mL in the presence and absence of S9 metabolic activation (Laue and Hostettler, 2019b). In an OECD 471 guideline and GLP-compliant Ames assay, 2-methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one was non-mutagenic at concentrations up to 5000 µg/plate in S. typhimurium strains TA98, TA1535, TA100, TA1537 as well as E. coli WP2uvrA either in the presence or absence of S9 metabolic activation (Dakoulas, 2020). In an OECD 487 guideline and GLP-compliant in vitro micronucleus assay conducted in human peripheral blood lymphocytes, no significant induction of micronuclei was observed at concentrations of 84-172 µg/mL, 58.8-146 µg/mL and 21.5-50 µg/mL for 4 hours in the absence and presence of S9 metabolic activation and for 24 hours in the absence of S9 metabolic activation, respectively (Xie, 2020). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 2-methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one (Gooderham et al., 2020).
Additionally, the alkenes groups present may undergo epoxidation and subsequent conjugation with glutathione or hydrolysis. No increases in the frequency of revertant colonies were observed in an OECD 471 guideline and GLP-compliant Ames assay for beta-farnesene conducted in S. typhimurium strains TA97a, TA98, TA100, TA1535 and TA1537 and E. coli WP2uvrA (pKM 101) in the presence and absence of S9 metabolic activation (ECHA, 2009b; Schreib, 2020b). In OECD 473 guideline and GLP-compliant in vitro chromosomal aberration assay, farnesene (purity: 96%; isomer not specified) did not induce statistically significant increases in the frequency of aberrant human lymphocytes in the presence of absence of S9 metabolic activation (ECHA, 2009c). In a non-guideline compliant in vitro chromosomal aberration assay and in vitro micronucleus assay, farnesene did not induce statistically significant increases in the frequency of aberrant cells and micronucleated cells in human lymphocytes incubated with concentrations up to 400 µg/mL of the test substance for 72 hours (Çelik et al., 2014). In an OECD 476 guideline and GLP-compliant mouse lymphoma assay, farnesene (purity: 91.6%; isomer not specified) was non-mutagenic in the presence of absence of S9 metabolic activation in L5178Y TK +/+ 3. 7c mouse lymphoma cells (heterozygous at the thymidine kinase locus) (ECHA, 2009d). Farnesene (mixture of isomers including 8.5% (E)-β; 6.2% (Z)-β; 7.7% (E, Z)-α; 9.8% (E, E)-α; 2.2% (Z, E)-α) was not mutagenic in an OECD guideline 471 and GLP-compliant Ames assay in S. typhimurium strains TA98, TA100, TA1535 and TA1537 and E. coli WP2uvrA with and without S9 metabolic activation using the plate incorporation method at concentrations up to 5000 µg/plate (Bhalli, 2016b). In an OECD 478 guideline and GLP-compliant in vitro micronucleus assay, no statistically significant induction of micronuclei was observed in human peripheral blood lymphocytes treated with farnesene (mixture of isomers including 8.5% (E)-β; 6.2% (Z)-β; 7.7% (E, Z)-α; 9.8% (E, E)-α; 2.2% (Z, E)-α) in the presence of absence of S9 metabolic activation (Bhalli, 2017a). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of beta-farnesene (Gooderham et al., 2020).

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding diethyl mercaptosuccinate (CAS 23060-14-2) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4972) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of aliphatic and aromatic sulfides and thiols (JECFA, 2000, 2004, 2008, 2011; SLR, C5). The Expert Panel calculated the anticipated per capita intake ("eaters only") of diethyl mercaptosuccinate from use as a flavor ingredient to be 0.01 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that diethyl mercaptosuccinate will undergo S-methylation to produce the corresponding methyl sulfide followed by S-oxidation to yield methyl sulfoxide and methyl sulfone derivatives that are excreted in the urine (Bremer and Greenberg, 1961; Damani, 1987; Hoodi and Damani, 1984; Keith et al., 1983; Rettie et al., 1991; Szumlanski et al., 1988; Woodson et al., 1982). Alternatively, hydrolysis of the carboxyl ester is expected to yield the corresponding carboxylic acid and alcohol derivatives that will undergo complete oxidation and β-cleavage in the fatty acid pathway, or conjugation followed by excretion in the urine (Anders, 1989; Bosron and Ting-Kai, 1980; Daniel, 1969; Heymann, 1980; Rusoff et al., 1960; Williams, 1959). In an Ames assay, diethyl mercaptosuccinate was non-mutagenic and non-cytotoxic at concentrations up to 5000 µg/plate in S. typhimurium strains TA100 and TA98 with or without S9 using the pre-incubation method (Kino, 2020a). The structural relative 3-mercapto-3-methyl-1-pentyl acetate (FEMA 3997) was non-mutagenic at concentrations up to 5000 µg/plate in an OECD 471 guideline and GLP-compliant Ames assay in S. typhimurium TA98, TA100, TA102, TA1535 and TA1537 in the presence or absence of S9 metabolic activation using the plate incorporation and pre-incubation methodologies (McGarry, 2012). In an OECD 487 guideline and GLP-compliant in vitro micronucleus assay, the same structural relative did not induce significant increases in the frequency of micronuclei at concentrations up to 1,323 µg/mL in the presence and absence of S9 metabolic activation (Lloyd, 2014). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of diethyl mercaptosuccinate (Gooderham et al., 2020). In an OECD 408 guideline and GLP-compliant 90-day oral toxicity study, no toxicologically significant adverse effects were observed when the structural relative 4-mercapto-4-methyl-2-pentanone (FEMA 3997) was administered to Wistar-Dawley DC IGS rats by gavage (Bauter, 2017). Under the conditions of the study and based on the toxicological endpoint evaluated, the NOAEL for the test substance was 0.26 mg/kg bw/day of 3-mercapto-3-methyl-1-pentyl acetate (FEMA 3997), which is greater than 1,300,000 times the anticipated daily per capita intake of diethyl mercaptosuccinate from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 3-mercapto-3-methyl-1-pentyl acetate (CAS 2411762-60-0) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4973) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of aliphatic and aromatic sulfides and thiols (JECFA, 2000, 2004, 2008, 2011; SLR, C5). The Expert Panel calculated the anticipated per capita intake ("eaters only") of 3-mercapto-3-methyl-1-pentyl acetate from use as a flavor ingredient to be 0.001 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that 3-mercapto-3-methyl-1-pentyl acetate will undergo S-methylation to produce the corresponding methyl sulfide followed by S-oxidation to yield methyl sulfoxide and methyl sulfone derivatives that are excreted in the urine (Bremer and Greenberg, 1961; Damani, 1987; Hoodi and Damani, 1984; Keith et al., 1983; Rettie et al., 1991; Szumlanski et al., 1988;
Woodson et al., 1982). Alternatively, hydrolysis of the carboxyl ester is expected to yield the corresponding carboxylic acid and alcohol derivatives that will undergo complete oxidation and β-cleavage in the fatty acid pathway, or conjugation followed by excretion in the urine (Anders, 1989; Bosron and Ting-Kai, 1980; Daniel, 1969; Heymann, 1980; Russoff et al., 1960; Williams, 1959). 3-Mercapto-3-methylpentyl acetate was non-mutagenic in a Ames assay conducted in S. typhimurium TA98 and TA100 using the pre-incubation method in a dose-range assay at concentrations up to 5000 µg/plate in both strains in the presence and absence of S9, and in the main assay at concentrations up to 5000 µg/plate in both strains in the presence of S9, at concentrations up to 1500 µg/plate in TA98 in the absence of S9 and at concentrations up to 500 µg/plate in TA100 in the absence of S9 metabolic activation (Kino, 2020b). The structural relative 3-mercapto-3-methyl butanol (FEMA 3854) was non-mutagenic at concentrations up to 5000 µg/plate in a GLP-compliant Ames assay conducted in S. typhimurium strains TA98, TA100, TA1535 and TA1537 with and without S9 metabolic activation using a 60-minute pre-incubation procedure (Jones, 1990). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 3-mercapto-3-methyl-1-pentyl acetate (Gooderham et al., 2020). In a 14-day dietary toxicity study, no toxicologically significant adverse effects were observed when the structural relative 3-mercaptohexyl acetate (FEMA 3851) was administered to Sprague-Dawley rats at 0 and 10 mg/kg bw/day (Wnorowski, 1996). No subchronic toxicity data on the material of structural relative values were available for consideration.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding germacrene D ≥85% (CAS 23986-74-5) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4974) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The substance was evaluated individually within the context of the chemical group of aliphatic and alicyclic hydrocarbons (JECFA, 2006, 2015; SLR, A6). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of germacrene D ≥85% from use as a flavor ingredient to be 14 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The primary constituent, germacrene D, is known to occur naturally in Anise oil, Angelica root oil, Hop oil (Humulus lupulus), Anise Hyssoop (Agastache foeniculum) (Pursh) Kuntze), Winter savory (Satureja montana L.), Lemon balm (Melissa officinalis L.), Lovage leaf, Thymus, other types, German chamomile oil (Matricaria chamomila L.), Ginger (Zingiber officinale Roscoe), Curry leaf oil (Bergera koenigii L.), Calamint nepeta oil, Ashanti pepper (Piper guineense Schum and Thom), Wormwood oil (Artemisia absinthium L.), Citrus oils, Ocimum basilicum var., Red sage (Texas sage) (S. coccinea Juss. Ex Murr.), Mint oils, Pistacia oils, Moroccan chamomile oil (Chamaemelum mixtum L.), Clary sage (Salvia sclarea L.), Caraway (Van Dongen and Donders, 2021). Based on the quantitative data, a consumption ratio of 7 could be calculated for the primary constituent, germacrene D (Stolberg and Grundschober, 1987). The Expert Panel noted the assay of the material was ≥85% of the named material with trans-caryophyllene, other aliphatic and aromatic hydrocarbons and each of the aliphatic and aromatic tertiary alcohols and related esters, and epoxide derivatives as the secondary components (<5%, <4%, <1%, respectively) and considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Expert Panel concluded that metabolic data exist for a representative member of the principal identified congeners groups that indicate that the group would be predicted to be metabolized primarily by well-established detoxication pathways (Adams et al., 2011). In an OECD 471 guideline and GLP-compliant Ames assay, germacrene D (purity 89%) was non-mutagenic and non-cytotoxic at concentrations up to 5 µg/plate in S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA102 in the presence and absence of S9 metabolic activation using the plate incorporation and pre-incubation methods (Schreib, 2002c). (-)-Germacrene D (purity 45%) was non-mutagenic and non-cytotoxic at concentrations up to 5000 µg/plate in an OECD 471 guideline and GLP-compliant Ames assay conducted in triplicate in S. typhimurium TA98, TA100, TA1535, TA1537 and E. coli WP2uvrA in the presence and absence of S9 metabolic activation using the plate incorporation method (Sawant, 2017). In an OECD 487 guideline and GLP-compliant in vitro micronucleus assay, no significant induction of micronuclei was observed at concentrations up to 86 µg/mL of (-)-germacrene D (purity 45%) incubated with human lymphocytes with 24 hours in the absence of S9 metabolic activation as well as 3 hours with a 21-hour recovery period in the absence and presence of S9 metabolic activation, respectively (Bhalli, 2017b). In an in vitro mouse lymphoma assay, the constituent b-caryophyllene (FEMA 2252) was incubated with L5178Y TK +/- cells for 4 hours at 15-140 µg/mL in the presence and absence of S9 metabolic activation. Doubling of mutant frequencies were observed at cytotoxic concentrations and are likely to be false positives, therefore b-caryophyllene (FEMA 2252) was considered to be non-mutagenic in the absence and presence of S9 metabolic activation (Seifried et al., 2006). In an in vitro micronucleus assay, no significant differences in micronuclei induction were observed in human lymphocytes treated with up to 100 µg/mL of the constituent b-caryophyllene (FEMA 2252) (Di Sotto et al., 2010). In two additional in vitro assays, no evidence of genotoxicity was found for the constituent b-caryophyllene (FEMA 2252) in the UDS assay in rat hepatocytes up to 10 µl/mL (approximately 9 µg/mL based on the specific density of the substance) or in an in vitro sister chromatid exchange assay in CHO K-1 hamster cells up to 333 µM (approximately 68 µg/mL) (Sasaki et al., 1989). In vivo micronucleus assays, male mice administered single or repeated gavage doses (three consecutive days) of the constituent b-caryophyllene (FEMA 2252) at dose levels up to 2000 mg/kg bw/day did not exhibit significant increases in micronucleated polychromatic erythrocytes in sampled blood smears (Molina-Jasso et al., 2009). In an in vivo sister chromatid exchange and chromosome abberation assay, the constituent b-caryophyllene (FEMA 2252) was orally administered to groups of male Swiss-Webster mice at single doses of 0 (corn oil), 20, 200 or 2000 mg/kg bw. No significant differences in mitotic indices, sister chromatid exchanges as well as the amount and types of chromosome aberrations
were observed in the bone marrow of all treated mice compared to the control group (Alvarez-Gonzalez et al., 2014). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of Germacrene D ≥85% (Gooderham et al., 2020). In an OECD 408 guideline and GLP-compliant 90-day dietary toxicity study, b-caryophyllene (FEMA 2252) was administered to male and female Sprague Dawley rats at concentrations of 0, 222, 456 and 1367 mg/kg bw/day or 0, 263, 1033 and 4278 mg/kg bw/day, respectively. NOAELS of 222 mg/kg bw/day and 263 mg/kg bw/day were established for b-caryophyllene (FEMA 2252) in male and female rats, respectively (Bastaki et al., 2020). In an OECD 407 guideline-compliant repeated dose 28-day study, female Swiss mice were orally administered via a Tween 80 saline vehicle solution 300 mg/kg bw/day or 2000 mg/kg bw/day of the constituent b-caryophyllene (FEMA 2252). No adverse clinical chemistry, hematological, urinalysis, organ weights and histopathological findings up to the highest tested dose were reported (da Silva Oliveira et al., 2018). The Expert Panel assigned a conservative NOAEL for b-caryophyllene (FEMA 2252) of 222 mg/kg bw/day which is greater than 1,110,000 times the anticipated daily per capita intake of germacrene D ≥85% from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding Scutellaria baicalensis root extract (CAS 94279-99-9) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4975) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. The substance was evaluated individually within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of Scutellaria baicalensis root extract from use as a flavor ingredient to be 28 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The material is produced from the roots of the Scutellaria baicalensis plant. Though some preparations of this material are consumed as traditional medicine, a consumption ratio could not be calculated. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel concluded that metabolic data exist for a representative member of the principal identified congenic groups that indicate that constituents of the groups would be predicted to be metabolized primarily by well-established detoxication pathways. In an OECD 471 guideline and GLP-compliant Ames assay, the concentrated extract of Scutellaria baicalensis root (purity 93%) was non-mutagenic in S. typhimurium strains TA1537, TA1535, TA98, TA100 and TA102 with and without S9 metabolic activation using the plate incorporation method at concentrations up to 5000 µg/plate (Tekale, 2018a). In another OECD 471 guideline and GLP-compliant Ames assay, a related preparation GHX02 (approximately 33% root extract of Scutellaria baicalensis, 33% Trichosanthis seeds, 17% Armeniaca species and 17% Coptidis rhizoma) was non-mutagenic at concentrations of 313-5000 µg/plate in S. typhimurium TA100, TA1535, TA98, TA1537 and E. coli WP2uvrA (pKM101) ( Ji et al., 2020). In a GLP-compliant in vitro chromosome aberration assay, significant increases in the frequency of numerical chromosome aberrations were observed in all tested concentrations, but not in structural chromosome aberrations after CHL cells were incubated with GHX02. The Expert Panel noted that the long-term exposure condition as recommended by the OECD 473 test guideline was not tested in this study, nor did it meet the 300 well-spread metaphases scoring minimum to adequately assess the significant of chromosome aberrations ( Ji et al., 2020). No clinical signs of toxicity were observed in an OECD 474 guideline and GLP-compliant in vivo micronucleus assay when ICR male mice were administered CXH02 up to concentrations of 5000 mg/kg bw/day ( Ji et al., 2020). No statistically significant increases in %tail DNA was observed in left liver lobe samples of Sprague-Dawley rats administered GXH02 in an OECD 489 guideline and GLP-compliant in vivo comet assay ( Ji et al., 2020). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of Scutellaria baicalensis root extract (Gooderham et al., 2020). In an OECD 407 guideline and GLP-compliant repeated dose 28-day dietary toxicity study, no significant treatment-related adverse clinical effects were observed when the concentrated extract of Scutellaria baicalensis root (purity 93%) was administered to Wistar rats. The highest concentration tested of 1250 ppm was determined to be the NOAEL, corresponding to a concentrations of 129 mg/kg bw/day in the males and 119 mg/kg bw/day in the females (Shah, 2019). No adverse effects on the respiratory, cardiovascular, and central nervous system were observed when Sprague-Dawley rats and beagle dogs were administered UP446, a 4:1 mixture of Scutellaria baicalensis extract and catechin extract obtained from repeated crystallization of an aqueous extract of Acacia catechu with not less than 60% baicalin and not less than 10% catechin content, orally at concentrations up to 5000 mg/kg bw/day in rats and up to 1000 mg/kg bw/day in beagle dogs (Yimam et al., 2016). In an OECD 408 guideline and GLP-compliant 90-day repeated dose oral toxicity study, no adverse treatment-related effects were observed when the same related preparation was administered to Sprague Dawley rats. The highest concentration of 1000 mg/kg bw/day was identified as the NOAEL (Yimam et al., 2010). No significant dose-dependent and treatment-related adverse clinical effects were observed when Sprague Dawley rats were administered the same related preparation by gavage mixed in a solution of 0.5% carboxymethylcellulose in distilled water in a GLP-compliant 26-week repeated dose oral toxicity study. The NOAEL was identified as the highest administered concentration of 2000 mg/kg bw/day (Lee et al., 2013). The Expert Panel assigned a conservative NOAEL for Scutellaria baicalensis root extract of 119 mg/kg bw/day, which is greater than 238,000 times the anticipated daily per capita intake of Scutellaria baicalensis root extract (1% propylene glycol solutions of the concentrated product extract) from use as a flavor ingredient. No reproductive or developmental effects were reported for female Sprague-Dawley and New Zealand white rabbits administered UP446 at concentrations up to 1000 mg/kg bw/day by gavage from gestation day 6-18 or 6-17 in rabbits and rats, respectively, in a GLP-compliant study. The authors considered the maternal and fetal NOAEL to be greater than 1000 mg/kg bw/day for rats and rabbits (Yimam et al., 2015a). In another GLP-compliant reproductive and developmental toxicity study in female Sprague-Dawley rats,
the related preparation UP446 was administered at concentrations up to 1000 mg/kg bw/day from gestation day 6 to day 20 of lactation. No significant, treatment related signs of toxicity were reported. The authors considered the maternal and developmental NOAEL to be greater than 1000 mg/kg bw/day for rats (Yimam et al., 2015b). In a GLP-compliant reproductive and embryonic study, a NOAEL of 1000 mg/kg bw/day for male and female Sprague-Dawley rats administered UP446 by gavage at concentrations up to 1000 mg/kg bw/day (Yimam et al., 2015c). Based on its review of available reproductive and developmental toxicity data, the Expert Panel assigned a conservative NOAEL for the related preparation UP446 to be 1000 mg/kg bw/day, which is greater than 2,000,000 times the anticipated daily per capita intake of *Scutellaria baicalensis* root extract (1% propylene glycol solution of the concentrated product extract) from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding lemon seed (*Citrus limon*) oil (CAS 84929-31-7) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4976) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. The substance was evaluated individually within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated per capita intake ("eaters only") of lemon seed (*Citrus limon*) oil from use as a flavor ingredient to be 28 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel concluded that metabolic data exist for a representative member of the principal identified congeneric groups that indicate that constituents of the groups would be metabolized primarily by well-established detoxication pathways. In an OECD 487 guideline and GLP-compliant in vitro micronucleus induction assay in human lymphocytes, the constituents oleic acid (FEMA 2815) and palmitic acid (FEMA 2832) did not produce significant increases in the induction of micronuclei in any treatment condition either in the presence or absence of S9 metabolic activation (Bhalli, 2014b; Morris, 2014a). No increases in the frequency of revertant colonies were reported when the lemon seed oil constituent palmitic acid (FEMA 2832) or docosanoic acid (CAS 112-85-6) were tested in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 as well as *E. coli* WP2 uvrA in a OECD 471 guideline and GLP-compliant Ames assay method either in the presence or absence of S9 metabolic activation (Bhalli, 2014a; Nagao, 2002a). No increase in the incidence of chromosomal aberrations was reported when Chinese hamster lung (CHL) cells were incubated with the constituent docosanoic acid (CAS 112-85-6) with and without S9 metabolic activation (Nagao, 2002b). The constituent crotonaldehyde was non-mutagenic in several Ames assays, including an NTP Ames assay using *S. typhimurium* strains TA98, TA1535 and TA1537 in the presence and absence of rat liver and hamster liver S9 and in strain TA100 in the absence of S9 (Cheh, 1986; ECHA, 1981; Florin et al., 1980; Haworth et al., 1983; Jagannath, 1979; Neudecker et al., 1981; Sasaki and Endo, 1978). A mix of positive and negative results were obtained for crotonaldehyde in an in vitro micronucleus assay using human lymphocytes, a sister chromatid exchange and chromosomal aberration assay and an in vitro mouse lymphoma assay (Demir et al., 2011; Diaz et al., 2007; Dittembere et al., 1995; Galloway et al., 1987; NTP, 1981). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of lemon seed (*Citrus limon*) oil (Gooderham et al., 2020). The administration of the lemon seed oil constituent docosanoic acid to Sprague-Dawley rats in an OECD 422 guideline and GLP-compliant combined subchronic study including reproduction and developmental toxicity endpoints resulted in a NOAEL of 1000 mg/kg bw/day, which is 2,000,000 times greater than the anticipated daily per capita intake of lemon seed oil as a flavor ingredient (Nagao et al., 2002). In subchronic reproductive toxicity studies, a NOAEL of 10 mg/kg bw/day was established for male and female parental F344 rats and 2.5 mg/kg bw/day for male SPF Wistar rats administered the constituent crotonaldehyde (ECHA, 1987a, 2006; Jha and Kumar, 2006; Li et al., 2019b; Zhang et al., 2020). In a chronic drinking water study, the administration of the constituent sodium oleate (FEMA 2815) to male and female F344 rats resulted in a NOAEL of 2.5% (equivalent to 2500 mg/kg bw/day) (Hiasa et al., 1985). The Expert Panel reviewed chronic and subchronic toxicity studies of the constituent crotonaldehyde in rats and mice and determined the most conservative NOAEL/LOAEL to be 2.5 mg/kg bw/day, which is 300,000 time greater than the anticipated daily per capita intake of crotonaldehyde from its presence in lemon seed oil (Chung et al., 1986; ECHA, 1987b; Li et al., 2019a; NTP, 2014; Von Tungeln et al., 2002; Wolfe et al., 1987; Zhang et al., 2018a; Zhang et al., 2019; Zhang et al., 2018b).

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 10-hydroxy-4,8-dimethyldec-4-enal (CAS 65210-18-6) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4977) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. The substance was evaluated individually within the context of the chemical group of aliphatic primary alcohols, carboxylic acids, acetalts, and esters containing additional oxygenated functional groups (JEFFA, 2000; SLR, M1). The Expert Panel calculated the anticipated per capita intake ("eaters only") of 10-hydroxy-4,8-dimethyldec-4-enal from use as a flavor ingredient to be 0.1 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). This material is not known to occur in nature and thus no consumption ratio can be calculated. The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is anticipated that 10-hydroxy-4,8-dimethyldec-4-enal will oxidized to the corresponding aldehyde and to be further oxidized to the corresponding carboxylic acid (Bosron and Ting-Kai, 1980; Levi and Hodgson, 1989). The acid can then undergo beta-oxidative cleavage to carbon dioxide in major metabolic pathways, or may undergo a combination of omega- (omega-1) and beta-oxidation as well as selective dehydrogenation and hydration to yield polar metabolites that are excreted as glucuronate or sulfate conjugates in the urine.
and to a lesser extent, in the feces (Voet and Voet, 1990; Williams, 1959). Alternatively, 10-hydroxy-4,8-dimethyldec-4-enal may be reduced to the corresponding alcohol as a short-lived in vivo intermediate (Diliberto et al., 1990). In an Ames assay, 10-hydroxy-4,8-dimethyldec-4-enal was non-mutagenic at concentrations up to 5,000 µg/plate in S. typhimurium TA98, TA100, TA1535, TA1537 as well as E. coli WP2uvrA in the presence or absence of S9 metabolic activation (Kino, 2020c). When tested in the same strains in an OECD 471 guideline and GLP-compliant Ames assay, the structural relative 9-hydroxy-5,9-dimethyldec-4-enal was non-mutagenic up to concentrations of 5,000 µg/plate using the plate incorporation and pre-incubation methodologies (Sokolowski, 2013). The structural relative hydroxycitronellal (FEMA 2583) was non-mutagenic in an Ames assay using S. typhimurium TA98, TA100, TA1535, TA1537 and TA1538 in the absence and presence of S9 metabolic activation using both the plate incorporation and preincubation methodologies (Wild et al., 1983). No significant induction of micronucleated polychromatic erythrocytes were observed when the same structural relative was provided to NMRI mice (4/dose) at up to 861 mg/kg bw by intraperitoneal administration (Wild et al., 1983). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 10-hydroxy-4,8-dimethyldec-4-enal (Gooderham et al., 2020). In an OECD 407 guideline and GLP-compliant 28-day toxicity study, the administration of the structural relative 9-hydroxy-5,9-dimethyldec-4-enal to Sprague-Dawley rats at concentrations of 0, 50, 200 and 800 mg/kg bw/day resulted in a NOAEL of 800 mg/kg bw/day (Broich, 2014). In a 2-year, chronic dietary toxicity study, the structural relative hydroxycitronellal (FEMA 2583) provided to male and female rats at 50 and 250 mg/kg bw/day resulted in a NOAEL of 250 mg/kg bw/day (Williams and Burdock, 2009). Based on the results for the various steviol glycosides, the Panel did not identify specific concerns related to the potential genotoxicity of Rebaudioside B 95% (Gooderham et al., 2020). In a 108-week carcinogenicity study for stevioside, no carcinogenic effects were observed (Toyoda et al., 1997). In a 2-year feeding study, male and female rats were administered the equivalent of 0, 50, 150, or 550 mg/kg bw/day of a stevia extract comprised of 74% stevioside and 16% rebaudioside A. The authors considered the NOAEL from this 2-year rat feeding study of a stevia extract to be equal to 550 mg/kg bw/day (Yamada et al., 1985), which is greater than 600,000 times the anticipated daily per capita intake of rebaudioside B 95% from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding 2-(furan-2-yl)-4,6-dimethyl-1,3,5-dithiazinane (CAS 142062-38-2) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4979) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. The substance was evaluated individually and within the context of the chemical group sulfur-containing heterocyclic and heteroaromatic derivatives (JECFA, 2003, 2008, 2012, 2015; SLR, D16). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of 2-(furan-2-yl)-4,6-dimethyl-1,3,5-dithiazinane from use as a flavor ingredient to be 0.001 µg/person/day, which is below the threshold of toxicological concern for structural class II (90 µg/person/day) (Munro et al., 1996). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is anticipated that 2-(furan-2-yl)-4,6-dimethyl-1,3,5-dithiazinane will be metabolized similarly to thiazole derivatives. Because of the presence of alkyl substituents, metabolism is expected to be primarily via side-chain oxidation and ring S- and N-oxidation followed by excretion in the urine un conjugated or as glutathione conjugates after glucuronidation (JECFA, 2003). An in vitro hydrolysis study with the structurally related substance 2 or 4-isobutylyl(4 or 2),6-dimethyltetrahydro-4H-1,3,5-dithiazine (FEMA 3781) tested in simulated gastric juice and simulated intestinal fluid indicates that it is not likely that hydrolysis will occur (FEMA, 1989). In an Ames assay, that 2-(furan-2-yl)-4,6-dimethyl-1,3,5-dithiazinane was non-mutagenic at concentrations up to 5,000 µg/plate in S. typhimurium TA98, TA100, TA1535 and TA1537 in the presence and absence of S9 metabolic activation (Shukla, 2020). Based on these results, as well as the structure of the substance and the arrangement...
and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 2-(furan-2-yl)-4,6-dimethyl-1,3,5-dithiazine (Gooderham et al., 2020). In an OECD 408 guideline and GLP-compliant 90-day repeat dose toxicity study following a 14-day range finding study, the administration of the structurally related substance 2,4,6-trisobutyl-5,6-dihydro-4H-1,3,5-dithiazine (FEPA 4017) to Spargue-Dawley rats at concentrations of 0, 140, 1050, or 2100 ppm (equivalent to 0, 9, 68 or 132 mg/kg bw/day and 0, 11, 77 or 154 mg/kg bw/day for males and females, respectively) resulted in a NOAEL of 140 ppm (equivalent to 9 and 11 mg/kg bw/day in males and females, respectively) (Bauter, 2012, 2013). The Expert Panel determined that the most conservative NOAEL of 9 mg/kg bw/day for the structural relative 2,4,6-trisobutyl-5,6-dihydro-4H-1,3,5-dithiazine (FEPA 4017) is 540,000,000 times the anticipated daily per capita intake of the candidate substance. 2-(furan-2-yl)-4,6-dimethyl-1,3,5-dithiazine, from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding a mixture of (8Z,11Z)-heptadeca-8,11-dienal and (Z)-heptadec-8-enal (CAS 2415657-73-5) and concluded that the use as a flavor ingredient is GRAS (FEPA 4980) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. The substance was evaluated individually and within the context of the chemical group unsaturated linear and branched-chain aliphatic, non-conjugated aldehydes, related primary alcohols, carboxylic acids and esters (JECHA, 1999, 2004, 2007, 2012). The Expert Panel calculated the anticipated per capita intake (“eaters only”) of the mixture of (8Z,11Z)-heptadeca-8,11-dienal and (Z)-heptadec-8-enal from use as flavor ingredient to be 1 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1998). The Expert Panel noted the assay of the material was >95% mixture of aldehydes containing 63-70% (8Z,11Z)-heptadeca-8,11-dienal, 19-29% (Z)-heptadec-8-enal as well as up to 10% of other linear and branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, carboxylic acids and related esters and saturated aliphatic, acyclic, branched-chain primary alcohols, aldehydes, carboxylic acids and related esters, and considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Expert Panel concluded that metabolic data exist for a representative member of the principal identified congeneric groups that indicate that the group would be predicted to be metabolized primarily by well-established detoxication pathways (Abumrad et al., 1984; Beedham, 1988; Borgstrom, 1974; Bosron and Ting-Kai, 1980; Dawson et al., 1964; Dhopshwar and Mead, 1973; Eckfeldt and Yonetani, 1982; Feldman and Weiner, 1972; Gaillard and Derauche, 1968; Gibson et al., 1982; Harris et al., 1980; Levi and Hodgson, 1989; Masoro, 1977; Voet and Voet, 1990; Wakl and Barnes, 1971; Williams, 1959). The candidate substance, a mixture of (8Z,11Z)-heptadeca-8,11-dienal and (Z)-heptadec-8-enal, was not-mutagenic in an OECD 471 guideline and GLP-compliant Ames assay in S. typhimurium strains TA98, TA100, TA1535 and TA1537 as well as E. coli WP2uvrA at concentrations up to 5000 µg/plate either with or without S9 metabolic activation (Sokolowski, 2020). The structural relative 10-undecenal (FEMA 3095) was similarly non-mutagenic in an OECD 471 guideline and GLP-compliant Ames assay in S. typhimurium strains TA98, TA100, TA1535 and TA1537 (Bhatia et al., 2010; Sokolowski, 2020). No significant induction of chromosome aberrations was observed when the same structural relative was tested in a GLP-compliant in vitro chromosome aberration assay in Chinese hamster lung cells (CHL/PU) (MHLW, 2014). The structural relative 10-undecenal (FEMA 3095) was also negative in an in vivo micronucleus test in NMRI mice at doses up to 2000 mg/kg bw (Bhatia et al., 2010; Honarvar et al., 2007a). In an OECD 471 guideline and GLP-compliant Ames assay, a related preparation, a reaction mass of (9E)-9-undecenal and (8Z)-9-undecenal and undec-10-enal (purity: 91.9% sum of three isomers), was non-mutagenic in S. typhimurium TA98, TA100, TA1535, TA1537 and E. coli WP2 uvrA in the absence and presence of S9 using the plate incorporation method (Verspeck-Rip, 2014). No significant induction of micronuclei in human lymphocytes or induction of gene mutations at the HPRT locus of CHO V79 cells were observed when the same related preparation was tested in an OECD 487 guideline and GLP-compliant in vitro micronucleus assay and in an OECD 476 guideline and GLP-compliant in vitro mammalian cell gene mutation test (ECHA, 2018c). The constituent oleic acid (FEMA 2815) was non-mutagenic at concentrations up to 5000 µg/plate in an Ames assay conducted in S. typhimurium TA98, TA100, TA1535, TA1537 and E. coli WP2uvrA in the absence and presence of S9 (Mortelmans et al., 1986; Shimizu et al., 1985). No significant induction of micronuclei was observed in an OECD 487 guideline and GLP-compliant in vitro micronucleus assay in human lymphocytes tested with concentrations of up to 80 µg/mL in a 4-hr exposure group and 40-100 µg/mL in a 24-hr exposure group of the constituent oleic acid (FEMA 2815) (Morris, 2014b). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of a mixture of (8Z,11Z)-heptadeca-8,11-dienal and (Z)-heptadec-8-enal (Gooderham et al., 2020). In an OECD 422 guideline and GLP-compliant combined repeat dose and reproductive/development toxicity study, the administration of the related preparation of a reaction mass of (9E)-9-undecenal and (9Z)-9-undecenal and undec-10-enal to Sprague-Dawley rats by gavage resulted in a NOAEL of 1000 mg/kg bw/day (ECHA, 2018d), which is 50,000,000 times greater than the anticipated daily per capita intake of a mixture of (8Z,11Z)-heptadeca-8,11-dienal and (Z)-heptadec-8-enal from use as a flavor ingredient. In an OECD 407 guideline and GLP-compliant 28-day toxicity study, the administration of the structural relative 10-undecenal (FEMA 3095) administered to Wistar rats at concentrations up to 1000 mg/kg bw/day resulted in a NOAEL of 1000 mg/kg bw/day (ECHA, 2015). In an OECD 408 guideline and GLP-compliant 90-day dietary toxicity study, the administration of the structural relative 10-undecenal (FEMA 3095) to Sprague-Dawley Cr:CD® (SD) IGS BR rats in the diet resulted in a NOAEL of 200 ppm, or approximately 14.3 mg/kg bw/day, which is 715,000 times greater than the anticipated daily per capita intake of the mixture of (8Z,11Z)-heptadeca-8,11-dienal and (Z)-heptadec-8-enal from use as a flavor ingredient (Liwiska and Watson, 2012).
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