# GRAS FLAVORING SUBSTANCES 27

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**27. GRAS FLAVORING SUBSTANCES:** This list of substances will appear in the 27th 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.



**CHANGE IN GRAS STATUS OF QUINOLINE, ETHYLENE OXIDE, AND STYRENE:** The FEMA GRAS statuses of quinoline (FEMA No. 3470), ethylene oxide (FEMA No. 2433), and styrene (FEMA No. 3233) under their conditions of intended use as flavor ingredients were reviewed. For quinoline, the Expert Panel concluded that additional data, including in vivo genotoxicity and chronic toxicity testing, were required to support the continuation of its GRAS status. Until such data are available for review, the flavor ingredient quinoline has been removed from the FEMA GRAS list. There is little evidence that ethylene oxide or styrene are used for the technical effect of flavoring; based on this lack of evidence, the Panel concluded that both ethylene oxide and styrene should be removed from the FEMA GRAS list.

## TABLE 1: Primary Names & Synonyms

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

| FEMA NO. | SUBSTANCE PRIMARY NAME AND SYNONYMS |
|---|---|
| 4779 | **(±)-2-Mercapto-5-methylheptan-4-one**<br>(±)-5-Methyl-2-sulfanylheptan-4-one |
| 4780 | **Caryophylla-3(4),8-dien-5-ol**<br>Mixture of 10,10-Dimethyl-2,6-dimethylenebicyclo[7.2.0]-undecan-5-ol and 4,11,11-Trimethyl-8-methylenebicyclo[7.2.0]undec-3-en-5-ol |
| 4781 | **L-Cysteine methyl ester hydrochloride**<br>Methyl (*R*)-2-amino-3-mercaptopropanoate hydrochloride |
| 4782 | **2(3)-Hexanethiol** |
| 4783 | **Mixture of 1-Vinyl-3-cyclohexenecarbaldehyde and 4-Vinyl-1-cyclohexenecarbaldehyde**<br>Mixture of 1-Ethenyl-3-cyclohexene-1-carboxaldehyde and 4-Ethenyl-1-cyclohexene-1-carboxaldehyde |
| 4784 | **(±)-4-Hydroxy-6-methyl-2-heptanone** |
| 4785 | **2-Octyl-2-dodecenal** |
| 4786 | **2-Hexyl-2-decenal** |
| 4787 | ***trans*-6-Octenal**<br>(*E*)-6-Octenal<br>(6*E*)-Octenal |
| 4788 | **(E)-3-Benzo[1,3]dioxol-5-yl-*N*,*N*-diphenyl-2-propenamide**<br>(2*E*)-3-(1,3-benzodioxol-5-yl)-*N*,*N*-diphenylprop-2-enamide |
| 4789 | **2,6-Dimethyl-5-heptenol** |
| 4790 | **(±)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, ethyl ester**<br>(±)-Ethyl bicyclo[2.2.1]hept-5-ene-2-carboxylate<br>(±)-5-Norbornene-2-carboxylic acid, ethyl ester |
| 4791 | **3-(Acetylthio)hexanal** |
| 4792 | **(±)-3-Mercapto-1-pentanol** |
| 4793 | **(3*R*,3*S*)-3-[[(4-Amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]methyl]-*N*-cyclopentyl-2-oxo-3-piperidinecarboxamide**<br>(3*R*,3*S*)-3-[[(4-Amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]methyl]-*N*-cyclopentyl-2-oxopiperidine-3-carboxamide |
| 4794 | **(±)-1-Cyclohexylethanol**<br>(±)-Methylcyclohexylcarbinol<br>(±)-Cyclohexanemethanol |
| 4795 | **(±)-8-Methyldecanal** |
| 4796 | **Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside C 30%** |
| 4797 | **(±)-Naringenin**<br>(±)-5,7-Dihydroxy-2-(4-hydroxyphenyl)-4*H*-chroman-4-one |
| 4798 | **2-(((3-(2,3-Dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)pyridine**<br>2-((5-(2,3-Dimethoxyphenyl)-2*H*-1,2,4-triazol-3-ylthio)methyl)pyridine<br>2-(((3-(2,3-dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)pyridine |
| 4799 | **(2*R*)-3',5-Dihydroxy-4'-methoxyflavanone** |
| 4800 | **Glucosylated *Rubus suavissimus* extract 20-30% glucosylated rubusoside glycosides**<br>Glucosylated Sweet Blackberry leaves extract<br>20-30% glucosylated rubusoside glycosides |
| 4801 | **Olive fruit extract**<br>*Olea europaea* fruit extract |

| FEMA NO. | SUBSTANCE PRIMARY NAMES AND SYNONYMS |
|---|---|
| 4802 | **(*S*)-1-(3-(((4-Amino-2,2-dioxido-1*H*-benzo[c][1,2,6]thiadiazin-5-yl)oxy)methyl)piperidin-1-yl)-3-methylbutan-1-one**<br>1-[(3*S*)-3-[[(4-Amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]methyl]-1-piperidinyl]-3-methyl-1-butanone |
| 4803 | **8-Methylnonanal**<br>Isodecanal |
| 4804 | **Mixture of Ricinoleic acid, Linoleic acid, and Oleic acid** |
| 4805 | **Steviol glycoside extract,** *Stevia rebaudiana*, Rebaudioside A 22% |
| 4806 | **Steviol glycoside extract,** *Stevia rebaudiana*, Rebaudioside C 22% |
| 4807 | **Pinocarvyl acetate**<br>6,6-Dimethyl-2-methylenebicyclo[3.1.1]hept-3-yl acetate |
| 4808 | ***N*-Ethyl-5-methyl-2-(1-methylethenyl) cyclohexanecarboxamide**<br>*N*-Ethyl-5-methyl-2-(prop-1-en-2-yl) cyclohexanecarboxamide |
| 4809 | **2-(4-Methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide**<br>*N*-(1*H*-Pyrazol-5-yl)-*N*-(thiophen-2-ylmethyl)-2-(p-tolyloxy)acetamide |
| 4810 | **Ethyl-2-(4-hydroxy-3-methoxyphenyl)acetate**<br>Ethyl homovanillate<br>Ethyl 4-hydroxy-3-methoxyphenylacetate |
| 4811 | **Ginger Mint Oil (*Mentha x gracilis*)**<br>Red stemmed mint oil<br>Vietnamese mint oil |
| 4812 | **Palmitoylated Green Tea Extract Catechins**<br>Palmitoylated *Camilla sinensis* Extract Catechins<br>Lipid Soluble Green Tea Extract (Catechin Palmitate Esters) |
| 4813 | **2-(5-Isopropyl-2-methyl-tetrahydro-thiophen-2-yl)-ethanol** |
| 4814 | **Glucosylated *Rubus suavissimus* extract, 60% glucosylated rubusoside glycosides**<br>Glucosylated Sweet Blackberry Leaves Extract<br>60% glucosylated rubusoside glycosides |
| 4815 | **Sandalwood austrocaledonicum oil**<br>*Santalum austrocaledonicum* oil |
| 4816 | **Sugar Cane distillate** |

## TABLE 2: Average Usual Use Levels/Average Maximum Use Levels

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

| | (±)-2-Mercapto-5-methylheptan-4-one | Caryophylla-3(4),8-dien-5-ol | *L*-Cysteine methyl ester hydrochloride | 2(3)-Hexanethiol | Mixture of 1-Vinyl-3-cyclohexenecarb-aldehyde and 4-Vinyl-1-cyclohexenecarb-aldehyde | (±)-4-Hydroxy-6-methyl-2-heptanone | 2-Octyl-2-dodecenal | 2-Hexyl-2-decenal | *trans*-6-Octenal | (*E*)-3-Benzo[1,3]dioxol-5-yl-*N*,*N*-diphenyl-2-propenamide |
|---|---|---|---|---|---|---|---|---|---|---|
| CATEGORY | FEMA No. 4779 | 4780 | 4781 | 4782 | 4783 | 4784 | 4785 | 4786 | 4787 | 4788 |
| Baked Goods | 0.03/0.1 | 0.1/1 | 10/100 | 0.02/0.06 | | 50/100 | 0.1/1 | 0.1/1 | 0.1/1 | 0.2/2 |
| Beverages, Non-Alcoholic | 0.01/0.1 | 1/5 | | 0.005/0.03 | 5/10 | 30/80 | 1/5 | 1/5 | 0.03/0.3 | 0.02/0.2 |
| Beverages, Alcoholic | 0.02/0.1 | 1/5 | | 0.005/0.03 | | 30/80 | 1/5 | 1/5 | 0.03/0.3 | 0.04/2 |
| Breakfast Cereals | 0.03/0.1 | 0.1/1 | | 0.01/0.04 | | 40/100 | 0.1/1 | 0.1/1 | | 0.2/2 |
| Cheeses | | 0.1/1 | 10/100 | | | | 0.1/1 | 0.1/1 | 0.1/1 | |
| Chewing Gum | 0.1/0.2 | 1/5 | | 0.02/0.06 | 100/1000 | 60/100 | 1/5 | 1/5 | 0.1/1 | 10/100 |
| Condiments and Relishes | 0.01/0.1 | 0.1/1 | 10/100 | 0.02/0.06 | | | 0.1/1 | 0.1/1 | | |
| Confections and Frostings | 0.05/0.1 | 1/5 | | 0.02/0.06 | 5/50 | | 1/5 | 1/5 | 0.1/1 | 0.5/5 |
| Egg Products | | 0.1/1 | 10/100 | 0.015/0.05 | | | 0.1/1 | 0.1/1 | 0.05/1 | 0.2/2 |
| Fats and Oils | | 0.1/1 | | | | | 0.1/1 | 0.1/1 | 0.03/0.5 | 0.5/10 |
| Fish Products | | 0.1/1 | 10/100 | | | | 0.1/1 | 0.1/1 | | |
| Frozen Dairy | 0.05/0.1 | 0.1/1 | | 0.02/0.06 | | 50/100 | 0.1/1 | 0.1/1 | 0.1/1 | 0.2/2 |
| Fruit Ices | 0.005/0.05 | 1/5 | | 0.01/0.04 | | | 1/5 | 1/5 | | 0.2/4 |
| Gelatins and Puddings | 0.03/0.1 | 1/5 | 10/100 | 0.015/0.04 | | 40/100 | 1/5 | 1/5 | 0.1/1 | 0.2/4 |
| Granulated Sugar | | 0.1/5 | | | | | 0.1/1 | 0.1/1 | | 0.4/4 |
| Gravies | 0.01/0.1 | 0.1/1 | 10/100 | 0.02/0.06 | | | 0.1/1 | 0.1/1 | 0.02/0.5 | |
| Hard Candy | 0.1/0.2 | 1/5 | | 0.02/0.05 | 5/50 | 50/100 | 1/5 | 1/5 | 0.05/1 | 1/10 |
| Imitation Dairy | | 0.1/1 | | | | | 0.1/1 | 0.1/1 | 0.1/1 | 0.2/2 |
| Instant Coffee and Tea | | 0.1/1 | 10/100 | 0.02/0.06 | | 50/100 | 0.1/1 | 0.1/1 | 0.03/0.5 | 0.04/0.2 |
| Jams and Jellies | | 1/5 | | 0.02/0.06 | | | 1/5 | 1/5 | | 0.2/2 |
| Meat Products | | 0.1/1 | 10/100 | 0.02/0.08 | | | 0.1/1 | 0.1/1 | | |
| Milk Products | | 0.1/1 | | 0.005/0.04 | | 40/80 | 0.1/1 | 0.1/1 | 0.2/2 | 0.2/2 |
| Nut Products | | 0.1/1 | | 0.01/0.04 | | | 0.1/1 | 0.1/1 | 0.05/0.2 | |
| Other Grains | | 0.1/1 | | 0.01/0.06 | | | 0.1/1 | 0.1/1 | | |
| Poultry | | 0.1/1 | 10/100 | | | | 0.1/1 | 0.1/1 | | |
| Processed Fruits | 0.02/0.1 | 0.1/1 | | 0.01/0.05 | | | 0.1/1 | 0.1/1 | | 0.2/2 |
| Processed Vegetables | | 0.1/1 | 10/100 | | | | 0.1/1 | 0.1/1 | | |
| Reconstituted Vegetables | | 0.1/1 | 10/100 | | | | 0.1/1 | 0.1/1 | | |
| Seasonings and Flavors | 0.005/0.2 | 1/5 | 10/100 | 0.01/0.1 | 10/100 | 50/100 | 1/5 | 1/5 | 0.05/0.5 | |
| Snack Foods | 0.02/0.1 | 0.1/1 | | 0.01/0.06 | | | 0.1/1 | 0.1/1 | | |
| Soft Candy | 0.05/0.1 | 1/5 | | 0.01/0.04 | 10/100 | 50/100 | 1/5 | 1/5 | 0.1/1 | 0.5/10 |
| Soups | 0.03/0.1 | 0.1/1 | 10/100 | 0.02/0.06 | | | 0.1/1 | 0.1/1 | 0.02/0.5 | 0.5/10 |
| Sugar Substitutes | | 0.1/1 | | | | | 0.1/1 | 0.1/1 | | 0.4/8 |
| Sweet Sauces | 0.03/0.1 | 0.1/1 | 10/100 | 0.02/0.06 | | 50/100 | 0.1/1 | 0.1/1 | 0.1/1 | |

## TABLE 2 Continued: Average Usual Use Levels/Average Maximum Use Levels

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

| | 2,6-Dimethyl-5-heptenol | (±)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, ethyl ester | 3-(Acetylthio) hexanal | (±)-3-Mercapto-1-pentanol | (3*R*,3*S*)-3-[[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl) oxy]methyl]-*N*-cyclopentyl-2-oxo-3-piperidinecarboxamide | (±)-1-Cyclohexylethanol | (±)-8-Methyldecanal | Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside C 30% | (±)-Naringenin | 2-((3-(2,3-Dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl) thio)methyl)pyridine |
|---|---|---|---|---|---|---|---|---|---|---|
| **CATEGORY** | **4789** | **4790** | **4791** | **4792** | **4793** | **4794** | **4795** | **4796** | **4797** | **4798** |
| **Baked Goods** | 1/10 | 0.5/1 | 0.5/3 | 2/10 | 3/8 | | 2/20 | 30/90 | 200/600 | 2/6 |
| **Beverages, Non-Alcoholic** | 1/5 | 0.2/1 | 0.1/1 | 1/6 | 5/8 | | 0.5/5 | 20/75 | 100/300 | 1/2 |
| **Beverages, Alcoholic** | 1/5 | 0.2/1 | | | 2/8 | | 0.5/5 | 20/75 | 100/300 | |
| **Breakfast Cereals** | 1/5 | 0.5/1 | 0.5/2 | 1/8 | 3/8 | | 1/5 | 30/90 | 200/600 | 5/10 |
| **Cheeses** | | | | | | | | | 1000/1000 | 2/6 |
| **Chewing Gum** | 2/20 | 0.5/2 | 1/5 | 3/10 | 10/27 | 1000/3000 | 2/10 | 100/125 | 200/400 | |
| **Condiments and Relishes** | | | | | | | | | 200/400 | 5/10 |
| **Confections and Frostings** | 2/10 | 0.4/2 | | | 3/8 | 50/100 | 2/10 | 20/75 | 200/400 | |
| **Egg Products** | 0.2/2 | | | | | | 0.2/2 | | | 2/6 |
| **Fats and Oils** | 1/10 | 0.02/0.5 | | | | | 1/10 | | 100/200 | 4/8 |
| **Fish Products** | | | | | | | | | | 4/10 |
| **Frozen Dairy** | 1/2 | 0.3/1 | 0.5/1 | 1/8 | 2/8 | | 1/2 | 20/75 | 100/500 | |
| **Fruit Ices** | 1/2 | 0.3/1 | | | 2/8 | 30/60 | 0.5/5 | 20/75 | 100/200 | |
| **Gelatins and Puddings** | 1/10 | 0.2/1 | | | 2/8 | | 1/10 | 20/75 | 100/400 | |
| **Granulated Sugar** | | | | | | | | | | |
| **Gravies** | | | 0.05/2 | 1/8 | 2/8 | | | 20/50 | 100/500 | 4/10 |
| **Hard Candy** | 1/10 | 0.4/2 | | | 5/8 | 100/300 | 1/10 | | 100/400 | |
| **Imitation Dairy** | 1/10 | | | | | | 1/10 | 20/75 | 100/500 | |
| **Instant Coffee and Tea** | 1/10 | | 0.02/1 | 1/8 | 2/8 | | 1/10 | | 100/200 | |
| **Jams and Jellies** | 1/10 | 0.4/2 | 0.02/1 | 1/8 | | | 1/10 | 20/75 | 100/400 | |
| **Meat Products** | | 0.05/0.5 | | | 2/8 | | | 10/20 | 100/200 | 4/10 |
| **Milk Products** | 1/5 | | 0.02/1 | 1/8 | 3/8 | | 1/5 | 30/90 | 100/500 | |
| **Nut Products** | | | | | | | | | 50/100 | 2/6 |
| **Other Grains** | | | | | | | | | | 2/6 |
| **Poultry** | | | | | | | | | 100/200 | 2/6 |
| **Processed Fruits** | | 0.1/1 | | | | | | | 50/400 | |
| **Processed Vegetables** | | | | | | | | | 50/100 | 2/6 |
| **Reconstituted Vegetables** | | | | | | | | | 50/100 | 2/6 |
| **Seasonings and Flavors** | 1/10 | 0.2/1 | | | 2/8 | | 1/10 | 20/50 | 500/1000 | 10/20 |
| **Snack Foods** | 1/10 | | 0.02/1 | 1/6 | 2/8 | | 1/10 | | 200/400 | 10/20 |
| **Soft Candy** | 1/10 | 0.3/2 | | | 5/8 | 50/200 | 1/10 | | 100/400 | |
| **Soups** | 1/10 | 0.05/0.8 | | | 2/8 | | 1/10 | | 100/300 | 4/8 |
| **Sugar Substitutes** | | | | | | | | | 100/200 | |
| **Sweet Sauces** | | | | | 3/8 | | | | 100/400 | |

## 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).

| | (2*R*)-3′,5-Dihydroxy-4′-methoxyflavanone | Glucosylated *Rubus suavissimus* extract 20-30% glucosylated rubusoside glycosides | Olive fruit extract | (5)-1-(3-((((4-Amino-2,2-dioxido-1*H*-benzo-[c][1,2,6] thiadiazin-5-yl)-oxy) methyl)-piperidin-1-yl)-3-methylbutan-1-one | 8-Methylnonanal | Mixture of Ricinoleic acid, Linoleic acid, and Oleic acid | Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside A 22% | Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside C 22% | Pinocarvyl acetate | *N*-Ethyl-5-methyl-2-(1-methylethenyl) cyclohexanecarboxamide |
|---|---|---|---|---|---|---|---|---|---|---|
| **CATEGORY** | **4799** | **4800** | **4801** | **4802** | **4803** | **4804** | **4805** | **4806** | **4807** | **4808** |
| **Baked Goods** | | | 120/720 | 6/6 | 2/20 | 5/20 | 70/70 | 100/100 | | 20/30 |
| **Beverages, Non-Alcoholic** | 20/25 | 150/350 | 120/720 | 2.5/6 | 0.5/10 | 1/5 | 70/70 | 110/110 | 0.1/5.0 | 5/10 |
| **Beverages, Alcoholic** | 20/25 | 75/200 | 120/720 | 2.5/6 | 0.5/10 | 1/5 | 70/70 | 100/100 | 0.5/7.5 | 15/30 |
| **Breakfast Cereals** | 20/25 | 150/400 | 120/720 | 6/6 | 1/10 | 1/5 | 70/70 | 100/100 | | 10/20 |
| **Cheeses** | | | 120/720 | | | 5/20 | | | | |
| **Chewing Gum** | | | | 6/6 | 2/20 | 1/5 | 70/70 | 100/100 | 0.5/7.5 | 2000/3000 |
| **Condiments and Relishes** | | | 120/720 | 6/6 | | 5/10 | 70/70 | 100/100 | | |
| **Confections and Frostings** | 20/25 | | | 6/6 | 2/20 | 1/5 | 70/70 | 100/100 | 0.5/7.5 | 200/300 |
| **Egg Products** | | | 120/720 | | 0.2/2 | 1/10 | 70/70 | | | |
| **Fats and Oils** | | | 120/720 | 3/6 | 1/20 | 10/50 | 70/70 | 100/100 | | |
| **Fish Products** | | | 120/720 | | | 1/5 | | | | |
| **Frozen Dairy** | | 200/300 | 120/720 | 3/6 | 1/5 | 1/5 | 70/70 | 100/100 | 0.1/5.0 | |
| **Fruit Ices** | | 100/300 | | 3/6 | 0.5/5 | 1/5 | 70/70 | 100/100 | | 200/300 |
| **Gelatins and Puddings** | | | | 3/6 | 1/10 | 1/5 | 70/70 | 100/100 | | |
| **Granulated Sugar** | | | | | | | | | | |
| **Gravies** | | 100/150 | 120/720 | 3/6 | | 5/20 | 70/70 | 100/100 | | |
| **Hard Candy** | 20/25 | | | 3/6 | 1/20 | 1/5 | 70/70 | 100/100 | 0.5/7.5 | 200/300 |
| **Imitation Dairy** | | | | 2.5/6 | 1/10 | 5/20 | 70/70 | 100/100 | 0.1/5.0 | |
| **Instant Coffee and Tea** | 20/25 | 150/350 | | 2.5/6 | 1/10 | 1/5 | 70/70 | 100/100 | | 10/20 |
| **Jams and Jellies** | 20/25 | | | 6/6 | 1/10 | 1/5 | 70/70 | 100/100 | | 10/20 |
| **Meat Products** | | 100/150 | 120/720 | | | 5/20 | | | | |
| **Milk Products** | 20/25 | 200/300 | 120/720 | 2.5/6 | 1/10 | 5/20 | 70/70 | 100/100 | 0.1/5.0 | 5/10 |
| **Nut Products** | | | 120/720 | 3/6 | | 1/5 | 70/70 | 100/100 | | |
| **Other Grains** | | | | | | | | | | |
| **Poultry** | | | 120/720 | | | 5/25 | | | | |
| **Processed Fruits** | | | | 3/6 | | 1/5 | 70/70 | 100/100 | | 5/10 |
| **Processed Vegetables** | | | | | | 1/5 | 70/70 | 100/100 | | |
| **Reconstituted Vegetables** | | | | | | 1/5 | | | | |
| **Seasonings and Flavors** | | 100/150 | 120/720 | | 1/10 | 5/50 | 70/70 | 100/100 | | 50/150 |
| **Snack Foods** | 20/25 | | 120/720 | 6/6 | 1/10 | 5/50 | 70/70 | 100/100 | | 200/300 |
| **Soft Candy** | 20/25 | | | 6/6 | 1/10 | 1/5 | 70/70 | 100/100 | 0.5/7.5 | 500/1000 |
| **Soups** | | 100/150 | 120/720 | 3/6 | 1/10 | 5/25 | 70/70 | 100/100 | | |
| **Sugar Substitutes** | 20/25 | | | | | 1/5 | 70/70 | 100/100 | | |
| **Sweet Sauces** | 20/25 | | 120/720 | 3/6 | | 1/5 | 70/70 | 100/100 | | |

## 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).

| | 2-(4-Methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl) acetamide | Ethyl-2-(4-hydroxy-3-methoxyphenyl)acetate | Ginger Mint Oil (*Mentha x gracilis*) | Palmitoylated Green Tea Extract Catechins | 2-(5-Isopropyl-2-methyltetrahydro-thiophen-2-yl)ethanol | Glucosylated Rubus extract, 60% glucosylated rubusoside glycosides | Sandalwood Austrocaledonicum oil | Sugar Cane Distillate* |
|---|---|---|---|---|---|---|---|---|
| **CATEGORY** | **4809** | **4810** | **4811** | **4812** | **4813** | **4814** | **4815** | **4816** |
| Baked Goods | | 25/200 | | 100/200 | 0.2/2 | 30/150 | 5/10 | 0.01(2250)/0.01(2250)* |
| Beverages, Non-Alcoholic | 1/3 | 10/75 | | | 0.05/2 | 30/150 | 1/2 | |
| Beverages, Alcoholic | 2/6 | 10/75 | | | 0.1/2 | 30/150 | 0.5/1 | |
| Breakfast Cereals | | | | 50/75 | 0.2/2 | 30/150 | | |
| Cheeses | | | | | | | | |
| Chewing Gum | 75/150 | 100/500 | 4000/8000 | | 0.5/5 | 30/150 | 3/3 | |
| Condiments and Relishes | | 25/200 | | 100/200 | | | | |
| Confections and Frostings | 5/15 | | 250/1000 | 50/100 | 0.5/5 | 30/150 | | 0.01(2250)/0.01(2250)* |
| Egg Products | | | | | 0.1/2 | | | |
| Fats and Oils | 1/3 | | | 200/500 | 0.2/5 | | | |
| Fish Products | | | | 250/300 | | | | |
| Frozen Dairy | 1/3 | 25/100 | 250/1000 | | 0.1/2 | 50/150 | 3/4 | |
| Fruit Ices | 1/3 | 25/100 | | | 0.05/2 | 50/150 | | |
| Gelatins and Puddings | 1/3 | | | | 0.2/5 | 30/150 | 0.3/1 | |
| Granulated Sugar | | | | | | | | |
| Gravies | | | | | 0.2/5 | | | |
| Hard Candy | 5/15 | 25/100 | 2500/5000 | | 0.5/5 | | 90/90 | |
| Imitation Dairy | 1/3 | | | | 0.2/5 | | | |
| Instant Coffee and Tea | 1/3 | 10/75 | | | 0.2/5 | 30/150 | | |
| Jams and Jellies | | | | | 0.2/5 | | | |
| Meat Products | | 25/100 | | 250/300 | | | | |
| Milk Products | 1/3 | 10/100 | | | 0.1/5 | 50/150 | | |
| Nut Products | | | | 50/100 | | | | |
| Other Grains | | | | 150/300 | | | | |
| Poultry | | | | 250/300 | | | | |
| Processed Fruits | | | | | | 30/150 | | |
| Processed Vegetables | | | | | | | | |
| Reconstituted Vegetables | | | | | | | | |
| Seasonings and Flavors | | 50/300 | | | 0.1/2 | | | |
| Snack Foods | | 25/200 | | 100/200 | 0.1/2 | 30/150 | | 0.01(2250)/0.01(2250)* |
| Soft Candy | 5/15 | | 2500/5000 | 50/100 | 0.2/5 | 30/150 | 5/10 | |
| Soups | 1/3 | 25/100 | | 100/200 | 0.2/5 | 30/150 | | |
| Sugar Substitutes | | | | | | 30/150 | | |
| Sweet Sauces | 5/15 | | | | | 30/150 | | 0.01(2250)/0.01(2250)* |

*Figures in parentheses represent the amount of diluted aqueous Sugar Cane Distillate in the commercial product as used in food.

## TABLE 3: Updated Average Usual Use Levels/Average Maximum Use Levels

Average usual use levels (ppm)/average maximum use levels (ppm) for flavoring substances previously recognized as FEMA GRAS. Superscript 'a' represents a new use level.

| | Potassium cinnamate | Quillaia extract | Glycine | *N*-(Heptan-4-yl) benzo[*d*][1,3]dioxole-5-carboxamide | 3-[(4-Amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl) oxy]-2,2-dimethyl-*N*-propylpropanamide | Glutamyl-valyl-glycine | Luo Han Fruit Concentrate |
|---|---|---|---|---|---|---|---|
| **FEMA NO.** | **2288** | **2973** | **3287** | **4232** | **4701** | **4709** | **4711** |
| **GRAS PUBLICATION** | **3** | **3** | **4** | **22** | **25** | **25** | **25** |
| **CATEGORY** | | | | | | | |
| Baked Goods | 233/384 | 24/30 | 50/150 | 1/2 | 10/22 | 15/30 | 40/60 |
| Beverages, Non-Alcoholic | 300/400 | 91.5/103 | 250/1000 | 2/5 | 0/0 | 20/50 | 40/60 |
| Beverages, Alcoholic | 570/712 | 90/100 | | 2[a]/5[a] | 5[a]/22[a] | | 40/60 |
| Breakfast Cereals | | 15[a]/75[a] | | | 15/22 | 80/160 | 40/80 |
| Cheeses | | 15[a]/75[a] | | 1/3 | | 20/50 | |
| Chewing Gum | 224[a]/300 | 7.5[a]/30[a] | | | 30/300 | 10[a]/30[a] | 200[a]/400[a] |
| Condiments and Relishes | | 15[a]/75[a] | 150/3000[a] | 2/4 | 3/22 | 30/60 | 5/40 |
| Confections and Frostings | | 7.5[a]/30[a] | | | 10/22 | | 40/80 |
| Egg Products | | 7.5[a]/30[a] | | 2[a]/5[a] | | 15/45 | |
| Fats and Oils | 746[a]/1000[a] | | | 2/4 | | 30/60 | |
| Fish Products | | 7.5[a]/30[a] | | 1/3 | | 15/45 | |
| Frozen Dairy | 192/263 | 15[a]/75[a] | | | 5/22 | 20/50 | 5/80 |
| Fruit Ices | | 7.5[a]/30[a] | | | 5/22 | 20/50 | 5/40 |
| Gelatins and Puddings | 459[a]/500[a] | 7.5[a]/30[a] | | | 5/22 | | 40/80 |
| Granulated Sugar | | | | | | | |
| Gravies | 746[a]/1000[a] | 7.5[a]/30[a] | 150/4000[a] | 2/4 | | 30/60 | 5/40 |
| Hard Candy | 0.01/0.01 | 18/30[a] | 25/150 | | 15/75 | | 40/80 |
| Imitation Dairy | | 7.5[a]/30[a] | 50/150 | | | 20/50 | 5/40 |
| Instant Coffee and Tea | 224[a]/300[a] | 1.5[a]/30[a] | 150/150 | | | 10/30 | |
| Jams and Jellies | 373[a]/500[a] | 7.5[a]/30[a] | | | 10/22 | | 10/40 |
| Meat Products | | 7.5[a]/75[a] | | 1/3 | | 15/45 | |
| Milk Products | | 1.5[a]/30[a] | | | 3/22 | 15/45 | 40/80 |
| Nut Products | | 30[a]/120[a] | | 2[a]/5[a] | | | 5/40 |
| Other Grains | | 7.5[a]/30[a] | | | | | |
| Poultry | | 15[a]/75[a] | | 1/3 | | 15/45 | |
| Processed Fruits | 37[a]/50[a] | 1.5[a]/30[a] | | | | | 5/40 |
| Processed Vegetables | | 7.5[a]/30[a] | | 1/3 | | 15/45 | |
| Reconstituted Vegetables | | 7.5[a]/30[a] | | 2[a]/5[a] | | 15/45 | |
| Seasonings and Flavors | | 15[a]/75[a] | | 5/10 | | 80/160 | 5/40 |
| Snack Foods | | 15[a]/75[a] | | 5/10 | | 80/160 | 5/40 |
| Soft Candy | 249/356 | 16[a]/30[a] | 25/150 | | 15/75 | | 40/80 |
| Soups | | 15[a]/75[a] | 150/6000[a] | 2/4 | | 20/50 | |
| Sugar Substitutes | 746[a]/1000[a] | 7.5[a]/30[a] | | | | 80/160 | |
| Sweet Sauces | 746[a]/1000[a] | 15[a]/75[a] | | | 10/22 | 30/60 | 5/40 |

## Supplementary Information 1: Identity for Natural Flavor Complexes as Evaluated by the Expert Panel

| FEMA NO. | FEMA PRIMARY NAME | THE IDENTITY DESCRIPTION AS REVIEWED BY THE FEMA EXPERT PANEL |
|---|---|---|
| **4796** | Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside C 30% | Total steviol glycosides >95%, including 28-33% rebaudioside C, 17-23% rebaudioside A, 10-15% stevioside, 25-36% other steviol glycosides (including rebaudiosides B, D, E and F, steviolbioside, rubusoside and dulcoside A). |
| **4800** | Glucosylated *Rubus suavissimus* extract 20-30% glucosylated rubusoside glycosides | 20-30% Multiply-glucosylated rubusoside glycosides; 25% glycerol; up to 10% other carbohydrates; no more than 25% water. |
| **4801** | Olive fruit extract | 65-67% Phenolic derivatives (primarily measured as hydroxytyrosol and tyrosol); 9-10% saturated alicyclic primary alcohols, aldehydes, acids and related esters; the intended condition of use is as a mixture of 12% olive fruit extract and 88% maltodextrin. |
| **4805** | Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside A 22% | Total principal steviol glycosides 60-63%, including 18-22% rebaudioside A, 5-8% stevioside, 8-14% rebaudioside D; rebaudiosides B, C, E, F, N, O, M, steviolbioside, rubusoside, and dulcoside A individually present at concentrations up to 6%. Additional steviol glycosides, 36-42%. |
| **4806** | Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside C 22% | Total principal steviol glycosides 56-59%, including 13-22% rebaudioside C, 13-18% rebaudioside A, 5-8% stevioside; rebaudiosides B, D, E, F, N, O, and M, steviolbioside, rubusoside and dulcoside A individually present at concentrations up to 4%. Additional steviol glycosides, 38-45%. |
| **4811** | Ginger Mint Oil (*Mentha x gracilis*) | 43-65% Aliphatic tertiary alcohols, typically measured as linalool; 23-48% aliphatic and aromatic hydrocarbons; 1-4% alicyclic monoterpene secondary alcohols and ketones, typically measured as l-menthone or l-menthol. |
| **4812** | Palmitoylated Green Tea Extract Catechins | 74-86% Catechin mono-, di- and tri-palmitate esters derived from green tea; 14-15% palmitic acid; no individual free catechin present at concentrations above 1%. |
| **4814** | Glucosylated *Rubus suavissimus* extract 60% glucosylated rubusoside glycosides | 60-70% Multiply-glucosylated rubusoside glycosides; 7-8% rubusoside; 20-30% dextrins. |
| **4815** | Sandalwood austrocaledonicum oil | 80-85% Alicyclic primary alcohols, aldehydes and acids, typically measured as santalol derivatives; 4-5% aliphatic and aromatic hydrocarbons; 2-4% aliphatic and aromatic tertiary alcohols; 0.5-1.5% aliphatic and aromatic ethers. |
| **4816** | Sugar Cane Distillate | Aqueous solution of 0.0005% sugar cane distillate of which the major marker constituents are phenyl-substituted secondary ketones alcohols and related esters, primarily measured as beta-damascenone and acetophenone. |

Since its initial publication of GRAS determinations for flavor ingredients (Hall and Oser, 1965), the FEMA Expert Panel has consistently made available to the public information on its determinations, including the 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 GRAS determinations included within GRAS 27.[1] 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). For more information on the FEMA GRAS program, please see "About the FEMA GRAS™ Program" on femaflavor.org.

The Panel reviewed the GRAS application and supporting information regarding (±)-2-mercapto-5-methylheptan-4-one (CAS 1416051-88-1) and concluded that it is GRAS (FEMA 4779) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic thiols and sulfides (SLR B5, JECFA 2000, 2004, 2008, 2011, 2012). The Panel noted that based on an anticipated annual volume of use of 0.5 kg, the *per capita* intake ("eaters only") of (±)-2-mercapto-5-methylheptan-4-one from use as a flavor ingredient is calculated to be 0.07 µg/person/day (0.001 µg/kg bw/day), which is significantly below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The substance naturally occurs in hazelnut, but only qualitative data are available and, thus, no consumption ratio can be calculated. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. Based on the functional groups present, the substance is anticipated to be metabolized primarily by reductive metabolism of the ketone moiety and/or oxidation of a terminal methyl group to an alcohol, followed by glucuronic acid conjugate formation and excretion in the urine (Parkinson, 1996). Based on the lack of structural alerts of the substance and the identity and arrangement of functional groups therein, the Panel identified no specific concerns related to the potential genotoxicity of the substance. A No-Observed-Adverse-Effect Level (NOAEL) of 1.89 mg/kg bw/day in a 12-week toxicity study of male and female rats for the structural analog 3-mercapto-2-pentanone is more than 1,500,000 times greater than the anticipated daily *per capita* intake of (±)-2-mercapto-5-methylheptan-4-one from its intended use as a flavor ingredient in food (Morgareidge, 1971).

The Panel reviewed the GRAS application and supporting information regarding caryophylla-3(4),8-dien-5-ol (CAS 34298-31-2; 38284-26-3) and concluded that it is GRAS (FEMA 4780) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of alicyclic ketones, secondary alcohols and related esters (SLR A5; JECFA 2004) The Panel noted that based on the anticipated annual volume of use (50 kg) the *per capita* intake ("eaters only") of caryophylla-3(4),8-dien-5-ol from use as a flavor ingredient is calculated to be 7 µg/person/day (0.1 µg/kg bw/day), which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The substance naturally occurs in clary sage, clove bud, pepper and scotch spearmint oil, but only qualitative data is available and, thus, no consumption ratio can be calculated (Nijssen et al. 2015). The 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 substance is anticipated to be metabolized in a manner analogous to that of other terpene alcohols: this is expected to involve either conjugation of the secondary alcohol with glucuronic acid or sulfate followed by excretion in the urine, or epoxidation of the exo-alkene moieties followed by ring opening to yield polyols that are excreted in the urine unchanged or after glucuronic acid or glutathione conjugation. Evidence of genotoxicity was not observed in an Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 in the presence and absence of metabolic activation for the structural analog *beta*-caryophyllene epoxide (Richold et al., 1979). Based on the data, and also the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of caryophylla-3(4),8-dien-5-ol. A NOAEL of 109 mg/kg bw/day for male rats and 137 mg/kg bw/day for female rats in a 90-day oral feeding study of the structural analog *beta*-caryophyllene oxide (FEMA 4085) is more than 900,000 times the anticipated daily *per capita* intake of caryophylla-3(4),8-dien-5-ol from use as a flavor ingredient (Bauter, 2012; Capen et al., 1999).

The Panel reviewed the GRAS application and supporting information regarding L-cysteine methyl ester hydrochloride (CAS 18598-63-5) and concluded that it is GRAS (FEMA 4781) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2; Smith et al., 2005a). This substance was evaluated within the context of the chemical group of amino acids and related substances (SLR B3; JECFA 2006, 2012). The Panel noted that based on the anticipated annual volume of use (100 kg) the *per capita* intake ("eaters only") of L-cysteine methyl ester hydrochloride from use as a flavor ingredient is calculated to be 15 µg/person/day (0.3 µg/kg bw/day), which is significantly below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The substance has not been reported to occur naturally. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. By analogy to other amino acid esters, the substance is anticipated to be metabolized primarily by hydrolysis to the corresponding acid, L-cysteine, and enter the amino acid pool. Oxidation to methanol and resulting formaldehyde formation was not concluded to be significant. Excretion would occur mainly in the urine (Hosokawa 2008; Fukami and Yokoi 2012; Nelson and Cox, 2008). L-Cysteine showed some increase in human lymphocyte sister chromatid exchange, but the results not dependent upon dose and were considered by the Panel to be due to metabolic impact of administration of high doses of an amino acid rather than genotoxic potential. The Panel noted that this result may also be due to peroxide formation

[1] These key findings are subject to change pending additional information

from trace metals, which is a common occurrence for amino acids and is not considered to be biologically relevant to humans. L-Cysteine did not induce chromosomal aberrations in V79 Chinese hamster fibroblasts at concentrations up to 121 µg/ml. Based on the negative CHO cell chromosomal aberration assays and the understanding of the role of metabolic impact on genotoxicity assays for L-cysteine, the Panel did not identify specific concerns related to the potential genotoxicity of L-cysteine methyl ester hydrochloride (Xing and Na, 1996; Speit et al., 1980; Natarajan and van Kesteren-van Leeuwen, 1981; Stich et al., 1981; Tavares et al., 1998). In a 6-month male and female rat oral gavage study, the Panel concluded that the appropriate NOAEL was 100 mg/kg bw/day based on adaptive effects at higher doses. This NOAEL is more than 400,000 times the anticipated daily *per capita* intake of L-cysteine methyl ester hydrochloride from use as a flavor ingredient (Takasaki et al., 1973).

The Panel reviewed the GRAS application and supporting information regarding 2(3)-hexanethiol (CAS 1679-06-7/1633-90-5) and concluded that it is GRAS (FEMA 4782) for use as a flavor in the food categories at the new use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated within the context of the chemical group of simple aliphatic and aromatic sulfides and thiols (SLR A8; JECFA 2000, 2004, 2008, 2011, 2012). The Panel noted that based on the anticipated annual volume of 0.5 kg, the *per capita* intake ("eaters only") of 2(3)-hexanethiol from use as a flavor ingredient is calculated to be 0.07 µg/person/day (0.001 µg/kg bw/day), which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The substance naturally occurs in white truffles, but no quantitative data is available to calculate a consumption ratio (Nijssen et al., 2015). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. Based on analogy to other aliphatic thiols, the substance is anticipated to undergo S-methylation to yield the corresponding methyl sulfide that is then oxidized to the sulfoxide and subsequently the sulfone that is excreted unchanged in the urine. Additionally, omega-oxidation of the terminal methyl groups could occur leading to *beta*-oxidation. Based on the structure of the substance the Panel did not identify specific concerns related to the potential genotoxicity of 2(3)-hexanethiol. A NOAEL of 0.56 mg/kg bw/day in a 90-day male and female rat dietary study for the structural analog cyclopentanethiol (FEMA 3262) is conservatively 450,000 times higher than the anticipated daily *per capita* intake of 2(3)-hexanethiol from use as a flavor ingredient (Moran et al., 1980; Morgareidge, 1970; Collinson, 1989; Fairchild and Atokinger, 1958).

The Panel reviewed the GRAS application and supporting information regarding the mixture of 1-vinyl-3-cyclohexenecarbaldehyde and 4-vinyl-1-cyclohexenecarbaldehyde (CAS 1049017-63-1 and 1049017-68-6, respectively) and concluded that it is GRAS (FEMA 4783) for use as a flavor in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This mixture was evaluated individually in the context of the chemical group of alicyclic primary alcohols, aldehydes, acids and related esters (SLR A5; JECFA, 2002, 2011). The Panel noted that based on the anticipated volume of 100 kg, the *per capita* intake ("eaters only") of the mixture of 1-vinyl-3-cyclohexenecarbaldehyde and 4-vinyl-1-cyclohexenecarbaldehyde from use as a flavor ingredient is calculated to be 15 µg/person/day (0.3 µg/kg bw/day), which is significantly below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The mixture has not been reported to occur naturally. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. By analogy to other alicyclic aldehydes, the substance is expected to be metabolized by oxidation to the corresponding acid and excreted in the urine either unchanged or after conjugation with glucuronic acid or glycine (Ishida et al., 1989). Evidence of mutagenicity was not observed in an Ames assay with *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 or *Escherichia coli* WP2uvrA following treatment with the mixture of 1-vinyl-3-cyclohexenecarbaldehyde and 4-vinyl-1-cyclohexenecarbaldehyde in the presence or absence of metabolic activation. Statistically significant increases in chromosomal aberrations of Chinese Hamster V79 cells resulted from administration of the mixture of 1-vinyl-3-cyclohexenecarbaldehyde and 4-vinyl-1-cyclohexenecarbaldehyde in the absence or presence of metabolic activation, but in a mouse bone marrow micronucleus assay the number of polychromatic erythrocytes was not increased relative to the vehicle control. The extensive genotoxicity data for the structural analog, *p*-mentha-1,8-dien-7-al (FEMA 3557), was also reviewed and the Panel considered that the weight of evidence for this substance indicated no genotoxic potential. Based on weight of evidence for the substance and the structural analog, including an overall negative genotoxicity profile *in vivo,* the Panel did not identify specific concerns related to the potential genotoxicity of the mixture of 1-vinyl-3-cyclohexenecarbaldehyde and 4-vinyl-1-cyclohexenecarbaldehyde (Sokolowski, 2011; Hall, 2011a; Hall, 2011b; Bowen, 2011; Lloyd, 2009; Lloyd, 2012; Fujita et al. 1994; Ishidate et al. 1984; Yoo, 1986; Kuroda et al., 1984; Eder et al., 1993). A NOAEL of 120 mg/kg bw/day in a 90-day male and female rat oral gavage study for the structural analog, perillyl alcohol (FEMA 2664), is 480,000 times higher than the anticipated daily *per capita* intake of the mixture of 1-vinyl-3-cyclohexenecarbaldehyde and 4-vinyl-1-cyclohexenecarbaldehyde from use as a flavor ingredient (Crowell, 1997; Belanger, 1998; NCI, 1996; Stark et al., 1995; Burke et al., 1997; FDA, 1993; Mills et al., 1995; Reddy et al., 1997; Maltzman et al., 1991; Broitman et al., 1996; Belanger, 1998; Haag & Gould, 1994).

The Panel reviewed the GRAS application and supporting information regarding (±)-4-hydroxy-6-methyl-2-heptanone (CAS 57548-36-4) and concluded that it is GRAS (FEMA 4784) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of diketones, hydroxyketones and simple derivatives (SLR B1E; JECFA 1999, 2011) The Panel noted that based on the anticipated annual volume of use (1 kg), the *per capita* intake ("eaters only"") of (±)-4-hydroxy-6-methyl-2-heptanone from use as a flavor ingredient is calculated to be 0.2 µg/person/day (0.003 µg/kg bw/day), which is significantly below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The material was not reported to occur naturally in food. The Panel considered the specification of

the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. Based on analogy with related compounds, it is anticipated that (±)-4-hydroxy-6-methyl-2-heptanone would be metabolized along several pathways, namely (a) conjugation with glucuronic acid and/or sulfate followed by excretion; (b) reduction of the keto function followed by conjugation and excretion; and (c) *omega*-oxidation of carbon centers to the corresponding alcohol and carboxylic acid. No increases in the number of reverse mutations were observed in an Ames assay for the structural analog acetoin in *S. typhimurium* strains TA98, TA100 and TA102 in either the absence or presence of metabolic activation, and a separate Ames assay for acetoin in *S. typhimurium* strains TA97, TA98, TA100 and TA1535 also produced negative results in either the absence or presence of metabolic activation. The structurally related substance acetoin was weakly mutagenic, with effects less than two-fold of the control values, at a single dose in *S. typhimurium* strain TA100 without metabolic activation. No increased incidences in micronuclei were observed in peripheral blood erythrocytes when acetoin was administered to male and female Han Wistar rats and male and female B6C3F1 mice in a 13-week inhalation exposure study at concentrations up to 800 ppm. Based on a weight of evidence consideration for the structural analog, acetoin, and also based on the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of (±)-4-hydroxy-6-methyl-2-heptanone (Aeschbacher et al., 1989; NTP, 2013a,b,c). A 13-week male and female CFE rat drinking water study resulted in a NOAEL of 330 mg/kg bw/day for the conservative structural analog acetoin (FEMA 2008). This is >100,000,000 times higher the anticipated daily *per capita* intake of (±)-4-hydroxy-6-methyl-2-heptanone from use as a flavor ingredient. (Gaunt et al., 1972, FDA, 1993).

The Panel reviewed the GRAS application and supporting information regarding 2-octyl-2-dodecenal (CAS 25234-33-7) and concluded that it is GRAS (FEMA 4785) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of aliphatic branched-chain saturated and unsaturated alcohols, aldehydes, acids and related esters (SLR M1; JECFA 2004, 2009). The Panel noted that based on the anticipated annual volume of use (3 kg), the *per capita* intake ("eaters only") of 2-octyl-2-dodecenal from use as a flavor ingredient is calculated to be 0.4 µg/person/day (0.007 µg/kg bw/day), which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). The material was not reported to occur naturally in food. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. Based on the metabolic behavior of *alpha,beta*-unsaturated aldehydes, it is anticipated that 2-octyl-2-dodecenal would be metabolized along several pathways, namely (a) oxidation of the aldehyde function to the carboxylic acid and (b) a series of *beta*-oxidations to the corresponding carboxylic acid and (c) *omega*-oxidation to the corresponding alcohol and carboxylic acid. The carboxylic acid metabolite might be expected to be conjugated with glucuronic acid and glycine (Deuel, 1957; Weiner, 1980; Blair and Bodley, 1969; Kassahun et al., 1991). A number of studies for the structural analog *trans*-2-hexenal were reviewed, including *in vitro* and *in vivo* genotoxicity studies. Based on the overall weight of evidence for *trans*-2-hexenal, and also based on the structure of the substance and the identity and arrangement of the functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of 2-octyl-2-dodecenal (Kirby et al., 1983; Zeiger et al., 1985; Agarwal et al., 1985; Seed, 1982; Divincenzo et al., 1985; Tomita et al., 1982; Phillips et al., 1982; Hodgson et al., 1982; Putman et al., 1983; Eder et al., 1992, 1993; Marnett et al., 1985; Dittberner et al., 1995; Canonero et al., 1990; Griffin and Segall, 1986; NTP,1997, 2001, 2003; Banerjee and Giri, 1986; Mukherjee et al., 1988; Oda, 1979; Kuroda et al., 1984; Yoo, 1986; Ishidate et al.,1984). Other structural analogs, 2-ethyl-1-hexanol (FEMA 3151) and citral (FEMA 2303) were also reviewed (Astill, 1996a,b; Astill, 1993; Rhodes et al., 1984; Lake et al., 1975; Narotsky et al., 1994; Dieter et al., 1993; Hagan et al., 1967; NTP, 2001; Geldof et al., 1992; Hoberman et al., 1989; Vollmuth et al., 1990; Nogueira et al., 1994; Gaworski et al., 1992; Gray and Beamand, 1984; Sjoberg et al., 1986; NTP, 1991; Hardin et al., 1987; EPA, 1991; Ritter et al., 1987; Tyl et al., 1992). A 13-week dietary study for the structural analog *trans*-2-hexenal (FEMA 2560) in male and female CFW rats resulted in a NOAEL of 80 mg/kg bw/day. This NOAEL is at least 10,000,000 times the anticipated daily *per capita* intake of 2-octyl-2-dodecanal from use as a flavor ingredient (Gaunt et al., 1971).

The Panel reviewed the GRAS application and supporting information regarding 2-hexyl-2-decenal (CAS 13893-39-5) and concluded that it is GRAS (FEMA 4786) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of aliphatic branched-chain saturated and unsaturated alcohols, aldehydes, acids and related esters (SLR M1; JECFA 2004, 2009). The Panel noted that based on the anticipated annual volume of use (5 kg), the *per capita* intake ("eaters only") of 2-hexyl-2-decenal from use as a flavor ingredient is calculated to be 0.7 µg/person/day (0.01 µg/kg bw/day), which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). The material was not reported to occur naturally in food. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. Based on the metabolic behavior of *alpha,beta*-unsaturated aldehydes, it is anticipated that 2-hexyl-2-decenal would be metabolized along several pathways, namely (a) oxidation of the aldehyde function to the carboxylic acid and (b) a series of *beta*-oxidations to the corresponding carboxylic acid and (c) *omega*-oxidation to the corresponding alcohol and carboxylic acid. The carboxylic acid metabolite might be expected to be conjugated with glucuronic acid and glycine (Deuel, 1957; Weiner, 1980; Blair and Bodley, 1969; Kassahun et al., 1991). A number of studies for the structural analog *trans*-2-hexenal were reviewed, including *in vitro* and *in vivo* genotoxicity studies. Based on the overall weight of evidence for *trans*-2-hexenal, and also based on the structure of the substance and the identity and arrangement of the functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of 2-hexyl-2-decenal. (Kirby et al., 1983; Zeiger

et al., 1985; Agarwal et al., 1985; Seed, 1982; Divincenzo et al., 1985; Tomita et al., 1982; Phillips et al., 1982; Hodgson et al., 1982; Putman et al., 1983; Eder et al., 1992, 1993; Marnett et al., 1985; Dittberner et al., 1995; Canonero et al., 1990; Griffin and Segall, 1986; NTP,1997, 2001, 2003; Banerjee and Giri, 1986; Mukherjee et al., 1988; Oda, 1979; Kuroda et al., 1984; Yoo, 1986; Ishidate et al.,1984). Other structural analogs, 2-ethyl-1-hexanol (FEMA 3151) and citral (FEMA 2303) were also reviewed (Astill, 1996a,b; Astill, 1993; Rhodes et al., 1984; Lake et al., 1975; Narotsky et al., 1994; Dieter et al., 1993; Hagan et al., 1967; NTP, 2001; Geldof et al., 1992; Hoberman et al., 1989; Vollmuth et al., 1990; Nogueira et al., 1994; Gaworski et al., 1992; Gray and Beamand, 1984; Sjoberg et al., 1986; NTP, 1991; Hardin et al., 1987; EPA, 1991; Ritter et al., 1987; Tyl et al., 1992). A 13-week dietary study for the structural analog *trans*-2-hexenal (FEMA 2560) in male and female CFW rats resulted in a NOAEL of 80 mg/kg bw/day. This NOAEL is at least 10,000,000 times the anticipated daily *per capita* intake of 2-hexyl-2-decanal from use as a flavor ingredient (Gaunt et al., 1971).

The Panel reviewed the GRAS application and supporting information regarding *trans*-6-octenal (CAS 63196-63-4) and concluded that it is GRAS (FEMA 4787) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). The substance was evaluated individually within the context of the chemical group of linear and branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids, and related esters (SLR M1, JECFA 1999, 2004, 2012). The Panel noted that based on the anticipated annual volume of use (0.1 kg), the *per capita* intake ("eaters only") of *trans*-6-octenal from use as a flavor ingredient is calculated to be 0.02 µg/person/day (0.0003 µg/kg bw/day), which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The material was not reported to occur naturally in food. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. Based on the metabolism of unsaturated acyclic fatty acids, it is anticipated that *trans*-6-octenal will be oxidized and the resulting linear unsaturated medium chain carboxylic acid will participate in the fatty acid metabolism pathway to produce carbon dioxide and water (Nelson and Cox, 2008; Kawaguchi, 2012). No increases in the number of reverse mutations were observed in Ames assays for *trans*-6-octenal in *S. typhimurium* strains TA98 or TA100 in either the presence or absence of metabolic activation. Based on the available data, and also based on the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of *trans*-6-octenal. A 98-day male and female SPF CFE weanling rat drinking water study for the structural analog *cis*-3-hexenol (FEMA 2563) resulted in NOAELs of approximately 120-150 mg/kg bw/day. The lowest reported NOAEL for the structural analog is at least 480,000,000 times the anticipated daily *per capita* intake of *trans*-6-octenal from use as a flavor ingredient (Moreno, 1973; Gaunt et al., 1969; Newell et al., 1949).

The Panel reviewed the GRAS application and supporting information regarding (*E*)-3-benzo[1,3]dioxol-5-yl-*N,N*-diphenyl-2-propenamide (CAS 1309389-73-8) and concluded that it is GRAS (FEMA 4788) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). The substance was evaluated individually within the context of the chemical group of aliphatic and aromatic amines and amides (SLR A7, C21, JECFA 2006, 2008, 2011, 2012) The Panel noted that based on the anticipated annual volume of use (100 kg), the *per capita* intake ("eaters only") of (*E*)-3-benzo[1,3]dioxol-5-yl-*N,N*-diphenyl-2-propenamide from use as a flavor ingredient is calculated to be 15 µg/person/day (0.3 µg/kg bw/day), which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. Based on the metabolism of similar diphenyl amide compounds, it is anticipated that (*E*)-3-benzo[1,3]dioxol-5-yl-*N,N*-diphenyl-2-propenamide will undergo cytochrome P450-induced para-oxidation. Given the large number of carbon centers a number of possible polar acid and alcohol metabolites may result. These are expected to conjugate with glucuronide or sulfate and be excreted in the urine, or to a minor extent unchanged in the feces. Amide hydrolysis is not expected to be a favorable process *in vivo* given other metabolic options; therefore amide hydrolysis products are not expected to be major metabolites (Foster, 2009; Yuan, 2008; Bhat and Chandrasekhara, 1986a; Schwen, 1982). No increases in the number of reverse mutations were observed for (*E*)-3-benzo[1,3]dioxol-5-yl-*N,N*-diphenyl-2-propenamide in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* WP2uvrA strain in either the presence or absence of metabolic activation. Based on the available data for the substance, and also based on the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of (*E*)-3-benzo[1,3]dioxol-5-yl-*N,N*-diphenyl-2-propenamide (Uhde, 2004). A male and female reproductive mouse study resulted in a NOAEL of 20 mg/kg bw/day for piperine. A 14-day male and female rat dietary study resulted in NOAELs of 1443 and 1381mg/kg bw/day, respectively for (*E*)-3-benzo[1,3]dioxol-5-yl-*N,N*-diphenyl-2-propenamide. An 8-week male and female rat dietary study for black pepper oleoresin, containing the structural analog piperine, FEMA 2909, resulted in NOAELs equivalent to 20 mg/kg bw/day piperine. This is 80,000 times higher than the anticipated daily *per capita* intake of (*E*)-3-benzo[1,3]dioxol-5-yl-*N,N*-diphenyl-2-propenamide from use as a flavor ingredient (Piyachaturawat et al., 1983; Bhat and Chandrasekhara, 1986b; Platel and Srinivasan, 2000, 2001; Daware et al., 2000; Posternak et al., 1969).

The Panel reviewed the GRAS application and supporting information regarding 2,6-dimethyl-5-heptenol (CAS 4234-93-9) and concluded that it is GRAS (FEMA 4789) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). The substance was evaluated within the context of the chemical group of linear and branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids, and related esters (SLR M1, JECFA 1999, 2004, 2012). The Panel noted that based on the anticipated annual volume of use (5 kg), the *per capita* intake ("eaters only") of 2,6-dimethyl-5-heptenol from use as a flavor ingredient is calculated to be 0.7 µg/person/day (0.01 µg/kg bw/day), which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The material was reported to occur naturally in *Litsea*

*cubeba* and *Passiflora quadrangularis*, also known as Badea or giant passion fruit, but only qualitative data are available and thus no consumption ratio can be calculated (Nijssen et al., 2015). The 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 main impurity is 2,6-dimethyl-5-heptenal (FEMA 2389) (Oser and Hall, 1965). Based on *alpha*-methyl-branched fatty acid alcohol derivatives, it is anticipated that 2,6-dimethyl-5-heptenol will undergo metabolism by oxidation to the corresponding aldehyde, 2,6-dimethyl-5-heptenal (FEMA 2389) and subsequent acid followed by excretion in the urine, or will undergo conjugation with glucuronic acid and excretion in the urine. No increases in the number of reverse mutations were observed in Ames assays for the structural analog and primary metabolite 2,6-dimethyl-5-heptenal in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 in the presence and absence of metabolic activation. 2,6-Dimethyl-5-heptenal also gave negative results in a rat hepatocyte unscheduled DNA synthesis assay and in a mouse bone marrow micronucleus assay. Based on the lack of genotoxicity displayed for the structural analog, 2,6-dimethyl-5-heptenal, and also based on the structure of the substance and the identity and arrangement of the functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of 2,6-dimethyl-5-heptenol (Heck et al., 1989; Wild et al., 1983; Oser, 1958; Oda, 1979; Sasaki et al., 1989; Kasamaki et al., 1982; Kono, et al., 1995; Yoo, 1986; Kuroda et al., 1984; Ishidate et al., 1984). A 90-day male and female rat dietary study for the primary metabolite, 2,6-dimethyl-5-heptenal (FEMA 2389), resulted in a NOAEL of 37 mg/kg bw/day which is 3,000,000 times the anticipated daily *per capita* intake of 2,6-dimethyl-5-heptenol from use as a flavor ingredient (Gaunt et al., 1983, NTP 2001; Dieter et al., 1993; Oser, 1958a; Hagan et al., 1967; NTP, 2000; Hoberman et al., 1989; Vollmuth et al., 1990; Nogueira et al., 1994; Gaworski et al., 1992).

The Panel reviewed the GRAS application and supporting information regarding (±)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, ethyl ester (CAS 10138-32-6) and concluded that it is GRAS (FEMA 4790) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). The substance was evaluated individually within the context of the chemical group of alicyclic primary alcohols, aldehydes, acids and related esters (SLR A5, JECFA, 2002, 2011). The Panel noted that based on the anticipated annual volume of use (2 kg), the *per capita* intake ("eaters only") of (±)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, ethyl ester from use as a flavor ingredient is calculated to be 0.3 µg/person/day (0.005 µg/kg bw/day), which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The material was not reported to occur naturally in food. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. (±)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, ethyl ester is expected to be hydrolyzed in humans (via carboxylesterases, which occur in most human tissues and predominately in hepatocytes) to the corresponding bicycloheptene carboxylic acid and ethanol. The resulting bicycloheptene carboxylic acid is expected to be conjugated and excreted in the urine as the corresponding glucuronic acid and glycine conjugates or as the corresponding hippuric acids. Some of the carboxylic acid may also be excreted unchanged. No increases in the number of reverse mutations were observed in an Ames assay for (±)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, ethyl ester in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2uvrA in either the presence or absence of metabolic activation. (±)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, ethyl ester did induce chromosomal aberrations in human lymphocytes treated for 21 hours in the absence of metabolic activation, but it did not induce chromosomal aberrations in human lymphocytes treated for 3 hours with an 18 hour recovery period in either the presence or absence of metabolic activation. (±)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, ethyl ester did not increase mutant frequencies in mouse lymphoma L5178Y cells under any treatment conditions in either the presence or absence of metabolic activation. (±)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, ethyl ester did not produce biologically relevant increases in the frequency of micronucleated binucleate cells in either the presence or absence of metabolic activation in human lymphocytes under any treatment conditions. In an *in vivo* chromosomal aberration study in male ICR mice, no significant increases in the frequency of bone marrow cells with structural or numerical aberrations were observed. Based on weight of evidence from the available studies supplied, the Panel did not identify specific concerns related to the potential genotoxicity of (±)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, ethyl ester (May, 2010; May 2012; Thompson, 2007; Akhurst, 1995; Pritchard, 2011). A 90-day oral gavage study in CFE male and female rats resulted in a NOAEL of 15 mg/kg bw/day (males) for the structural analog isobornyl acetate (FEMA 2160). This is >3,000,000 times the anticipated daily *per capita* intake of (±)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, ethyl ester from use as a flavor ingredient (Gaunt et al., 1971; Lea, 1996).

The Panel reviewed the GRAS application and supporting information regarding 3-(acetylthio)hexanal (CAS 22236-44-8) and concluded that it is GRAS (FEMA 4791) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic thiols and sulfides (SLR B5C, JECFA 2000, 2004, 2008, 2011, 2012). The Panel noted that based on the anticipated annual volume of use (1 kg), the *per capita* intake ("eaters only") of 3-(acetylthio)hexanal from use as a flavor ingredient is calculated to be 0.2 µg/person/day (0.002 µg/kg bw/day), which is below the threshold of toxicological concern for structural class III (90 µg/person/day). The material was reported to occur in ciflorette (*Fragaria* x *ananassa*) strawberry, but only qualitative data are available and thus no consumption ratio can be calculated (Nijssen et al., 2015). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. 3-(Acetylthio)hexanal is anticipated to be metabolized along a number of pathways: oxidation of the aldehyde function to the carboxylic acid followed by excretion further unchanged or by conjugation with glycine and glucuronic acid and subsequent excretion; hydrolysis of the acetyl function to 3-thiohexanal which can be further metabolized by oxidation of the aldehyde group and the thiol function (by S-oxidation to the sulfoxide) and finally *omega*-oxidation of the terminal hexane function to the

primary alcohol and carboxylic acid and their conjugates. Thus, the metabolism of 3-(acetylthio)hexanal is anticipated to produce a array of metabolites that are expected to be cleared primarily in the urine (Diechmann and Gerarde, 1969). Based on the structure of the substance and the identity and arrangements of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of 3-(acetylthio)hexanal. A 90-day dietary toxicity study in male and female rats conducted at a single dose resulted in a NOEL of 6.48 mg/kg bw/day for the structural analog ethyl thioacetate (FEMA 3282). This is >2,500,000 times higher than the anticipated daily *per capita* intake of 3-(acetylthio)hexanal from use as a flavor ingredient (Shellenberger, 1970).

The Panel reviewed the GRAS application and supporting information regarding (±)-3-mercapto-1-pentanol (CAS 548740-99-4) and concluded that it is GRAS (FEMA 4792) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic thiols and sulfides (SLR B5A, JECFA 2000, 2004, 2008, 2011, 2012). The Panel noted that based on the anticipated annual volume of use (2 kg), the *per capita* intake ("eaters only") of (±)-3-mercapto-1-pentanol from use as a flavor ingredient is calculated to be 0.3 µg/person/day (0.005 µg/kg bw/day), which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The material was reported to occur in beer, black tea, and wine, but only qualitative data are available and thus no consumption ratio can be calculated (Nijssen et al., 21015). The 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 metabolism of (±)-3-mercapto-1-pentanol is anticipated to involve oxidation of the thiol to the unstable sulfenic acid (RSOH) with further oxidation to the corresponding sulfinic (RSO2H) and sulfonic acids (RSO3H). Additionally, methylation of the thiol to yield the corresponding sulfide, which is then oxidized to the sulfoxide and sulfone will occur. Other metabolic options include reaction with endogenous thiols to form mixed disulfides, and conjugation of the alcohol with glucuronic acid or sulfate. All oxidation and conjugation products would be anticipated to lead to excretion. No increases in the number of reverse mutations were observed in Ames assays for the structural analogs 3-mercapto-3-methylbutanol (FEMA 3854) and 3-mercapto-2-methyl-1-butanol (FEMA 3993) in *S. typhimurium strains* TA98, TA100, TA1535, TA1537, and TA1535, TA97, TA98, TA100, and TA102, respectively (Jones, 1990; Gocke, 1997). Based on the data for structural analogs, the structure of the substance and the identity and arrangements of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of (±)-3-mercapto-1-pentanol. A 90-day dietary study in male and female albino weanling rats resulted in a NOAEL of 0.705 mg/kg bw/day for the structural analog 2-mercapto-3-butanol (FEMA 3502) (Morgareidge, 1974). This is >140,000 times higher than the anticipated daily *per capita* intake of (±)-3-mercapto-1-pentanol from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding (3*R*,3*S*)-3-[[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]methyl]-*N*-cyclopentyl-2-oxo-3-piperidinecarboxamide (CAS 1446687-20-2) and concluded that it is GRAS (FEMA 4793) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of miscellaneous nitrogen-containing substances (SLR D19, JECFA 2006, 2009, 2012, 2015). The Panel noted that based on the anticipated annual volume of use (100 kg), the *per capita* intake ("eaters only") of (3*R*,3*S*)-3-[[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]methyl]-*N*-cyclopentyl-2-oxo-3-piperidinecarboxamide from use as a flavor ingredient is calculated to be 15 µg/person/day (0.2 µg/kg bw/day), which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The 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 Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Studies on (3*R*,3*S*)-3-[[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]methyl]-*N*-cyclopentyl-2-oxo-3-piperidinecarboxamide indicate a bioavailability of 0.46%. The metabolism of the structural analog, 3-[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]-2,2-dimethyl-*N*-propylpropanamide (FEMA 4701) was investigated in Sprague-Dawley rat and human liver microsomes, and the principal metabolites included hydroxylated. On this basis, (3*R*,3*S*)-3-[[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]methyl]-*N*-cyclopentyl-2-oxo-3-piperidinecarboxamide is anticipated to primarily be excreted in the feces unchanged, or after hydroxylation (Arthur et al., 2015) No increases in reverse mutations were observed in an Ames assay when *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* WP2uvrA were incubated with (3*R*,3*S*)-3-[[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]methyl]-*N*-cyclopentyl-2-oxo-3-piperidinecarboxamide at concentrations up to 5000 µg/plate in the presence and absence of metabolic activation. No evidence of mutagenic potential was identified for the structural analog 3-[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]-2,2-dimethyl-*N*-propylpropanamide (FEMA 4701) in an Ames assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 either in the presence or absence of metabolic activation, in a chromosomal aberration assay in Chinese hamster ovary WBL cells, and in a bone marrow micronucleus assay in male Swiss albino CD-1 mice. Based on the data for the substance and for structural analogs, the Panel did not identify specific concerns related to the potential genotoxicity of (3*R*,3*S*)-3-[[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]methyl]-*N*-cyclopentyl-2-oxo-3-piperidinecarboxamide (Arthur et al., 2015). A 90-day dietary study in Crl:CD (SD) male and female rats resulted in a NOAEL of 20 mg/kg bw/day for the structural analog 3-[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]-2,2-dimethyl-*N*-propylpropanamide (FEMA 4701) (Arthur et al., 2015). This is >80,000 times higher than the anticipated daily *per capita* intake of (3*R*,3*S*)-3-[[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]methyl]-*N*-cyclopentyl-2-oxo-3-piperidinecarboxamide from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding (±)-1-cyclohexylethanol (CAS 1193-81-3) and concluded that it is GRAS (FEMA 4794) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of saturated aliphatic acyclic secondary alcohols, ketones, and related saturated and unsaturated esters (SLR A1, JECFA 1999). The Panel noted that based on the anticipated annual volume of use (50 kg), the *per capita* intake ("eaters only") of (±)-1-cyclohexylethanol from use as a flavor ingredient is calculated to be 7 µg/person/day (0.1 µg/kg bw/day), which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. (±)-1-Cyclohexylethanol is an alicylic secondary alcohol and is expected to be rapidly absorbed, metabolized and the metabolites cleared in the urine. The main pathways of metabolism are anticipated to be conjugation with glucuronic acid through the hydroxyl function and hydroxylation of the cyclohexyl group followed by conjugation with glucuronic acid (Williams, 1959). In both cases it would be anticipated that the conjugates would be excreted in the urine. No increases in reverse mutations were observed in an Ames assay for 1-cyclohexylethyl butyrate in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 in either the presence or absence of metabolic activation. Based on the data for the structural analog, as well as on the structure of the substance and the identity and arrangements of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of (±)-1-cyclohexylethanol (Stevens, 1978b). A 28-day oral gavage study in Charles River CD rats resulted in a NOAEL of 3000 mg/kg bw/day for the structural analog 1-cyclohexylethyl butyrate (CAS 63449-88-7). This is >24,000,000 times higher than the anticipated daily *per capita* intake of (±)-1-cyclohexylethanol from use as a flavor ingredient (Stevens, 1978a).

The Panel reviewed the GRAS application and supporting information regarding (±)-8-methyldecanal (CAS 127793-88-8) and concluded that it is GRAS (FEMA 4795) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids (SLR M1; JECFA 1998). The Panel noted that based on the anticipated annual volume of use (5 kg), the *per capita* intake ("eaters only") of (±)-8-methyldecanal from use as a flavor ingredient is calculated to be 0.7 µg/person/day (0.01 µg/kg bw/day), which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The material was reported to occur in lemongrass, citronella, orange, and many other oils, including rose oil, but only qualitative data are available and thus no consumption ratio can be calculated (Nijssen et al., 2015). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. (±)-8-Methyldecanal is anticipated to be metabolized in a manner consistent with detoxification of linear aliphatic acyclic aldehydes, which involves absorption through the gastrointestinal tract, oxidation to the corresponding acid by $NAD^+$-dependent aldehyde dehydrogenase, and complete metabolism to endogenous products via fatty acid oxidation, tricarboxycylic acid pathways, or via reaction with glutathione and ultimate excretion in the urine (Walkenstein and Weinhouse, 1953; Dunster and Watson, 2012). No evidence of mutagenic potential was observed in multiple Ames assays for the structural analog 2-methylundecanal in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 in either the presence or absence of metabolic activation. Based on the data for the structural analog, as well as on the structure of the substance and the identity and arrangements of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of (±)-8-methyldecanal (Harnasch, 1999; Verspeek-Rip, 2002). A 12-week dietary study in male and female rats resulted in a NOAEL of 112 mg/kg bw/day for a mixture of six aldehydes, including the structural analog 2-methylundecanal (FEMA 2749) at 19.1 mg/kg bw/day. This is >1,500,000 times higher than the anticipated daily *per capita* intake of (±)-8-methyldecanal from use as a flavor ingredient (Trubek, 1958).

The Panel reviewed the GRAS application and supporting information regarding rebaudioside C 30% (CAS 63550-99-2) and concluded that it is GRAS (FEMA 4796) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel noted that based on the anticipated annual volume of use (1000 kg), the *per capita* intake ("eaters only") of rebaudioside C 30% from use as a flavor ingredient is calculated to be 147 µg/person/day (2 µg/kg bw/day), which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The material occurs in the Stevia plant which is used as a tea, but a consumption ratio cannot be calculated. The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation . The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Metabolic studies with steviol glycosides in multiple species, including humans, have demonstrated that intact steviol glycosides are poorly absorbed after oral exposure but that they are hydrolyzed by the microflora in the gut to steviol. A large portion of this steviol is absorbed and is conjugated to steviol glucuronide, which undergoes enterohepatic circulation. The remaining steviol is excreted in the feces. No steviol epoxide, which may have genotoxic potential, was detected in human plasma (Carakostas et al., 2008; Nakayama et al., 1986; Koyama et al., 2003; Geuns, 2003; Kraemer and Maurer, 1994; Simonetti et al., 2004; Geuns et al., 2006, 2007; Hutapea et al., 1997). The genotoxicity of 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. Based on the results for various steviol glycosides, the Panel did not identify specific concerns related to the potential genotoxicity of rebaudioside C 30% (Brusick, 2008). No effects on testicular morphology or spermatogenesis were identified in a multi-generation reproductive study for dietary administration of rebaudioside A. No treatment-related effects of rebaudioside A were observed in either the

F0 or F1 generations on reproductive performance parameters including mating performance, fertility, and gestation lengths in a two-generation reproductive study. (Curry et al., 2008; Yodyingyuad and Bunyawong, 1991; Carakostas et al., 2008). Multiple toxicity studies for various steviol glycosides have been conducted. The Panel noted that a 13-week dietary study in Fischer 344 rats for the structural analog stevioside (FEMA 4763) resulted in a NOAEL of 2500 mg/kg bw/day. In the 108-week carcinogenicity study for stevioside, no carcinogenic effects were observed, and a NOAEL of 970 mg/kg bw/day was set by the United Nations Joint FAO/WHO Expert Committee on Food Additives (JECFA). This NOAEL identified by JECFA is >390,000 times higher than the anticipated daily *per capita* intake of rebaudioside C 30% from use as a flavor ingredient (Carakostas et al., 2008; Aze et al., 1991; Toyoda et al., 1997; JECFA, 1999, 2006; Curry and Roberts, 2008; Maki et al, 2008).

The Panel reviewed the GRAS application and supporting information regarding (±)-naringenin (CAS 480-41-1) and concluded that it is GRAS (FEMA 4797) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of phenol and phenol derivatives (SLR C12; JECFA 2001, 2011, 2015). The Panel noted that based on the anticipated annual volume of use (5200 kg), the *per capita* intake ("eaters only") of (±)-naringenin from use as a flavor ingredient is calculated to be 766 µg/person/day (13 µg/kg bw/day), which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The material as reviewed by the Panel was reported to occur in grapefruit and the calculated consumption ratio is 33 annual *per capita*. The 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 Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). The disposition of (±)-naringenin was examined in male Sprague-Dawley rats and the authors concluded that glucuronide conjugates were formed and excreted (El Mohsen et al., 2004; Hsiu et al., 2002; Yanez et al., 2008; Choudhury et al. 1999; Kanaze et al., 2007; Felgines et al., 2000). No increases in reverse mutations were observed in Ames assays in *S. typhimurium* strains TA100, TA98, TA1535, TA1537, TA1538 either in the presence or absence of metabolic activation for (±)-naringenin. Based on these results, as well as on the structure of the substance and the identity and arrangement of the functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of (±)-naringenin (Batzinger, 1977; Bjeldanes & Chang, 1977; Brown & Dietrich, 1979; MacGregor and Jurd, 1978; Zeiger et al., 1987; Sahu et al., 1981). Multiple carcinogenicity studies have been conducted in rats for the very conservative, with respect to safety, structural analog quercetin. The Panel reviewed the results of these studies, and agreed with the International Agency for Research on Cancer (IARC) conclusion that quercetin is not classifiable as a carcinogen to humans. A conservative NOAEL based on the lowest dose tested from the 2-year dietary study in F344/N rats was assigned at 40 mg/kg bw/day. This is >3,000 times higher than the anticipated daily *per capita* intake of (±)-naringenin from use as a flavor ingredient (Ortiz-Andrade et al., 2008; Brown et al., 1977; Brown and Dietrich, 1979; Jurado et al., 1991; Lina et al., 1990; Booth et al., 1965; Booth, 1974; Gumbmann et al., 1978).

The Panel reviewed the GRAS application and supporting information regarding 2-(((3-(2,3-dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)pyridine (CAS 902136-79-2) and concluded that it is GRAS (FEMA 4798) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of miscellaneous nitrogen-containing substances (SLR D19, JECFA 2006, 2009, 2012, 2015). The Panel noted that based on the anticipated annual volume of use (2000 kg), the *per capita* intake ("eaters only") of 2-(((3-(2,3-dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)pyridine from use as a flavor ingredient is calculated to be 295 µg/person/day (5 µg/kg bw/day), which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The material was not reported to occur naturally in food. The 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 Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). *In vitro* and *in vivo* metabolic profiling was conducted to explore the disposition of the substance. In the *in vivo* metabolism studies in rats multiple metabolic pathways were identified, including formation of a sulfoxide metabolite, a thioether oxidation product, a demethylation metabolite, and a phenyl hydroxylation product. Formation of a desmethyl, *O*-sulfate, and glucuronic acid conjugate were also observed (Bailey, 2012; Chi, 2012, 2013). 2-(((3-(2,3-Dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)pyridine did not increase reverse mutations in an Ames assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and *E. coli* strain WP2uvrA either in the presence or absence of metabolic activation. 2-(((3-(2,3-Dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)pyridine did not induce structural or numerical chromosomal aberrations in human peripheral blood lymphocytes in either the presence or absence of metabolic activation. The substance did not induce increases in the numbers of micronucleated binucleate Chinese hamster ovary cells in either the presence or absence of metabolic activation under any treatment condition. Based on the uniformly negative data from these genotoxicity studies, the Panel did not identify specific concerns related to the potential genotoxicity of 2-(((3-(2,3-dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)pyridine (Yokoi, 2008; Cardoso, 2013a, b, c). A 28-day study in male and female CD [Crl:CD (SD)] rats resulted in a NOAEL of 100 mg/kg bw/day for 2-(((3-(2,3-dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)pyridine. A 90-day dietary study in male and female CD [Crl:CD (SD)] rats resulted in a NOAEL of 100 mg/kg bw/day for 2-(((3-(2,3-dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)pyridine (Rose, 2012, 2013). This is >20,000 times higher than the anticipated daily *per capita* intake of 2-(((3-(2,3-dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)pyridine from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding (2*R*)-3',5-dihydroxy-4'-

methoxyflavanone (CAS 1449417-52-0) and concluded that it is GRAS (FEMA 4799) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated within the context of the chemical group of phenol and phenol derivatives (SLR C12; JECFA 2001, 2011, 2015). The Panel noted that based on the anticipated annual volume of use (600 kg), the *per capita* intake ("eaters only") of (2*R*)-3',5-dihydroxy-4'-methoxyflavanone from use as a flavor ingredient is calculated to be 88 µg/person/day (2 µg/kg bw/day), which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The material was not reported to occur naturally in food. The 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 Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). It is anticipated that (2*R*)-3',5-dihydroxy-4'-methoxyflavanone would be metabolized along various routes: conjugation of the hydroxyl functions with glucuronic acid and sulfate and excretion of these conjugates; demethylation and ring-opening of the heterocyclic ring function to form the corresponding hydroxyphenylpropionic acid (Gee et al., 2000; Day et al., 2000; Donovan et al., 2006; Manach et al., 2005). (2*R*)-3',5-Dihydroxy-4'-methoxyflavanone did not increase reverse mutations in an Ames assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 either in the presence or absence of metabolic activation. The structural analog naringenin (FEMA 4797) gave no increases in reverse mutations were observed in Ames assays in *S. typhimurium* strains TA100, TA98, TA1535, TA1537, TA1538 either in the presence or absence of metabolic activation. Based on these results, as well as on the structure of the substance and the identity and arrangement of the functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of (2*R*)-3',5-dihydroxy-4'-methoxyflavanone (NTP, 1992; FDA 2010a,b; Brown and Dietrich, 1979; Nagao et al., 1981). Multiple carcinogenicity studies have been conducted in rats for the very conservative structural analog quercetin (Hirono et al., 1981, 1993; Ito et al., 1989; NTP, 1992; Dunnick and Hailey, 1992; Willhite, 1982). The Panel reviewed these studies, which provided evidence of carcinogenic activity in some cases, and also reviewed available information on the probable mode of action for any carcinogenic activity reported. The Panel agreed with the International Agency for Research on Cancer conclusion that quercetin is not classifiable as a carcinogen to humans IARC 1999). A conservative NOAEL from the 2-year dietary study in F344/N rats was assigned at 40 mg/kg bw/day. This is >27,000 times the anticipated daily *per capita* intake of (2*R*)-3',5-dihydroxy-4'-methoxyflavanone from use as a flavor ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding glucosylated *Rubus suavissimus* extract, 20-30% glucosylated rubusoside glycosides (CAS 1268518-76-8) and concluded that it is GRAS (FEMA 4800) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel noted that based on the anticipated annual volume of use (1000 kg), the *per capita* intake ("eaters only") of glucosylated *Rubus suavissimus* extract, 20-30% glucosylated rubusoside from use as a flavor ingredient is calculated to be 147 µg/person/day (3 µg/kg bw/day). The extract has a long history of use in Chinese herbal sweet tea and as an allergy remedy in Japan without known toxicity, but only qualitative data are available and thus no consumption ratio can be calculated. The Panel considered the identity description of the material to be sufficient for FEMA GRAS evaluation (see Appendix 1). The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Metabolic data exist for representative members of each congeneric group that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products. The Panel did not identify specific concerns related to the potential genotoxicity of glucosylated *Rubus suavissimus* extract, 20-30% glucosylated rubusoside. In a 9-week study using male and female obese-prone rats that were administered 220 mg/kg bw/day Chinese sweet leaf tea (*Rubus suavissimus*) extract, which corresponds to an average daily intake of 50 mg/kg bw of rubusoside, reduced body weight and reduced abdominal fat were reported. Liver and kidney weights in a low-fat diet group were slightly higher than those that were provided a fat supplement, but there were no effects on hematology or blood chemistry parameters (Koh et al., 2011). This dose is >20,000 times the anticipated daily *per capita* intake of glucosylated *Rubus suavissimus* extract, 20-30% glucosylated rubusoside from use as a flavor ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding olive fruit extract, *Olea europaea* (CAS 8001-25-0) and concluded that it is GRAS (FEMA 4801) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel noted that based on the anticipated annual volume of use (200 kg), the *per capita* intake ("eaters only") of olive fruit extract, *Olea europaea* from use as a flavor ingredient is calculated to be 30 µg/person/day (0.5 µg/kg bw/day). The extract is derived from commonly consumed olives (Nijssen et al., 2015). The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation (see Appendix 1). Metabolic data exist for representative members of each congeneric group that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Chen et al., 1998; Bonanome et al., 2000; De la Torre et al., 2008; Tuck et al., 2001; Visioli et al., 2001; de Bock et al., 2013; Caruso et al., 2001; D'Angelo et al., 2001; Manna et al., 2000; Mateos et al., 2005; Tuck et al., 2002). A related extract, olive pulp extract, increased reverse mutations in *S. typhimurium* strains TA98 and TA100 in the presence of metabolic activation, but not in TA97a, TA1535, and *E. coli* strain WP2uvrA either in the presence or absence of metabolic activation or in TA98 and TA100 in the absence of metabolic activation. It also induced chromosomal aberrations in Chinese hamster ovary cells but only at a toxic concentration. It was negative in a rat bone marrow micronucleus assay. The major marker constituent, hydroxytyrosol, did not increase reverse mutations in *S.*

*typhimurium* strains TA98, TA100, TA1535, TA1537, and *E. coli* strain WP2(pKM101) either in the presence or absence of metabolic activation, and did not increase the number of structural or numerical chromosomal aberrations either in the presence or absence of metabolic activation. Based on these data, the Panel concluded that based on weight of evidence it did not have specific concerns related to the potential genotoxicity of olive fruit extract, *Olea europaea*. A 90-day oral toxicity study in male and female rats for a related extract, olive pulp extract, resulted in a NOAEL of 2000 mg/kg bw/day. A 90-day study for hydroxytyrosol in Wistar Hannover RccHan male and female rats resulted in a NOAEL of 500 mg/kg bw/day (de Bock et al., 2013; Aunon-Calles et al., 2013; D'Angelo et al., 2001). This is >1,000,000 times the anticipated daily *per capita* intake of olive extract, *Olea europaea*, from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding (*S*)-1-(3-(((4-amino-2,2-dioxido-1*H*-benzo[c][1,2,6]thiadiazin-5-yl)oxy)methyl)piperidin-1-yl)-3-methylbutan-1-one (CAS 1469426-64-9) and concluded that it is GRAS (FEMA 4802) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of miscellaneous nitrogen-containing substances (SLR D19, JECFA 2006, 2009, 2012, 2015). The Panel noted that based on the anticipated annual volume of use (5000 kg), the *per capita* intake ("eaters only") of (*S*)-1-(3-(((4-amino-2,2-dioxido-1*H*-benzo[c][1,2,6]thiadiazin-5-yl)oxy)methyl)piperidin-1-yl)-3-methylbutan-1-one from use as a flavor ingredient is calculated to be 740 µg/person/day (12 µg/kg bw/day), which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The material is not known to occur in nature and thus no consumption ratio can be calculated. The 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 Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). (*S*)-1-(3-(((4-Amino-2,2-dioxido-1*H*-benzo[c][1,2,6]thiadiazin-5-yl)oxy)methyl)piperidin-1-yl)-3-methylbutan-1-one was shown to be poorly bioavailable (%F = 0.2-1.73%). The substance is oxidized to several metabolites by microsomes *in vitro*. Metabolism *in vivo* is limited but includes the formation of two main hydroxylation products. All oxidation and conjugation reactions would be anticipated to lead to readily excretable metabolites (Arthur et al., 2015). No increases in the number of reverse mutations were observed in Ames assays for the (*S*)-1-(3-(((4-amino-2,2-dioxido-1*H*-benzo[c][1,2,6]thiadiazin-5-yl)oxy)methyl)piperidin-1-yl)-3-methylbutan-1-one in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2uvrA. (*S*)-1-(3-(((4-Amino-2,2-dioxido-1*H*-benzo[c][1,2,6]thiadiazin-5-yl)oxy)methyl)piperidin-1-yl)-3-methylbutan-1-one was also negative for genotoxicity in *in vitro* chromosomal aberration and micronucleus assays. The Panel noted that the poor bioavailability may have limited the ability of the substance to reach the target tissue in the *in vivo* study, but the material was tested up to 2000 mg/kg bw (a limit dose). Based upon the available results, the Panel did not identify specific concerns related to the genotoxicity of (*S*)-1-(3-(((4-amino-2,2-dioxido-1*H*-benzo[c][1,2,6]thiadiazin-5-yl)oxy)methyl)piperidin-1-yl)-3-methylbutan-1-one (Arthur et al., 2015). Developmental toxicity studies were conducted for (*S*)-1-(3-(((4-amino-2,2-dioxido-1*H*-benzo[c][1,2,6]thiadiazin-5-yl)oxy)methyl)piperidin-1-yl)-3-methylbutan-1-one. An initial range-finder study was conducted in bred female Crl:CD(SD) rats. (*S*)-1-(3-(((4-Amino-2,2-dioxido-1*H*-benzo[c][1,2,6]thiadiazin-5-yl)oxy)methyl)piperidin-1-yl)-3-methylbutan-1-one was administered to rats by gavage at 125, 250, 500, and 1000 mg/kg bw/day on gestation days 6-20. On gestation day 21, dams were necropsied and no remarkable findings were observed. On this basis, dosage levels of 250, 500, and 1000 mg/kg bw/day were chosen for the main embryo/fetal development study. In the main study, bred female rats were administered dosage levels of 250, 500, and 1000 mg/kg bw/day by gavage on gestation days 6-20, then necropsied on gestation day 21. No maternal toxicity, adverse effects on intrauterine fetal growth, or survival morphology was observed at any dose level, and thus the study resulted in a NOAEL for both maternal and fetal toxicity of 1000 mg/kg bw/day (Arthur et al., 2015). A 28-day study in male and female Crl:CD®(SD)] rats showed no mortality and no toxic effects and resulted in a NOAEL of 100 mg/kg bw/day. A follow-up 90-day dietary study was conducted in the same strain of rats at doses of 10, 30, and 100 mg/kg bw/day. No treatment-related effects were observed and the study resulted in a NOAEL of 100 mg/kg bw/day (Arthur et al., 2015). This is >8,000 times higher than the anticipated daily *per capita* intake of (*S*)-1-(3-(((4-amino-2,2-dioxido-1*H*-benzo[c][1,2,6]thiadiazin-5-yl)oxy)methyl)piperidin-1-yl)-3-methylbutan-1-one from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 8-methylnonanal (CAS 3085-26-5) and concluded that it is GRAS (FEMA 4803) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids (SLR M1; JECFA 1998). The Panel noted that based on the anticipated annual volume of use (5 kg), the *per capita* intake ("eaters only") of 8-methylnonanal from use as a flavor ingredient is calculated to be 0.7 µg/person/day (0.01 µg/kg bw/day), which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The material was reported to occur naturally in yuzu oil, derived from the yuzu fruit, but only qualitative data were available and thus no consumption ratio could be calculated (Tajima et. al., 1990). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. 8-Methylnonanal would be expected to be rapidly absorbed from the gastrointestinal tract and oxidized to the corresponding carboxylic acid followed by progressive *beta*-oxidation to finally yield propionic acid (Brabec, 1993; Brambilla et al., 1989; Esterbauer et al., 1990). No increases in the number of reverse mutations were observed in Ames assays for the structurally related substance 2-methylundecanal. The structurally related substance nonanal (FEMA 2782) was negative in Ames assays in the presence and absence of metabolic activation, but positive in the non-standard 6-thioguanine forward mutation assay. Nonanal was negative in an *in vitro* micronucleus assay, a chromosomal aberration assay, and a mouse lymphoma assay, and produced small increases in

sister chromatid exchange, but this was not dose-dependent. Based on weight of evidence, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of 8-methylnonanal. (Marnett et al., 1985; Connor et al., 1985; Mortelmans et al., 1986; Myhr and Caspary, 1991; Martelli et al., 1994; Harnasch, 1999; Verspeek-Rip, 2002). A 12-week dietary study in male and female rats for a mixture of aldehydes (octanal (FEMA 2797), nonanal (FEMA 2782), decanal (FEMA 2362), undecanal (FEMA 3092), 2-methylundecanal (FEMA 2749), and lauric aldehyde (FEMA 2615)) resulted in a NOAEL of 112 mg/kg bw/day for the structural analog 2-methylundecanal (FEMA 2749) according to the author of the study (Trubek, 1953). This is >9,000,000 times higher than the anticipated daily *per capita* intake of 8-methylnonanal from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding the mixture of ricinoleic acid, linoleic acid and oleic acid (CAS Pending) and concluded that it is GRAS (FEMA 4804) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated within the context of the chemical group of aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups (SLR B1B; JECFA 2000, 2011). The Panel noted that based on the anticipated annual volume of use (375 kg), the *per capita* intake ("eaters only") of the mixture of ricinoleic acid, linoleic acid and oleic acid from use as a flavor ingredient is calculated to be 55 µg/person/day (1 µg/kg bw/day), which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The material was reported to occur in Castor seed oil, but is not considered a commonly consumed food (Nijssen et al., 2015). The 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 Panel noted that the other components of the mixture included small amounts of stearic acid, palmitic acid, and C18:1 and C16:1 fatty acids. The mixture of ricinoleic acid, linoleic acid, and oleic acid is anticipated to be absorbed in the gastrointestinal tract and be subject to oxidation and *beta*-cleavage in the fatty acid pathway (Gosselin et al., 1976; Tunaru et al., 2012; Watson and Gordon, 1962; Watson et al., 1963). Linoleic acid gave negative results in an Ames assay in either the presence or absence of metabolic activation. Based on the data for structural analogs and the identity and arrangements of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of the mixture of ricinoleic acid, linoleic acid, and oleic acid. A 13-week dietary study in male and female F344/N rats and B6C3F1 mice conducted with castor oil at dietary levels of 0.6, 1.25, 2.50, 5 and 10% (w/w), providing doses equivalent to 600, 1250, 2500, 5000 and 10,000 mg/kg bw/d in rats and 900, 1875, 3750, 7500, 15,000 mg/kg bw/d in mice resulted in a NOAEL of 10% or 10,000 mg/kg bw/day for rats and 15,000 mg/kg bw/day for mice (El-Khatib and Cora, 1981; Szepsenwol and Boschetti, 1975; Szepsenwol, 1978; Hillyard and Abraham, 1979; Tinsley et al., 1981; Borgman and Wardlaw, 1975, Lee et al., 1986). This is >15,000,000 times the anticipated daily *per capita* intake of mixture the mixture of ricinoleic acid, linoleic acid and oleic acid from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside A 22% (CAS 91722-21-3) and concluded that it is GRAS (FEMA 4805) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel noted that based on the anticipated annual volume of use (10000 kg), the *per capita* intake ("eaters only") of Stevia extract RebA 22 from use as a flavor ingredient is calculated to be 1473 µg/person/day (25 µg/kg bw/day). The material occurs naturally in the plant stevia, but no consumption ratio could be calculated. The Panel considered the identity description to be adequate for FEMA GRAS evaluation (see Appendix 1). The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Metabolic data exist for representative members of each congeneric group that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Wingard et al., 1980; Hutapea et al., 1997; Gardana et al., 2003; Geuns et al., 2003, 2007; Koyama et al., 2003a,b; Renwick and Tarka, 2008; Nakayama et al., 1986; Geuns and Pietta, 2004; Simonetti et al., 2004; Roberts and Renwick, 2008; Wheeler et al., 2008). 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. Based on the results for the various steviol glycosides, the Panel did not identify specific concerns related to the potential genotoxicity of steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside A 22% (Toyoda et al., 1997; EFSA, 2010, 2011; Kim et al., 1987; Janzowski et al., 2000; Durling et al., 2009; Nishi et al., 1989; Stich et al., 1981a,b). Multiple toxicity studies for the major marker constituents (steviol glycosides) of steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside A 22% have been conducted. The Panel noted that a 13-week study in Fischer 344 rats for stevioside (FEMA 4763) resulted in a NOAEL of 2500 mg/kg bw/day. This is >100,000 times the anticipated daily *per capita* intake of Stevia extract RebA 22 from use as a flavor ingredient. In a 108-week carcinogenicity study for stevioside, no carcinogenic effects were observed (Galvin and Farr, 1994; JECFA, 2001, 2005b 2006b; NTP, 2010; Czok, 1970; Germond et al., 1987; Godfrey et al., 1999; Monien et al., 2009; Zhang et al., 1993; Durling et al., 2009; EFSA, 2011).

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside C 22% (CAS 91722-21-3) and concluded that it is GRAS (FEMA 4806) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel noted that based on the anticipated annual volume of use (10000 kg), the *per capita* intake ("eaters only") of steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside C 22% from use as a flavor ingredient is calculated to be 1473 µg/person/day (25

µg/kg bw/day). The material occurs naturally in the plant stevia, but no consumption ratio could be calculated. The Panel considered the identity description to be adequate for FEMA GRAS evaluation (see Appendix 1). The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Metabolic data exist for representative members of each congeneric group that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Wingard et al., 1980; Hutapea et al., 1997; Gardana et al., 2003; Geuns et al., 2003, 2007; Koyama et al., 2003a,b; Renwick and Tarka, 2008; Nakayama et al., 1986; Geuns and Pietta, 2004; Simonetti et al., 2004; Roberts and Renwick, 2008; Wheeler et al., 2008). 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. Based on the results for the various steviol glycosides, the Panel did not identify specific concerns related to the potential genotoxicity of steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside C 22% (Toyoda et al., 1997; EFSA, 2010, 2011; Kim et al., 1987; Janzowski et al., 2000; Durling et al., 2009; Nishi et al., 1989; Stich et al., 1981a,b). Multiple toxicity studies for the major marker constituents (steviol glycosides) of Stevia extract RebC 22 have been conducted. The Panel noted that a 13-week study in Fischer 344 rats for stevioside (FEMA 4763) resulted in a NOAEL of 2500 mg/kg bw/day. This is >100,000 times higher than the anticipated daily *per capita* intake of steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside C 22% from use as a flavor ingredient. In the 108-week carcinogenicity study for stevioside, no carcinogenic effects were observed (Galvin and Farr, 1994; JECFA, 2006b, 2001; JECFA, 2005b; NTP, 2010; Czok, 1970; Germond et al., 1987; Godfrey et al., 1999; Monien et al., 2009; Zhang et al., 1993; Durling et al., 2009; EFSA, 2011).

The Panel reviewed the GRAS application and supporting information regarding pinocarvyl acetate (CAS 1078-95-1) and concluded that it is GRAS (FEMA 4807) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated within the context of the chemical group of monocyclic and bicyclic secondary alcohols, ketones and related esters (SLR A5; JECFA 2006; 2009, 2015). The Panel noted that based on the anticipated annual volume of use (2 kg), the *per capita* intake ("eaters only") of pinocarvyl acetate from use as a flavor ingredient is calculated to be 0.3 µg/person/day (0.005 µg/kg bw/day), which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). The material was reported to occur in nature in celery and grapefruit juice, with a calculated consumption ratio of 45 (Nijssen et al., 2015; Stofberg and Grundschober, 1985). The 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 candidate substance is expected to be hydrolyzed in humans via carboxylesterases to acetic acid and the corresponding alcohol, 6,6-dimethyl-2-methylenebicyclo[3.1.1]heptanol (pinocarveol). Pinocarveol is anticipated to be excreted in urine following conjugation. The structural relative, ethyl bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (FEMA 4790) was not genotoxic in an Ames assay or in *in vitro* mouse lymphoma and chromosomal aberration assays in either the presence or absence of metabolic activation. The structural analog produced positive results in an *in vitro* micronucleus assay in the presence and absence of metabolic activation, but the mean values were within the historical control range and were not considered to be biologically relevant. The same structural analog gave negative results in an *in vivo* bone marrow chromosomal aberration study. Based on the results for the structural analog, as well as the absence of structural alerts for pinocarvyl acetate and the identity and arrangements of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of pinocarvyl acetate. (May, 2010, 2012; Pritchard, 2010, 2011). A 13-week gavage toxicity study for the structural analog isobornyl acetate (FEMA 2160) at 15, 90 and 270 mg/kg bw/day, showed renal effects in males at the middle and top doses, and no effects in female rats. Thus, the resulting NOAELs were 15 and 90 mg/kg bw/day, respectively, for male and female rats (Gaunt et al., 1971). The NOAEL of 15 mg/kg bw/day for the structural analog is >3,000,000 times higher than the anticipated daily *per capita* intake of pinocarvyl acetate from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *N*-ethyl-5-methyl-2-(1-methylethenyl)cyclohexanecarboxamide (CAS 1582789-90-9) and concluded that it is GRAS (FEMA 4808) for use as a flavor and flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). The substance was reviewed individually within the context of the chemical group of aliphatic and aromatic amines and amides (SLR A7, C21, JECFA 2006, 2008, 2011, 2012). The Panel noted that based on the anticipated annual volume of use of 1000 kg, the *per capita* intake ("eaters only") of *N*-ethyl-5-methyl-2-(1-methylethenyl)cyclohexanecarboxamide from use as a flavor and flavor ingredient is calculated to be 150 µg/person/day (3 µg/kg bw/day), which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The material was not reported to occur naturally in food. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. Based on analogy with the metabolism of structurally related compounds the candidate substance would be expected to undergo hydroxylation of the cyclohexane and angular alkyl structures followed by conjugation to polar, rapidly cleared excretion products. In addition there may occur limited hydrolysis of the amide function to the corresponding carboxylic acid that may be excreted as such but more likely following conjugation with glycine (Poet et al., 2005) In an Ames assay for the structural analog *N*-[(ethoxycarbonyl)methyl]-*p*-menthane-3-carboxamide, no significant increases in revertants were observed in either the absence or presence of metabolic activation in *S. typhimurium* strains TA98, TA100, TA1537, and *E. coli* strain WP2 uvrA. Statistically significant positive results were observed in the absence of metabolic activation for TA1535, but this was only observed in a confirmatory experiment whereas in the main experiment at similar concentrations no significant increases were observed. The authors of the study considered the biological significance of the results to be unclear. For *N*-ethyl-5-methyl-2-(1-methylethenyl)cyclohexanecarboxamide, based on the lack

of structural alerts for the substance and the type and arrangement of functional groups therein, the Panel did not identify any specific concerns related to the genotoxic potential of *N*-ethyl-5-methyl-2-(1-methylethenyl)cyclohexanecarboxamide (Thompson, 2005; Prueksaritanont et al., 1997). A 28-day gavage study in Crj:CD(SD) rats for the structural analog N-ethyl-2-isopropyl-5-methylcyclohexanearboxamide (FEMA 3455) resulted in a NOAEL of 8 mg/kg bw/day (James, 1974). This NOAEL is >3200 times greater than the anticipated intake of *N*-ethyl-5-methyl-2-(1-methylethenyl)cyclohexanecarboxamide from use as a flavoring substance.

The Panel reviewed the GRAS application and supporting information regarding 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide (CAS 1374760-95-8) and concluded that it is GRAS (FEMA 4809) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of miscellaneous nitrogen-containing substances (SLR D19, JECFA 2006, 2009, 2012, 2015). The Panel noted that based on the anticipated annual volume of use (2000 kg), the *per capita* intake ("eaters only") of 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide from use as a flavor ingredient is calculated to be 290 µg/person/day (5 µg/kg bw/day), which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The material is not reported to occur in nature. The 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 Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). In an *in vivo* mouse metabolism study, the substance was shown to be rapidly hydrolyzed to 4-methylphenoxyacetic acid and the corresponding secondary amine. In rats, multiple phase 1 and phase 2 metabolites were identified, including the hydrolysis products noted above. In the beagle, hydrolysis of the amide functionality was rapid. The available data indicated that 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide is readily metabolized and ultimately excreted in the urine or feces (Chi, 2014b,c,d; Zavorskas, 2012). No evidence of mutagenicity was observed in Ames assays for 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2 uvrA, either in the presence or absence of metabolic activation. No genotoxic potential was observed in an *in vitro* chromosomal aberration study or in a CD-1 mouse bone marrow micronucleus study. For the metabolism product *N*-(thiophen-2-ylmethyl)-1*H*-pyrazol-3-amine, an Ames assay was negative in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2 uvrA in either the presence or absence of S9 metabolic activation. The metabolite was negative in the presence of S9 activation in an *in vitro* chromosomal aberration assay, but positive in the absence of activation in the same system. To follow up on these results, an *in vivo* comet/micronucleus combination assay was conducted for the metabolite. No significant increases in DNA damage or the incidences of micronucleated polychromatic erythrocytes were observed. Based on these data, the Panel did not identify specific concerns related to the potential genotoxicity of 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide (Wells, 2012; Cardoso, 2013a,b; Wasil, 2013). There were no developmental toxicities in Crl:CD rats administered the substance by gavage on gestation days 6 to 20 (Charlap, 2013; Hood et al., 1979). A 28-day dietary study for 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide in male and female Crl:CD(SD) rats resulted in a NOAEL of >100 mg/kg bw/day. A 90-day gavage study in the same strain and both sexes was also conducted and resulted in a NOAEL of >100 mg/kg bw/day (Diehl, 2013, 2014). This NOAEL is >20,400 times greater than the anticipated intake of 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide from use as a flavoring substance.

The Panel reviewed the GRAS application and supporting information regarding ethyl-2-(4-hydroxy-3-methoxyphenyl)acetate (CAS 60563-13-5) and concluded that it is GRAS (FEMA 4810) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of hydroxyl- and alkoxy-substituted benzyl derivatives (SLR C18; JECFA 2002, 2009). The Panel noted that based on the anticipated annual volume of use (50 kg), the *per capita* intake ("eaters only") of ethyl-2-(4-hydroxy-3-methoxyphenyl)acetate from use as a flavor ingredient is calculated to be 7 µg/person/day (0.1 µg/kg bw/day), which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The material is reported to occur naturally in wine, but only qualitative data were available and a consumption ratio could not be calculated (van Jaarsveld et al. 2009; Cabaroglu et al., 1997). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. This substance is anticipated to be rapidly hydrolyzed to the corresponding carboxylic acid which would be expected to undergo conjugation with glycine (rodent species) and with glutamine in humans and to be excreted as such. Additionally, conjugation with glucuronic acid at the hydroxyl functionality is expected (Heymann, 1980; Anders, 1989; Strand & Scheline, 1975; Wong & Sourkes, 1966). Ethyl-2-(4-hydroxy-3-methoxyphenyl)acetate was negative in an Ames assay in either the presence or absence of S9 metabolic activation in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and *E. coli* strain WP2 uvrA. The structural analog vanillin (FEMA 3107) gave negative results in Ames assays in *S. typhimurium* strains TA98, TA100, TA97, TA1535, and TA1538 in either the absence or presence of metabolic activation (Sokolowski, 2014). Vanillin was also negative in a mouse lymphoma forward mutation assay in the absence and presence of metabolic activation, negative in an unscheduled DNA synthesis assay at concentrations up to 500 µg/mL, and weakly positive in a micronucleus assay in Hep-G2 cells (Heck et al., 1989; Sanyal et al., 1997). Based on the available data for ethyl-2-(4-hydroxy-3-methoxyphenyl)acetate, weight of evidence considerations for the structural analog vanillin, and the structure of ethyl-2-(4-hydroxy-3-methoxy-phenyl)acetate and the identity and arrangement of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of ethyl-2-(4-hydroxy-3-

methoxyphenyl)acetate. A 60-day drinking water study with evaluation of limited endpoints for the structural analog 3,4-dihydroxybenzoic acid (FEMA 4430) resulted in a NOAEL of 25 mg/kg bw/day. This NOAEL is >208,000 times greater than the anticipated intake of ethyl-2-(4-hydroxy-3-methoxyphenyl)acetate from use as a flavoring substance (Nakamura et al., 2001; FDA, 1993; Mancebo et al, 2003; Hagan et al, 1967).

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding ginger mint oil (1505459-14-2) and concluded that it is GRAS (FEMA 4811) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel noted that based on the anticipated annual volume of use (15,000 kg), the *per capita* intake ("eaters only") of ginger mint oil from use as a flavor ingredient is calculated to be 2200 µg/person/day (37 µg/kg bw/day). The oil is produced from the mint hybrid *Mentha* x *gracilis*, but no consumption ratio could be calculated. Ginger mint oil is produced by steam distillation of the flowering tips and leaves of the *Mentha* x *gracilis* plant. The Panel considered the identity description to be adequate for FEMA GRAS evaluation. Metabolic data exist for representative members of each congeneric group of ginger mint oil that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products. For the major marker constituent, linalool, metabolism studies are available that suggest that glucuronic acid conjugation and excretion is the primary route of metabolism. Allylic oxidation becomes an important pathway for linalool metabolism only after repeated dosing (Buck and Renwick, 1998; Parke et al., 1974; Rahman, 1974 Chadha and Madyastha, 1984; Eder et al., 1982). The major marker constituent, linalool, gave negative results in an *in vitro* chromosomal aberration assay in Chinese hamster fibroblast cells. It was negative in an unscheduled DNA synthesis assay in rat hepatocytes. Linalool was also negative in a bone marrow micronucleus assay in Swiss CD-1 mice. The Panel concluded that the presence of low levels of epoxide-containing substances did not lead to concerns for genotoxicity, since these would be expected to be rapidly converted to innocuous metabolites. Based on the available data, the Panel did not identify specific concerns related to the potential genotoxicity of ginger mint oil (Ishidate et al., 1984; Heck et al., 1989; Bertens 2000; Meerts, 2001; Thompson and Bowles, 2011). The major marker constituent, linalool, was tested in a developmental toxicity study in rats, resulting in a maternal NOAEL of 500 mg/kg bw/day, and a developmental NOAEL of >1000 mg/kg bw/day. (Lewis 2006; Politano et al., 2008). In a 12-week dietary study in male and female rats, a mixture of linalool and citronellol (1:1) resulted only in a slight retardation in body weight gain that was concluded to be biologically insignificant (Oser, 1967. Hagan et al., 1967). The NOAEL of 50 mg/kg bw/day (for each component of the mixture) is >1350 times greater than the anticipated daily *per capita* intake of ginger mint oil from use as a flavor ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding palmitoylated green tea extract catechins (CAS 1448315-04-5) and concluded that the uses of the substance be considered GRAS (FEMA 4812) for use as a flavoring ingredient. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel noted that based on the anticipated annual volume of use (700 kg), the *per capita* intake ("eaters only") of palmitoylated green tea extract catechins from use as a flavor ingredient is calculated to be 103 µg/person/day (2 µg/kg bw/day). The extract is derived from green tea leaves, but modified to palmitic acid derivatives and thus does not occur in nature. The Panel considered the identity description to be adequate for FEMA GRAS evaluation (see Appendix 1). The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Metabolic data exist for representative members of each congeneric group that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Hackett and Griffiths, 1982). Palmitoylated green tea extract catechins gave negative results in an Ames assay in *S. typhimurium* strains TA97a, TA98, TA100 and TA102 in either the absence or presence of metabolic activation. It was also negative in a bone marrow micronucleus assay at concentrations up to 10,000 mg/kg bw in ICR mice. The Panel reviewed the available data that confirmed that the substances tested within the genotoxicity studies were of similar composition to the substance proposed for use as a flavoring ingredient. Based on the available data, the Panel did not identify any specific concerns related to the genotoxic potential for palmitoylated green tea extract catechins (Mei, S. et al. 2010). 28-Day and 90-day studies in rats and a 90-day study in beagles were available for the palmitoylated green tea extract catechins (Mei, S. et al., 2010; Xu, Y., et al. 2010; Stanford, H. et al. 2011; Chengelis et al., 2008; Takami et al., 2008). The NOAEL of 500 mg/kg bw/day from the 90-day dietary study in male and female Sprague-Dawley rats was >290,000 times higher than the anticipated daily intake of palmitoylated green tea extract catechins when used as a flavoring substance. The Panel reviewed the available data that confirmed that the substances tested within the toxicity studies were of similar composition to the substance proposed for use as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2-(5-isopropyl-2-methyl-tetrahydrothiophen-2-yl)-ethanol (CAS 1612888-42-2) and concluded that it is GRAS (FEMA 4813) for use as a flavor at the use levels specified in the GRAS application (See Table 2; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of sulfur-containing heterocyclic compounds (SLR D15; JECFA 2003, 2008, 2012, 2015). The Panel noted that based on the anticipated annual volume of use (1 kg), the *per capita* intake ("eaters only") of 2-(5-isopropyl-2-methyltetrahydrothiophen-2-yl)-ethanol from use as a flavor ingredient is calculated to be 0.1 µg/person/day (0.003 µg/kg bw/day), which is significantly below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). The substance naturally occurs in lemon peel but only qualitative data are available and thus no consumption ratio can be calculated (Nijssen et al., 2015). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. 2-(5-Isopropyl-2-methyltetrahydrothiophen-2-yl)-ethanol is subject to

oxidative metabolism. Tetrahydrothiophenes are readily metabolized by formation and urinary excretion of stable sulfoxide and sulfone derivatives. The hydroxyl moiety also may undergo conjugation with glucuronic acid and facile elimination in the urine (Rance, 1989). Based on the structure of the substance and the identity and arrangements of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of 2-(5-isopropyl-2-methyl-tetrahydro-thiophen-2-yl)-ethanol. A 90-day oral gavage study for structural analog 2-methyl-4-propyl-1,3-oxathiane (FEMA 3578) at 0.44 mg/kg bw/day. There were no adverse test substance related differences observed. The only significant deviation was increased food intake among the males but this was thought to be in compensation for the highly flavored solutions that they were receiving. Thus the resulting NOAEL assigned by the panel was 0.44 mg/kg bw/day (BIBRA, 1976; Morgareidge, 1974). The NOAEL of 0.44 mg/kg bw/day for the structural analog is >176,000 times higher than the anticipated daily *per capita* intake of 2-(5-isopropyl-2-methyl-tetrahydro-thiophen-2-yl)-ethanol from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding glucosylated *Rubus suavissimus* extract, 60% glucosylated rubusoside glycosides (CAS pending) and concluded that it is GRAS (FEMA 4814) for use as a flavor ingredient in food categories at the use levels specified in the GRAS application. This material was evaluated individually within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel noted that based on the reported annual volume of use (500 kg), the *per capita* intake (""eaters only"") of glucosylated *Rubus suavissimus* extract, 60%, glucosylated rubusoside glycosides from use as a flavor ingredient is calculated to be 74 µg/person/day (1 µg/kg bw/day). This dose level would be equivalent to roughly 0.7 µg/kg bw/day of Rubusoside *alpha*-D-glycosides (main constituent). The material is not reported to occur in nature. The Panel considered the identity description to be adequate for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). It is anticipated that glucosylated *Rubus suavissimus* extract, 60% glucosylated rubusoside glycosides are not absorbed from the GI tract. These compounds are believed to be converted to rubusoside by the action of intestinal flora by analogy to steviol glycosides. It has been demonstrated that enzymatically-treated stevia and naturally occurring steviol glycosides are converted to steviol *in vitro* when incubated in fecal homogenates under anaerobic conditions (Koyama et al., 2003a, b; Gardana et al., 2003; Roberts and Renwick, 2008; Wheeler et al., 2008; Jeppesen et al., 1996, 2000, 2003; Costa et al., 2003a; Abudula et al., 2004; Xiao and Hermansen, 2005; Xiao et al., 2005; Chen et al., 2006a, 2006b, 2006c; Nakamura et al., 2003; Yamamoto et al., 1985; Suanarunsawat and Chaiyabutr, 1997; Dyrskog et al., 2005a, b; Chen et al., 2005; Chang et al., 2005; Maki et al., 2007; Maki et al., 2008a,b; Curi et al., 1986; Barriocanal et al., 2008; Cavalcante da Silva et al., 2006). Based on the identities of the constituents and arrangements of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity for glucosylated *Rubus suavissimus* extract, 60% glucosylated rubusoside glycosides. *beta*-Cyclodextrin is a nephrotoxin in dogs at 654 mg/kg bw per day. The intake of *beta*-cyclodextrin at the maximum anticipated concentration of 30% within the flavor complex is estimated to be 1.2 ug/kg bw/day, which is 545,000 times less than the concentration where nephrotoxicity was observed (Bellringer et al., 1995). In a subchronic rat study, four groups of Sprague Dawley rats (25 per group) were fed diets,that contained 0, 1.25, 2.5 and 5.0% of *alpha*-glucosyl steviol glycoside for 13 weeks. At 2.5 and 5.0%, slight increases in body weights were seen in both sexes of rats when compared to control rats. No treatment-related effect on food or water consumption was observed. After 13 weeks, hematological examination revealed that there was a decrease in the number of lymphocytes and white cell count in females at the 2.5 and 5.0% treatment level and a decrease in cell volume in the high dose group males. Blood biochemistry was done on 22 parameters. Small changes were seen in some parameters (decreases in calcium and globulin concentrations in males, decrease in glucose and increase in creatine in females) but none were believed to be significant or treatment related. No effect on organ weights was seen at any dose in either sex. No changes in any tissue were seen in gross and microscopic pathology examination. Thus the resulting NOAEL was 5000 mg/kg bw/day (Hooks, 1988). The NOAEL of 5000 mg/kg bw/day for the structural analog is >4,166,000 times higher than the anticipated daily *per capita* intake of glucosylated *Rubus suavissimus* extract, 60% glucosylated rubusoside glycosides from the intended use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding Sandalwood austrocaledonien oil (*Santalum austrocaledonicum* oil) (CAS 91845-48-6; 1070895-66-7) and concluded that it is GRAS (FEMA 4815) for use as a flavor in food categories at the use levels specified in the GRAS application. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel noted that based on the reported annual volume of use (10 kg), the *per capita* intake ("eaters only") of Sandalwood austrocaledonien oil from use as a flavor ingredient is calculated to be 2 µg/person/day (0.03 µg/kg bw/day). This dose level would be equivalent to roughly 0.011 µg/kg bw/day of (*E*)-*alpha*-santalol, the principal constituent. Sandalwood austrocaledonien oil is produced by steam distillation of the wood of *Santalum austrocaledonicum*. The Panel considered the identity description to be adequate for FEMA GRAS evaluation. The Panel also noted that the material is sufficiently different from Sandalwood yellow oil (FEMA 3005) based on species differentiation to grant a new FEMA number. Metabolic data exist for representative members of each congeneric group of Sandalwood austrocaledonien oil that would predict, at the levels of intake proposed, metabolism by well-established detoxication pathways to innocuous products. For the major marker constituent (*E*)-*alpha*-santalol, metabolism studies that are available that suggest oxidation to the corresponding aldehyde and carboxylic acid followed by *beta*-oxidation to short-chain acids and complete metabolism by the fatty acid pathway and the citric acid cycle. No increases in reverse mutations were observed in Ames assays in *S. typhimurium* strains TA97a, TA100, TA98, TA102, and TA1535, TA1537, TA1538 either in the presence or absence of metabolic activation for Sandalwood austrocaledonien oil (Sivaswamy, et al., 1991; Andres, 2014). The acute oral $LD_{50}$ of Sandalwood

austrocaledonien oil is greater than 2000 mg/kg bw (Keating, 1972; Colas, 2010).

The Panel reviewed the GRAS application and supporting information regarding Sugar Cane distillate (CAS pending) and concluded that it is GRAS (FEMA 4816) for use as a flavor ingredient in food categories at the use levels specified in the GRAS application. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel noted that based on the reported annual volume of use (30,000 kg; 0.15 kg concentrate), the *per capita* intake ("eaters only") of Sugar Cane distillate from use as a flavor ingredient is calculated to be 4,400 (0.022) µg/person/day (74 (0.0004) µg/kg bw/day). The distillate is isolated from Sugar Cane which is a complex hybrid of 5 species of the genus *Saccharum* (Nijssen et al., 2015). Sugar Cane distillate is isolated from pressed sugar cane, filtered and distilled to isolate the volatile components. The material in commerce is 0.0005% distillate in water. The Panel considered the identity description to be adequate for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). No evidence of mutagenicity was observed when the constituent damascenone was observed in an Ames assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 and *E. coli* strain WP2 uvrA in the absence or presence of metabolic activation (Wagner, 2000). Toxicity data provided for the constituent of Sugar Cane distillate, furfural, in a 28-day oral gavage study provided a NOAEL of 96 mg/kg bw/day which is at least 1290 (240,000,000) times the exposure of Sugar Cane distillate used as a flavor ingredient (Arts et al., 2004).

### *New Use Levels/Food Categories*

The Panel reviewed the GRAS application and supporting information regarding new use levels and additional food categories for potassium cinnamate (CAS 16089-48-8; FEMA 2288) and concluded that the new proposed uses are GRAS (See Table 3; Smith et al., 2005a). This substance was evaluated within the context of the chemical group of cinnamyl alcohol and related substances (Adams et al., 2004; SLR C11; JECFA 2001). The Panel noted that based on the anticipated increase in annual volume of use (2500 kg), and the most recent surveyed volume of 599 kg, the *per capita* intake ("eaters only") of potassium cinnamate from use as a flavor ingredient is calculated to be 456 µg/person/day (8 µg/kg bw/day), which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The material was reported to occur naturally in several foods, including beer, apple cider, citrus fruit, cocoa, grape, honey and others. Quantitative data were available and the consumption ratio was calculated to be 2. The 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 candidate substance is rapidly absorbed and converted to benzoyl-CoA which is conjugated with glycine to form hippuric acid, which is excreted in the urine. A variety of studies for cinnamic acid were available. Cinnamic acid was negative in Ames experiments in a number of strains in the presence and absence of metabolic activation. It was negative in an SOS chromotest in *E. coli* strain PQ37, and in a rec assay *in Bacillis subtilis* strains H17 (rec+) and M45 (rec-). The substance was negative in an *in vitro* Comet assay and in a sister chromatid exchange (SCE) assay. Cinnamic acid was positive in a mouse lymphoma assay (MLA), but it was noted that the potentially acidifying effect of cinnamic acid on the culture medium may have influenced the outcome. Cinnamic acid gave a positive response in an *in vitro* micronucleus assay in rat hepatoma tissue cells (HTC). However, the strain and experimental conditions used in the study are not compliant with OECD guidelines (Maistro et al., 2011; Heck et al., 1989; Sasaki et al., 1989; Yoo, 1986; Eder et al., 1991, Lijinsky and Andrews, 1980). The Panel discussed the available data and concluded that there was no concern for the genotoxic potential of cinnamic acid. In a developmental study there were no effects observed up to 50 mg/kg bw/day in pregnant rats on cinnamic acid (Zaitsev and Maganova, 1975).

The Panel reviewed proposed new use levels for Quillaia extract (CAS 68990-67-0) and concluded that they are considered GRAS (FEMA 2973) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (see Table 3). This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel noted that based on the anticipated increase in the annual volume of use (1743 kg) and the most recent surveyed volume (5300 kg), the anticipated *per capita* intake ("eaters only") of quillaia extract from use as a flavor ingredient is calculated to be 1040 µg/person/day (17 µg/kg bw/day). The material occurs naturally in the soap bark tree, but this is not commonly consumed as a food. The Panel considered the identity description and constituent identification data to be adequate for FEMA GRAS evaluation. Metabolic data exist for representative members of each congeneric group that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products. Based on the structures of the major constituents, the Panel did not identify any specific concerns related to the genotoxic potential of quillaia extract. In a 13-week study, male and female CFE rats were administered quillaia extract as part of the diet. The NOAEL of 400 mg/kg bw/day is >23,000 times the anticipated daily *per capita* intake of quillaia extract when used as a flavoring ingredient (JECFA, 2001).

The Panel reviewed the proposed New Use Levels for Glycine (CAS 56-40-6) and concluded that the additional uses are GRAS (FEMA 3287) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 3; Smith et al., 2005a). This substance was evaluated within the context of the chemical group of amino acids and related substances (SLR B3; JECFA 2006, 2012). The Panel noted that based on the anticipated increase in the annual volume of use (2000 kg) and the most recent surveyed volume (5890 kg), the *per capita* intake ("eaters only") of glycine from use as a flavor ingredient is calculated to be 1160 µg/person/day (19 µg/kg bw/day), which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). Glycine is naturally occurring in plants and endogenous in humans. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS

evaluation. An established body of data exists that describes the absorption of free amino acids through the intestinal mucosa and their subsequent entrance into the portal blood. A variety of carrier systems transport amino acids into cells. The use of free amino acids as precursors for protein synthesis is well-established. Any excretion of amino acids in the urine is limited, and regulated by renal tubular reabsorption. Ultimately, the ADME characteristics of free amino acids, including glycine, are balanced to maintain an adequate cellular pool for the continuous production of proteins (Nelson and Cox, 2008). Glycine was negative in Ames assays under a variety of conditions, and negative in a Rec assay (Haworth et al., 1983; Fujita et al., 1994; Kada, 1981; Kuroda et al. 1984). Based on the negative mutagenicity study data for glycine and other evidence from structural analogs and the identity and arrangements of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of glycine. The Panel stated that there are no toxicity concerns or safety issues; the properties of this substance are well known and toxicity studies have been published and reviewed previously supporting general recognition of safety.

The Panel reviewed the proposed New Use Levels for *N*-(heptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide (CAS 745047-51-2) and concluded that the additional uses are GRAS (FEMA 4232) for use as a flavor in the food categories at the use levels specified in the GRAS application (See Table 3; Smith et al., 2005a). The substance was reviewed individually within the context of the chemical group of aliphatic and aromatic amines and amides (SLR A7, C21, JECFA 2006, 2008, 2011, 2012). The Panel noted that based on the anticipated increase in the annual volume of use (1000 kg) and the most recent surveyed volume (1000 kg), the *per capita* intake ("eaters only") of *N*-(heptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide from use as a flavor ingredient is calculated to be 294 µg/person/day (5 µg/kg bw/day), which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The material was not reported to occur in nature. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. Based on the results of in vitro rat hepatocyte studies, the substance is metabolized by hydroxylation of the 4-heptamine side chain and by ring opening of the methylenedioxy group. These polar metabolites are anticipated to be conjugated and excreted (Denning, 2004). The substance gave negative results in an Ames assay with and without S9 metabolic activation *in S. typhimurium* strains TA98, TA100, TA1535, TA1537, and *E. coli* strain WP2 uvrA, and negative results in a chromosomal aberration assay in CHO ovary WBL cells. The substance was negative in a bone marrow micronucleus test in mice. Based on these results the Panel did not identify specific concerns related to the genotoxicity of *N*-(heptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide (Zhang, 2004a,b,c; Thompson, 2005; Pucaj, 2004). In a 90-day dietary study in Crl:CD(SD)IGS BR male and female rats, no mortality or treatment-related effects were observed, and a NOAEL of >20 mg/kg bw/day was established. This NOAEL is >4,000 times greater than the anticipated daily intake of *N*-(heptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide when used as a flavoring ingredient (Kot, 2005a).

The Panel reviewed the proposed New Use Levels for 3-[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]-2,2,dimethyl-*N*-propylpropanamide (CAS 1093200-92-0) and concluded that the additional uses are GRAS (FEMA 4701) for use as a flavor ingredient in the food categories at the use levels specified in the GRAS application (See Table 3; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of miscellaneous nitrogen-containing substances (SLR D19, JECFA 2006, 2009, 2012, 2015). The Panel noted that based on no anticipated increase in the annual volume of use from the new uses and the most recent surveyed volume (650 kg), the *per capita* intake ("eaters only") of 3-[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]-2,2,dimethyl-*N*-propylpropanamide from use as a flavor ingredient is calculated to be 72 µg/person/day (1 µg/kg bw/day), which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). 3-[(4-Amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]-2,2,dimethyl-*N*-propylpropanamide is not known to occur in nature. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. This substance shows very low bioavailability in rodent studies (bioavailability ~11%). It is therefore anticipated that oral absorption of this candidate substance in man would be limited. The metabolism of the substance is via oxidation to hydroxylated metabolites, which would be anticipated to be excreted unchanged, or conjugated with glucuronic acid and excreted in the urine (Arthur et al., 2015). The substance gave negative results in an Ames assay with and without S9 metabolic activation in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and *E. coli* strain WP2uvrA, and gave negative results in a chromosomal aberration assay in CHO ovary WBL cells. The substance was negative in a bone marrow micronucleus test in CD-1 mice (Arthur et al., 2015). Based on these data, the Panel did not identify specific concerns related to the potential genotoxicity of 3-[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5yl)oxy]-2,2-dimethyl-*N*-propylpropanamide. In a 90-day dietary study, 5, 10 or 20 mg of 3-[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5yl)oxy]-2,2-dimethyl-*N*-propylpropanamide were administered to male and female CD [Crl:CD(SD)] rats daily. There were no adverse treatment-related effects observed. The NOAEL of 20 mg/kg bw is >16,600 times greater than the estimated daily intake (Arthur et al., 2015).

The Panel reviewed the GRAS application and supporting information regarding glutamyl-valyl-glycine (CAS 38837-70-6) and concluded that it is GRAS (FEMA 4709) for use as a flavor ingredient in the new food categories and at the use levels specified in the GRAS application (See Table 3; Smith et al., 2005a). This substance was evaluated individually within the context of the chemical group of amino acids and related substances (SLR B3; JECFA 2006, 2012). The Panel noted that based on the anticipated proposed increase of 10,000 kg to the most recent surveyed annual volume of use (0 kg), the total proposed annual volume of use is 10,000 kg. Based on this total proposed annual volume of use, the *per capita* intake (""eaters only"") of glutamyl-valyl-glycine from use as a flavor ingredient is calculated to be 1473 µg/person/day (25 µg/kg bw/day), which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The material was reported to occur in fish sauce, soy sauce shrimp paste,

raw and dried scallops and scallops extract. While quantitative data is available, the consumption ratio cannot be calculated due to limited information related to the consumption of these food products. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. Based on available data from *in vitro* studies using human small intestinal mucosa homogenateglutamyl-valyl-glycine is readily hydrolyzed to their respective amino acids (Willis, 2005, 2010a, 2010b). Glutamyl-valyl-glycine did not increase reverse mutations in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537, and *E. coli* strain WP2uvrA either in the presence or absence of metabolic activation. The substance did not induce structural or numerical (polyploidy) chromosome aberrations in Chinese hamster lung fibroblast cells (CHL/IU) in either the presence or absence of metabolic activation. No clastogenic potential was observed in the bone marrow of Crlj:CD1(ICR) SPF mice administered glutamyl-valyl-glycine (Oda et al., 2008). Based on these results, as well as the panel's assessment of the structure of the substance including lack of structural alerts for genotoxicity, and the identity and arrangement of the functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of glutamyl-valyl-glycine. A 28-day dietary study in Crl:CD(SD) male and female rats resulted in a NOAEL of 1000 mg/kg/day. This NOAEL is 36,000 times higher than the anticipated daily *per capita* intake of glutamyl-valyl-glycine from use as a flavor ingredient (Okamura, 2010).

The Panel reviewed proposed new use levels for Luo Han Fruit Concentrate (CAS 1042967-53-2) and concluded that they are considered GRAS (FEMA 4711) for use as a flavor ingredient with in the food categories at the use levels specified in the GRAS application (see Table 3). This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel noted that based on the anticipated increase in the annual volume of use (1 kg) and the most recent surveyed volume (4940 kg), the anticipated *per capita* intake ("eaters only") of Luo Han fruit concentrate from use as a flavor ingredient is calculated to be 727 µg/person/day (12 µg/kg bw/day). The material occurs naturally in the edible fruit, *Siraitia grosvenorii* (aka, Monk fruit), but no consumption ratio could be calculated. The Panel considered the previously reviewed specifications to be adequate for FEMA GRAS evaluation. Luo Han Fruit Concentrate does not contain any significant levels of volatile components. The major marker constituent of Luo Han Fruit Concentrate is mogroside V (50%). Metabolic data exist for representative members of each congeneric group that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products. When incubated in an Ames assay with or without S9 metabolic activation in *S. typhimurium* strains TA100, TA98, TA1535 and TA1537 as well as with *E. coli* strain WP2/uvrA, Luo Han Fruit Concentrate was not mutagenic at concentrations up to 5000 µg/plate. In an *in vivo* mouse micronucleus assay, the investigators concluded that under the experimental conditions tested, Luo Han Fruit Concentrate did not induce structural or numerical chromosomal damage in the immature erythrocytes of the mouse up to the maximum tolerable dose (Heimbach, 2009). Based on the available data, the Panel did not identify any specific concerns related to the genotoxic potential of Luo Han Fruit Concentrate.

Three repeat dose oral toxicity studies have been completed and published with the Luo Han fruit concentrate, and in all studies the NOAEL was the highest dose tested and no adverse effects were seen at any tested dose (Heimbach, 2009). The NOAEL of 2520 mg/kg bw from one subchronic study is >200,000 times larger than the anticipated intake of Luo Han Fruit Concentrate when used as a flavoring ingredient under intended use conditions in food.

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