FEMA

30

GRAS

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

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

GRAS FLAVORING SUBSTANCES 30

STATEMENT REGARDING GENERALLY RECOGNIZED AS SAFE STATUS OF MINTLACTONE

The FEMA GRAS status of mintlactone (CAS No. 13341-72-5; FEMA No. 3764) under its conditions of intended use as a flavor ingredient was reviewed by the FEMA Expert Panel. After reviewing the available information relevant to the FEMA GRAS status of mintlactone, including recent studies, the Expert Panel concluded that additional data are required to support the continuation of its GRAS status. Such data should include OECD- and GLP-compliant *in vitro* and *in vivo* genotoxicity testing, and confirmation from the industry that the commercial substance will not degrade to mutagenic impurities. Until such data are available for review by the Expert Panel, the flavor ingredient mintlactone has been removed from the FEMA GRAS list.

TABLE 1 - Primary Names & Synonyms

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

FEMA NO.	PRIMARY NAMES AND SYNONYMS
4943	**Decanedioic acid** 1,8-Octanedicarboxylic acid 1,10-Decanedioic acid Sebacic acid Decanedicarboxylic acid
4944	***trans*-2-Dodecenedioic acid** (*E*)-Dodec-2-enedioic acid Dodec-2-enedioic acid Traumatic acid *trans*-Traumatic acid
4945	***cis*-8-Decenal** 8-Decenal, (8*Z*)- (8*Z*)-Dec-8-enal
4946	**2-Amino-2-deoxy-poly-D-glucosamine** Chitosan
4947	**Glucosylated stevia extract 40% with 14% Rebaudioside A**
4948	**2-Hexylpyridine** 2-(*n*-Hexyl)pyridine
4949	***Corynebacterium ammoniagenes* fermentation product** *C. ammoniagenes* dried fermentation broth
4950	***Stevia rebaudiana* extract with Rebaudiosides AM and M**
4951	**Glucosylated steviol glycosides 90% supraglucosylated rebaudioside A**
4952	**Glucosylated steviol glycosides 91% supraglucosylated rebaudioside D**
4953	**Glucosylated steviol glycosides 58% supraglucosylated stevioside**
4954	**Blue agave inulin (*Agave tequilana*)**
4955	***Emblica officinalis* fruit extract** *Phyllanthus emblica* extract Amla extract Indian gooseberry extract
4956	***Boehmeria nivea* leaf extract** Ramie leaf extract
4957	**Rebaudioside M 85%** Rebaudioside X 85%
4958	**4-Formyl-2-methoxyphenyl *l*-menthyl glutarate** 4-Formyl-2-methoxyphenyl-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl pentanedioate Pentanedioic acid, 1-(4-formyl-2-methoxyphenyl) 5-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl] ester

FEMA NO.	PRIMARY NAMES AND SYNONYMS
4959	**9-Dodecen-12-olide** Yuzu lactone Oxacyclotridec-10-en-2-one 1-Oxacyclotridec-10-en-2-one
4960	***trans*-alpha-Bergamotene** alpha-Bergamotene, *trans*- 2-Norpinene, 2,6-dimethyl-6-(4-methyl-3-pentenyl)-, *trans*-(-) Bicyclo(3.1.1)hept-2- ene, 2,6-dimethyl-6-(4-methyl-3-penten-1-yl)-, (1*S*,5*S*,6*R*)- Bicyclo(3.1.1)hept-2-ene, 2,6-dimethyl-6-(4-methyl-3-pentenyl)-, (1*S*-(1.*alpha*.,5.*alpha*.,6.*alpha*.))- *alpha*-trans-Bergamotene alpha-Bergamotene, (-)-*trans*- (-)-*trans*-alpha-Bergamotene (-)-*exo*-alpha-Bergamotene
4961	**4-Methyltrideca-2*E*,4-dienal**
4962	***Lepidium meyenii* root extract** *Lepidium peruvianum* root extract
4963	**Pandan leaf (*Pandanus amaryllifolius*) distillate extract**
4964	***Corynebacterium glutamicum* cell free fermentation product** *C. glutamicum* dried fermentation broth
4965	***N*-(1-((4-Amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)isonicotinamide**
4966	**4-Methylheptan-3-one**
4967	***delta*-Cadinene** δ-Cadinene Cadina-1(10),4-diene
4968	***Stevia rebaudiana* extract with Rebaudioside M ≥90%**
4969	**Yerba mate extract (*Ilex paraguariensis* A. St.-Hil.)** Mate absolute *Ilex paraguariensis* A. St.-Hil. extract
4970	**2-Methyl-1-(2-(5-(*p*-tolyl)-1*H*-imidazol-2-yl)piperidin-1-yl)butan-1-one**
4971	***beta*-Farnesene** 1,6,10-Dodecatriene, 7,11-dimethyl-3-methylene-, (6*E*)- 1,6,10-Dodecatriene, 7,11-dimethyl-3-methylene-, (*E*)- (6*E*)-7,11-Dimethyl-3-methylene-1,6,10-dodecatriene (*E*)-7,11-Dimethyl-3-methylene-1,6,10-dodecatriene (*E*)-*beta*-Farnesene *trans*-beta-Farnesene

TABLE 1 Continued - Primary Names & Synonyms

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

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

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)

	Decanedioic acid	*trans*-2-Dodecenedioic acid	*cis*-8-Decenal	2-Amino-2-deoxy-poly-D-glucosamine	Glucosylated stevia extract 40% with 14% RebaudiosideA
Category/FEMA No.	**4943**	**4944**	**4945**	**4946**	**4947**
Baked Goods	40/200	40/200	0.004/0.2	1500/2000	50/60
Beverages Type I, Non-Alcoholic	20/50	10/50	0.0002/0.01	1500/2000	50/60
Beverages Type II, Alcoholic	15/30	15/50	0.0002/0.01	1500/2000	50/60
Breakfast Cereals	50/100	50/200	0.002/0.1		50/60
Cheeses	40/100	50/200	0.0004/0.02	1500/2000	
Chewing Gum	100/300	100/500	0.004/0.2	1500/2000	
Condiments and Relishes	30/100	30/200	0.002/0.1	1500/2000	
Confections and Frostings	40/100	40/200	0.002/0.1	1500/2000	50/60
Egg Products	50/100	40/300	0.001/0.05		
Fats and Oils	50/100	40/100	0.004/0.2	1500/2000	50/60
Fish Products	50/100	50/300	0.001/0.05	1500/2000	
Frozen Dairy	40/100	40/300	0.0004/0.02		50/60
Fruit Ices	30/60	15/100	0.0004/0.02		50/60
Gelatins and Puddings	30/60	15/100	0.0004/0.02	1500/2000	50/60
Granulated Sugar		40/200	0.001/0.05		50/60
Gravies	40/100	40/200	0.001/0.05	1500/2000	
Hard Candy	50/200	50/300	0.001/0.05		50/60
Imitation Dairy Products	40/100	40/200	0.0004/0.02	1500/2000	50/60
Instant Coffee and Tea	30/100	15/100	0.001/0.05	1500/2000	50/60
Jams and Jellies	50/100	15/100	0.0004/0.02	1500/2000	50/60
Meat Products	50/100	50/300	0.001/0.05	1500/2000	
Milk Products	40/100	40/100	0.0004/0.02	1500/2000	50/60
Nut Products	40/100	40/200	0.001/0.05		50/60
Other Grains	50/200	50/200	0.0004/0.02	1500/2000	50/60
Poultry Products	50/100	50/300	0.001/0.05		
Processed Fruits	50/100	50/200	0.0004/0.02	1500/2000	50/60
Processed Vegetables	50/100	50/300	0.001/0.05	1500/2000	
Reconstituted Vegetable Protein	50/100	50/300	0.001/0.05	1500/2000	
Seasonings and Flavors	50/100	50/300	0.001/0.05	1500/2000	50/60
Snack Foods	50/100	50/300	0.0004/0.02		50/60
Soft Candy	50/200	50/300	0.001/0.05	1500/2000	50/60
Soups	50/300	50/200	0.0004/0.02	1500/2000	50/60
Sugar Substitutes	30/60	30/100	0.002/0.1	1500/2000	50/60
Sweet Sauces	40/100	40/100	0.001/0.05	1500/2000	50/60

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-Hexylpyridine	*Corynebacterium ammoniagenes* fermentation product	*Stevia rebaudiana* extract with Rebaudiosides AM andM	Glucosylated steviol glycosides 90% supraglucosylated rebaudioside A
Category/FEMA No.	**4948**	**4949**	**4950**	**4951**
Baked Goods	1/5	1000/7500	50/150	70/70
Beverages Type I, Non-Alcoholic	1/5		50/50	70/70
Beverages Type II, Alcoholic	1/5		50/50	70/70
Breakfast Cereals		1000/5000	50/50	70/70
Cheeses	1/5	2000/7500	50/50	70/70
Chewing Gum			50/50	70/70
Condiments and Relishes	1/5	3000/20000	50/50	70/70
Confections and Frostings			50/50	70/70
Egg Products	1/5	1000/10000	50/50	
Fats and Oils	1/5		50/50	
Fish Products	1/5	3000/10000	50/50	
Frozen Dairy			50/50	70/70
Fruit Ices			50/50	70/70
Gelatins and Puddings			50/50	70/70
Granulated Sugar				
Gravies	1/5	3000/20000	50/50	70/70
Hard Candy			50/50	70/70
Imitation Dairy Products		2000/10000	50/50	70/70
Instant Coffee and Tea			50/50	70/70
Jams and Jellies			50/50	70/70
Meat Products	1/5	2000/15000	50/50	
Milk Products			50/50	70/70
Nut Products		1000/10000	50/50	70/70
Other Grains			50/50	70/70
Poultry Products	1/5	2000/10000	50/50	
Processed Fruits			50/50	
Processed Vegetables	1/5		50/50	
Reconstituted Vegetable Protein	1/5		50/50	
Seasonings and Flavors	1/5	5000/50000	50/50	70/70
Snack Foods	1/5	1000/10000	50/50	70/70
Soft Candy			50/50	70/70
Soups	1/5	3000/20000	50/50	70/70
Sugar Substitutes				
Sweet Sauces			50/50	70/70

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)

	Glucosylated steviol glycosides 91% supraglucosylated rebaudioside D	Glucosylated steviol glycosides 58% supraglucosylated stevioside	Blue agave inulin (*Agave tequilana*)	*Emblica officinalis* fruit extract
Category/FEMA No.	**4952**	**4953**	**4954**	**4955**
Baked Goods	50/50	100/100	1400/14000	50/200
Beverages Type I, Non-Alcoholic	50/50	100/100	350/3500	30/100
Beverages Type II, Alcoholic	50/50	100/100		30/100
Breakfast Cereals	50/50	100/100		50/200
Cheeses	50/50	100/100		50/200
Chewing Gum	50/50	100/100	700/7000	100/300
Condiments and Relishes	50/50	100/100		50/200
Confections and Frostings	50/50	100/100		50/200
Egg Products				50/200
Fats and Oils				50/100
Fish Products				50/200
Frozen Dairy	50/50	100/100		50/150
Fruit Ices	50/50	100/100		20/100
Gelatins and Puddings	50/50	100/100		20/100
Granulated Sugar				
Gravies	50/50	100/100	1400/14000	50/200
Hard Candy	50/50	100/100	1400/14000	100/300
Imitation Dairy Products	50/50	100/100		50/300
Instant Coffee and Tea	50/50	100/100		50/200
Jams and Jellies	50/50	100/100		20/150
Meat Products			700/7000	50/300
Milk Products	50/50	100/100		50/150
Nut Products	50/50	100/100		50/200
Other Grains	50/50	100/100		50/300
Poultry Products			420/4200	50/300
Processed Fruits		100/100		30/200
Processed Vegetables		100/100		50/300
Reconstituted Vegetable Protein		100/100		50/300
Seasonings and Flavors	50/50	100/100	700/7000	50/200
Snack Foods	50/50	100/100	1400/14000	50/200
Soft Candy	50/50	100/100	1400/14000	100/300
Soups	50/50	100/100	1400/14000	50/200
Sugar Substitutes				20/100
Sweet Sauces	50/50	100/100		20/200

TABLE 2 Continued - Average Usual Use Levels/Average Maximum Use Levels

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

	Boehmeria nivea leaf extract	Rebaudioside M 85%	4-Formyl-2-methoxyphenyl /-menthyl glutarate	9-Dodecen-12-olide	*trans*-alpha-Bergamotene
Category/FEMA No.	**4956**	**4957**	**4958**	**4959**	**4960**
Baked Goods	60/120	15/20	5/50	0.5/2	269/269
Beverages Type I, Non-Alcoholic	40/80	15/20		0.01/0.2	24/24
Beverages Type II, Alcoholic	15/30	15/20		0.01/0.2	
Breakfast Cereals	50/150	15/20	1/10	0.3/1	34/34
Cheeses	80/160			0.1/0.5	
Chewing Gum	100/200	15/20		1/4	465/465
Condiments and Relishes	40/100	15/20		0.3/1	2/20
Confections and Frostings	40/100	15/20	1/10	0.3/1	56/56
Egg Products	50/100			0.1/0.5	
Fats and Oils	40/100			2/10	
Fish Products	20/80			0.1/0.5	
Frozen Dairy	40/120	15/20		0.1/0.5	
Fruit Ices	15/30	15/20		0.1/0.5	16/147
Gelatins and Puddings	30/60	15/20		0.1/0.5	83/83
Granulated Sugar					
Gravies	50/120	15/20		0.2/2	
Hard Candy	20/30	15/20		0.2/2	93/93
Imitation Dairy Products	40/120	15/20		0.5/3	
Instant Coffee and Tea	20/60	15/20		0.1/0.5	
Jams and Jellies	10/50	15/20		0.1/0.5	
Meat Products	40/120			0.1/0.5	6/10
Milk Products	40/120	15/20		0.1/0.5	
Nut Products	40/100	15/20			
Other Grains	50/100	15/20			
Poultry Products	50/100			0.1/0.5	
Processed Fruits	15/30	15/20		0.1/0.5	
Processed Vegetables	15/100	15/20			
Reconstituted Vegetable Protein	15/100	15/20			
Seasonings and Flavors	40/80	15/20			
Snack Foods	50/150	15/20		0.3/1	
Soft Candy	15/30	15/20		0.3/2	93/93
Soups	40/80	15/20		0.05/0.5	
Sugar Substitutes	10/40				
Sweet Sauces	40/80	15/20		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)

	4-Methyltrideca-2*E*,4-dienal	*Lepidium meyenii* root extract	Pandan leaf (*Pandanus amaryllifolius*) distillateextract	*Corynebacterium glutamicum* cell free fermentation product
Category/FEMA No.	**4961**	**4962**	**4963**	**4964**
Baked Goods	0.004/0.2	35/70	4/40	1000/11000
Beverages Type I, Non-Alcoholic	0.0002/0.01	15/35		
Beverages Type II, Alcoholic	0.0002/0.01	5/20		
Breakfast Cereals	0.002/0.1	35/70	2/40	1000/11000
Cheeses	0.0004/0.02	30/60	1/20	3000/11000
Chewing Gum	0.004/0.2			
Condiments and Relishes	0.002/0.1	25/50	2/40	3000/18000
Confections and Frostings	0.002/0.1			
Egg Products	0.001/0.05	40/80		1000/7000
Fats and Oils	0.004/0.2	10/50	2/40	
Fish Products	0.001/0.05	40/80	2/40	3000/9000
Frozen Dairy	0.0004/0.02	40/80		
Fruit Ices	0.0004/0.02	10/30		
Gelatins and Puddings	0.0004/0.02	30/80		
Granulated Sugar	0.001/0.05			
Gravies	0.001/0.05	25/50	2/40	3000/11000
Hard Candy	0.001/0.05			
Imitation Dairy Products	0.0004/0.02	50/120		3000/11000
Instant Coffee and Tea	0.001/0.05	10/30	2/40	
Jams and Jellies	0.0004/0.02			
Meat Products	0.001/0.05	50/100	1/20	3000/11000
Milk Products	0.0004/0.02	35/70	0.5/10	
Nut Products	0.001/0.05	35/70	1/20	1000/4000
Other Grains	0.0004/0.02	35/80	1/20	
Poultry Products	0.001/0.05	50/100	2/40	3500/7500
Processed Fruits	0.0004/0.02	10/30		
Processed Vegetables	0.001/0.05	50/100	1/20	
Reconstituted Vegetable Protein	0.001/0.05	50/100	1/20	
Seasonings and Flavors	0.001/0.05	100/200	2/40	20000/150000
Snack Foods	0.0004/0.02	50/100	1/20	7500/20000
Soft Candy	0.001/0.05			
Soups	0.0004/0.02	35/70	1/20	3500/18500
Sugar Substitutes	0.002/0.1			
Sweet Sauces	0.001/0.05	35/70		

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)

	N-(1-((4-Amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl) isonicotinamide	4-Methylheptan-3-one	*delta*-Cadinene	*Stevia rebaudiana* extract with Rebaudioside M ≥90%
Category/FEMA No.	**4965**	**4966**	**4967**	**4968**
Baked Goods	10/22	1/5	0.9/0.9	70/70
Beverages Type I, Non-Alcoholic	15/22	0.5/2		35/35
Beverages Type II, Alcoholic	10/22	0.5/2		35/35
Breakfast Cereals	20/22	1/5		100/100
Cheeses		0.5/2		35/35
Chewing Gum	22/22			35/35
Condiments and Relishes	20/22	0.5/2	0.3/0.3	35/35
Confections and Frostings	22/22			35/35
Egg Products				35/35
Fats and Oils		2/8		35/35
Fish Products				35/35
Frozen Dairy	15/22	1/5		35/35
Fruit Ices	15/22	0.5/2		35/35
Gelatins and Puddings	15/22	0.5/2		35/35
Granulated Sugar				
Gravies		1/5		35/35
Hard Candy	22/22	1/5	0.9/0.9	35/35
Imitation Dairy Products	15/22	0.5/2		35/35
Instant Coffee and Tea	10/22	0.5/2		35/35
Jams and Jellies	15/22			35/35
Meat Products		1/5		35/35
Milk Products	15/22	0.5/2		45/45
Nut Products		0.5/2		35/35
Other Grains		0.5/2		35/35
Poultry Products		1/5		35/35
Processed Fruits		0.5/2		35/35
Processed Vegetables		0.5/2		35/35
Reconstituted Vegetable Protein		0.5/2		35/35
Seasonings and Flavors				35/35
Snack Foods		1/5		35/35
Soft Candy	20/22	1/5		35/35
Soups		0.5/2		35/35
Sugar Substitutes				
Sweet Sauces	15/22			35/35

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)

	Yerba mate extract (*Ilex paraguariensis* A. St.-Hil.)	2-Methyl-1-(2-(5-(*p*-tolyl)-1*H*-imidazol-2-yl) piperidin-1-yl) butan-1-one	*beta*-Farnesene	Diethyl mercaptosuccinate	3-Mercapto-3-methyl-1-pentylacetate
Category/FEMA No.	**4969**	**4970**	**4971**	**4972**	**4973**
Baked Goods			10/50	1/10	0.001/0.05
Beverages Type I, Non-Alcoholic	400/1000		5/20	0.1/1	0.0001/0.002
Beverages Type II, Alcoholic	400/1000		5/20	0.1/1	0.0001/0.002
Breakfast Cereals			10/50		
Cheeses	400/1000		2/10		0.0005/0.005
Chewing Gum		100/300	30/90	1/10	0.0005/0.01
Condiments and Relishes	400/1000		5/15	1/10	0.0001/0.01
Confections and Frostings	400/1000		20/60	1/10	0.0005/0.005
Egg Products					0.0002/0.001
Fats and Oils			5/30		
Fish Products			1/5		
Frozen Dairy	400/1000		5/40	1/10	0.0002/0.003
Fruit Ices	400/1000		5/20	1/10	0.0002/0.003
Gelatins and Puddings	400/1000		2/10	1/10	0.0002/0.003
Granulated Sugar					
Gravies	400/1000		5/20	0.1/1	0.0005/0.005
Hard Candy	400/1000		10/50	1/10	0.0005/0.01
Imitation Dairy Products	400/1000		1/5		
Instant Coffee and Tea	400/1000		5/20	1/10	0.0003/0.005
Jams and Jellies	400/1000		2/10	1/10	
Meat Products			1/5	1/10	0.001/0.01
Milk Products	400/1000		10/30		0.0001/0.001
Nut Products			5/20	1/10	
Other Grains			10/50	0.1/1	
Poultry Products			1/5	0.1/1	
Processed Fruits	400/1000		5/30	0.1/1	
Processed Vegetables	400/1000		5/10	0.1/1	
Reconstituted Vegetable Protein	400/1000		5/20		
Seasonings and Flavors			10/50	0.1/1	0.01/0.5
Snack Foods			5/20		0.001/0.05
Soft Candy	400/1000		10/30	1/10	0.001/0.1
Soups	400/1000		5/20	1/10	0.0003/0.003
Sugar Substitutes			1/10		
Sweet Sauces	400/1000		2/10		0.001/0.01

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)

	Germacrene D ≥85%	*Scutellaria baicalensis* root extract	Lemon seed (*Citrus limon*) oil	10-Hydroxy-4,8-dimethyldec-4-enal	Rebaudioside B 95%
Category/FEMA No.	**4974**	**4975**	**4976**	**4977**	**4978**
Baked Goods	0.5/0.5	200/300	10/100		20/30
Beverages Type I, Non-Alcoholic	0.2/0.2	100/200	5/50	0.5/5	20/30
Beverages Type II, Alcoholic		100/200	5/50	0.5/5	20/30
Breakfast Cereals		200/300	10/100		20/30
Cheeses			5/100		
Chewing Gum	3.4/4.8	100/200		2/20	25/30
Condiments and Relishes		100/200	5/100		20/30
Confections and Frostings		100/200		2/20	20/30
Egg Products		100/200	5/100		
Fats and Oils			5/100		
Fish Products			10/100		
Frozen Dairy		200/300	5/50		20/30
Fruit Ices	0.3/0.3	100/200		0.5/5	20/30
Gelatins and Puddings		100/200			20/30
Granulated Sugar					
Gravies		200/300	10/100		20/30
Hard Candy	0.5/0.5	200/300		1/10	20/30
Imitation Dairy Products		200/300	5/100		20/30
Instant Coffee and Tea		100/200	5/50	0.5/5	20/30
Jams and Jellies		100/200		1/10	20/30
Meat Products		100/200	10/100		
Milk Products		200/300	5/100		20/30
Nut Products		200/400	5/100		20/30
Other Grains		200/300	5/100		20/30
Poultry Products			10/100		
Processed Fruits		100/200	5/50		20/30
Processed Vegetables		100/200	10/100		
Reconstituted Vegetable Protein		200/400	10/100		
Seasonings and Flavors		300/500	10/100		20/30
Snack Foods		100/200	10/100		20/30
Soft Candy		200/300		1/10	20/30
Soups		200/300	10/100		20/30
Sugar Substitutes		200/300			
Sweet Sauces		200/400			20/30

TABLE 2 Continued - Average Usual Use Levels/Average Maximum Use Levels

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

	2-(Furan-2-yl)-4,6-dimethyl-1,3,5-dithiazinane	Mixture of (8Z,11Z)- heptadeca-8,11-dienal and (Z)-heptadec-8-enal
Category/FEMA No.	**4979**	**4980**
Baked Goods	0.0025/0.005	0.2/0.5
Beverages Type I, Non-Alcoholic	0.0001/0.005	0.02/0.05
Beverages Type II, Alcoholic	0.0002/0.005	0.02/0.05
Breakfast Cereals		
Cheeses		0.2/0.5
Chewing Gum		
Condiments and Relishes	0.0001/0.0025	
Confections and Frostings	0.0001/0.0025	
Egg Products	0.0001/0.0025	0.1/0.3
Fats and Oils		0.2/0.5
Fish Products	0.0001/0.0005	
Frozen Dairy	0.001/0.005	
Fruit Ices	0.0001/0.0005	
Gelatins and Puddings	0.0001/0.0005	
Granulated Sugar		
Gravies	0.0001/0.001	0.2/0.5
Hard Candy	0.002/0.005	0.05/0.2
Imitation Dairy Products	0.002/0.005	
Instant Coffee and Tea	0.0001/0.005	
Jams and Jellies		
Meat Products	0.0001/0.005	0.1/0.3
Milk Products	0.0001/0.005	
Nut Products	0.0001/0.005	
Other Grains		
Poultry Products	0.0001/0.001	0.1/0.3
Processed Fruits		
Processed Vegetables		0.05/0.2
Reconstituted Vegetable Protein	0.001/0.005	0.05/0.2
Seasonings and Flavors	0.001/0.005	0.1/0.3
Snack Foods	0.0001/0.005	0.05/0.2
Soft Candy	0.0001/0.001	0.05/0.2
Soups	0.0001/0.0005	0.1/0.3
Sugar Substitutes		
Sweet Sauces	0.0001/0.005	

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
[a] represents a change from previous FEMA GRAS publications | [c] represents a correction and errata to previous GRAS publications

	Ethyl palmitate	Oak chips extract (*Quercus alba* L.; *Quercus petraea*)	Tetrahydro-4-methyl-2-(2-methylpropen-1-yl) pyran	*L*-Histidine	*N*-(Heptan-4-yl) benzo[*d*][1,3]dioxole-5-carboxamide
GRAS Publication	**29**	**3**	**4**	**13**	**27**
Category/FEMANo.	**2451**	**2794**	**3236**	**3694**	**4232**
Baked Goods	20/20	72/90	2/4	10/150	1/2
Beverages Type I, Non-Alcoholic	0.02[a]/0.2[a]	550[a]/1000[a]	0.5/0.8	200[a]/200[a]	2/5
Beverages Type II, Alcoholic	0.3/5	1000/1000	1[a]/1[a]		2/5
Breakfast Cereals					
Cheeses					1/3
Chewing Gum	0.1/0.1	115/200	5/10		
Condiments and Relishes					2/4
Confections and Frostings	0.05[a]/0.2[a]			20/150	
Egg Products					2/5
Fats and Oils					2/4
Fish Products					1/3
Frozen Dairy	20/20	52/200[a]	1/2		2[a]/5[a]
Fruit Ices					
Gelatins and Puddings		1[a]/1[a]	1/2		
Granulated Sugar					
Gravies			0.02/0.05		2/4
Hard Candy	40/40	2/200[a]	2/2		
Imitation Dairy Products					2[a]/5[a]
Instant Coffee and Tea	0.1[a]/0.3[a]				2[a]/5[a]
Jams and Jellies					
Meat Products				30/150	1/3
Milk Products				10/150	2[a]/5[a]
Nut Products	3/5				2/5
Other Grains					
Poultry Products					1/3
Processed Fruits					
Processed Vegetables					1/3
Reconstituted Vegetable Protein					2/5
Seasonings and Flavors					5/10
Snack Foods					5/10
Soft Candy		60/200[a]	3/7		
Soups					2/4
Sugar Substitutes					
Sweet Sauces					

TABLE 3 Continued - Updated Average Usual Use Levels/Average Maximum Use Levels

Average Usual Use Levels (ppm)/Average Maximum Use Levels (ppm) for flavoring substances previously recognized as FEMA GRAS
[a] represents a change from previous FEMA GRAS publications | [c] represents a correction and errata to previous GRAS publications

	3-(4-Hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one	Rebaudioside A	Glutamyl-valyl-glycine	Erythritol	*Cordyceps sinensis* fermentation product
GRAS Publication	**26**	**28**	**29**	**29**	**28**
Category/FEMA No.	**4390**	**4601**	**4709**	**4819**	**4878**
Baked Goods	50[a]/150[a]	20[c]/30[c]	15/30		30/50
Beverages Type I, Non-Alcoholic	50[a]/100[a]	20/30	20/50	5,000/25,000[a]	30[a]/1000
Beverages Type II, Alcoholic	15/50	20/30	20/50	5,000/25,000[a]	10[a]/1000
Breakfast Cereals	50[a]/100[a]	20/50[a]	80/160	12,500/25,000[a]	10[a]/100[a]
Cheeses	10/50		20/50		
Chewing Gum		200/200	10/30	5,000[a]/25,000[a]	20[a]/100[a]
Condiments and Relishes	10/100	20/30	30/60	5,000[a]/25,000[a]	1[a]/30[a]
Confections and Frostings	20/100	20/30	15[a]/40[a]	5,000[a]/25,000[a]	1[a]/30[a]
Egg Products			15/45		1[a]/30[a]
Fats and Oils			30/60		
Fish Products			15/45		1[a]/30[a]
Frozen Dairy	10/50	20/30	20/50	12,500/25,000[a]	10[a]/100[a]
Fruit Ices	20/50	20/30	20/50	5,000/25,000[a]	
Gelatins and Puddings	10/100	20/30	15[a]/40[a]	5,000[a]/25,000[a]	
Granulated Sugar	20/100				
Gravies	10/100	20/30	30/60	5,000[a]/25,000[a]	10[a]/100[a]
Hard Candy	20/100	20/30	20[a]/50[a]	5,000[a]/25,000[a]	1[a]/30[a]
Imitation Dairy Products	50[a]/100[a]	20/30	20/50	12,500/25,000[a]	10[a]/150[a]
Instant Coffee and Tea	15/50	20/30	10/30	5,000/25,000[a]	10[a]/150[a]
Jams and Jellies	20/50	20/30	20[a]/50[a]	5,000[a]/25,000[a]	10[a]/100[a]
Meat Products		20/75	15/45		16[a]/40[a]
Milk Products	10/50	20/45[a]	15/45	12,500/25,000[a]	15/100
Nut Products	20/50			12,500/25,000[a]	10[a]/150[a]
Other Grains	50[a]/100[a]			12,500/25,000[a]	50/150
Poultry Products		20/75	15/45		10[a]/150[a]
Processed Fruits	20/50	20/30		5,000/25,000[a]	20[a]/50[a]
Processed Vegetables	20/50	20/30	15/45	5,000[a]/25,000[a]	10[a]/150[a]
Reconstituted Vegetable Protein	50[a]/150[a]		15/45		10[a]/150[a]
Seasonings and Flavors	10/100	20/30	80/160		10[a]/150[a]
Snack Foods	50[a]/100[a]	20/30	80/160		10[a]/150[a]
Soft Candy	20/100	20/30	15[a]/40[a]	5,000[a]/25,000[a]	1[a]/30[a]
Soups	10/100	20/30	20/50	5,000[a]/25,000[a]	10[a]/100[a]
Sugar Substitutes	20/100		80/160		1[a]/30[a]
Sweet Sauces	10/100	20/30	30/60	5,000[a]/25,000[a]	1[a]/30[a]

TABLE 3 Continued - Updated Average Usual Use Levels/Average Maximum Use Levels

Average Usual Use Levels (ppm)/Average Maximum Use Levels (ppm) for flavoring substances previously recognized as FEMA GRAS
[a] represents a change from previous FEMA GRAS publications | [c] represents a correction and errata to previous GRAS publications

	Sodium gluconate
GRAS Publication	**29**
Category/FEMA No.	**4934**
Baked Goods	5,000[a]/20,000[a]
Beverages Type I, Non-Alcoholic	1,500/3,500[a]
Beverages Type II, Alcoholic	1,500/3,500[a]
Breakfast Cereals	2,500/5,000[a]
Cheeses	5,000[a]/20,000[a]
Chewing Gum	10,000[a]/20,000[a]
Condiments and Relishes	2,500[a]/5,000[a]
Confections and Frostings	1,500/2,500
Egg Products	2,500[a]/5,000[a]
Fats and Oils	5,000[a]/10,000[a]
Fish Products	5,000[a]/20,000[a]
Frozen Dairy	1,500/2,500
Fruit Ices	1,500/2,500
Gelatins and Puddings	1,500[a]/2,500[a]
Granulated Sugar	
Gravies	2,500/5,000[a]
Hard Candy	10,000[a]/20,000[a]
Imitation Dairy Products	5,000[a]/10,000[a]
Instant Coffee and Tea	1,500/2,500
Jams and Jellies	1,000/2,500
Meat Products	5,000[a]/20,000[a]
Milk Products	2,500[a]/5,000[a]
Nut Products	2,500/5,000[a]
Other Grains	1,500[a]/5,000[a]
Poultry Products	5,000[a]/20,000[a]
Processed Fruits	1,500/2,500
Processed Vegetables	2,500/5,000[a]
Reconstituted Vegetable Protein	5,000[a]/20,000[a]
Seasonings and Flavors	2,500/20,000[a]
Snack Foods	2,500/5,000[a]
Soft Candy	1,500[a]/2,500[a]
Soups	2,500/5,000[a]
Sugar Substitutes	1,500/3,500[a]
Sweet Sauces	1,500/3,500[a]

TABLE 4 - Identity for Natural Flavor Complexes as Evaluated by the FEMA Expert Panel

FEMA No.	FEMA Primary Name	The Identification Description as Reviewed by the FEMA Expert Panel
4947	Glycosylated stevia extract 40% with 14% Rebaudioside A	35-45% Glucosylated steviol glycosides; 11-17% Rebaudioside A; 8-15% Stevioside; Less than 3% all other individual steviol glycosides; Maltodextrin 23-45%
4949	*Corynebacterium ammoniagenes* fermentation product	20-25% Miscellaneous nitrogen-containing compounds; 2-5% Amino acids; 3-5% Minerals; <7% Carbohydrates typically monosaccharides; 50-55% Dextrins
4950	*Stevia rebaudiana* extract with Rebaudiosides AM and M	Total steviol glycosides >95%, inclusive of 60-75% Rebaudioside AM; 15-20% Rebaudioside M; Other individual rebaudiosides not further glucosylated present at ≤1% individually and 5-10% supraglucosylated rebaudiosides
4951	Glucosylated steviol glycosides 90% supraglucosylated rebaudioside A	Total steviol glycosides >95%, inclusive of 90-94% supraglucosylated rebaudioside A; 1-3% Not further glucosylated rebaudioside A; Trace amounts of other supraglucosylated individual rebaudiosides; <4% Dextrins
4952	Glucosylated steviol glycosides 91% supraglucosylated rebaudioside D	Total steviol glycosides >95%, inclusive of 91-95% supraglucosylated rebaudioside D; 1-4% Supraglucosylated rebaudioside A; 2-4% Not further glucosylated rebaudioside D; Trace amounts of other supraglucosylated individual rebaudiosides; <3% Dextrins
4953	Glucosylated steviol glycosides 58% supraglucosylated stevioside	Total steviol glycosides >95%, inclusive of 58-61% supraglucosylated stevioside; 24-35% Supraglucosylated rebaudioside A, 12-16% Supraglucosylated rebaudioside C; 1-2% Supraglucosylated rebaudioside D; Trace amounts of other supraglucosylated individual rebaudiosides; <4% Not further glucosylated stevioside; <2% Other not further glucosylated steviosides, individually; <3% Dextrins
4954	Blue agave inulin (*Agave tequilana*)	Derived from *Agave tequilana*, blue agave inulin (*Agave tequilana*) is measured as inulin >90%; Mono- and disaccharides typically fructose, glucose and sucrose <10%.
4955	*Emblica officinalis* fruit extract	Derived from the *Emblica officinalis* fruit, *Emblica officinalis* fruit extract is measured as no more than 20% phenols derivatives typically gallic acid and gallic acid esters; 7% Lactones typically mucic acid lactone and ascorbate; 3% Aliphatic carboxylic acids with additional oxygenated functional groups; 60% Carbohydrates and no more than 5% ash
4956	*Boehmeria nivea* leaf extract	Derived from the leaves of *Boehmeria nivea*, *Boehmeria nivea* leaf extract is an ethanolic extract and is measured as 45-60% carbohydrates, 8-15% protein and 5-10% fat.
4957	Rebaudioside M 85%	Total steviol glycosides >95%, inclusive of Rebaudioside M ≥85%; Rebaudioside D 3-12% and other individual steviol glycosides not further glucosylated each less than 1%
4962	*Lepidium meyenii* root extract	Derived from the root of *Lepidium meyenii* or *L. peruvianum*, *Lepidium meyenii* root extract is measured as no more than 2% total macamides; 10-20% Soluble polysaccharides; 10-15% Simple carbohydrates suspended in 75% glycerol
4963	Pandan leaf (*Pandanus amaryllifolius*) distillate extract	Derived from the leaves of *Pandanus amaryllifolius*, pandan leaf (*Pandanus amaryllifolius*) distillate extract is measured as less than 0.05% pyrroline derivatives suspended in an appropriate food grade solvent
4964	*Corynebacterium glutamicum* cell free fermentation product	No more than 30% glutamic acid; Up to 10% simple carbohydrates; Less than 5% sum of other individual amino acids; No more than 60% dextrins
4968	*Stevia rebaudiana* extract with Rebaudioside M ≥90%	Total steviol glycosides >95%, inclusive of Rebaudioside M ≥90%; other rebaudiosides not further glucosylated present at ≤4% individually
4969	Yerba mate extract (*Ilex paraguariensis* A. St.-Hil.)	Derived from *Ilex paraguariensis* A. St.-Hil., yerba mate extract (*Ilex paraguariensis* A. St.-Hil.) is measured as >95% dicaffeoylquinic acids, chlorogenic acid and its related positional and stereoisomer as well as other related caffeic and quinic acid derivatives; <0.05% Caffeine
4975	*Scutellaria baicalensis* root extract	Derived from the root of *Scutellaria baicalensis*, *Scutellaria baicalensis* root extract is measured as a 1% solution in propylene glycol, with the flavonoids baicalin, baicalein, wogonin and oroxylin A each present at <1%
4976	Lemon seed *(Citrus limon)* oil	Derived from the seeds of *Citrus limon*, lemon seed *(Citrus limon)* oil is measured as total fat as triglycerides ≥95%, inclusive of approximately 40-45% of linoleic and linolenic acids, approximately 30-35% of oleic acid and 15-20% of palmitic and stearic acids; Total volatile content of approximately 5%, inclusive of <2% each of: Saturated aliphatic, acyclic, linear primary alcohols, aldehydes, carboxylic acids and related esters; Aliphatic linear and branched-chain alpha, beta-unsaturated aldehydes and related alcohols acids and esters; Aliphatic and aromatic hydrocarbons

Supplementary Information. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 30

Since its initial publication of GRAS (Generally Recognized As Safe) determinations for flavor ingredients (Hall and Oser, 1965), the FEMA Expert Panel has made available information on its determinations, including conditions of intended use for individual flavor ingredients, and the scientific basis and information supporting these determinations. Included herein are the key findings for each of the new GRAS determinations included within GRAS 30. Comprehensive monographs of the information relevant to the evaluations are also published as part of the FEMA Expert Panel's ongoing GRAS re-evaluation program (see Hallagan and Hall, 2009; Hallagan et al., 2020). For more information on the FEMA GRAS program, please see "About the FEMA GRAS Program" on femaflavor.org.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding decanedioic acid (CAS 111-20-6) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4943) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups. (JECFA, 2000; SLR, B1D). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of decanedioic acid from use as a flavor ingredient to be 69 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The substance occurs naturally in beer, clover honey (*Trifolium Repens*), honey of leptospermum species (*Manuka* and *Kanuka*), leatherwood honey (*Eucryphia Lucida*), thistle honey (*Carduus Nutans*), thyme honey (*Thymus vulgaris*), willow honey (*Salix* species), wort, pork fat (Van Dongen and Donders, 2021). Based on the quantitative data, a consumption ratio of 12 could be calculated (Stofberg and Grundschober, 1987). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that decanedioic acid will undergo *beta*-oxidative cleavage and complete metabolism to CO_2 via the fatty acid pathway and the citric acid cycle (Smith et al., 2018). No increases in the frequency of revertant colonies were observed in an Ames assay for decanedioic acid in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 as well as *Escherichia coli* strain WP2 *uvr*A in the presence and absence of S9 metabolic activation (Shimizu et al., 1985). In an Ames assay with the structurally related substance adipic acid (FEMA 2011), there were no increases in the frequency of revertant colonies in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538, as well as *E. coli* strain WP2 *uvr*A either in the absence and presence of S9 metabolic activation (Kubo et al., 2002; Prival et al., 1991; Shimizu et al., 1985). In an OECD guideline 476- and GLP-compliant *in vitro* mammalian cell gene mutation assay for the same structural relative in V79 Chinese hamster lung cells, there were no significant increases in mutant frequency at the HPRT locus in the presence and absence of S9 metabolic activation (ECHA, 2009a). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional group therein, the Expert Panel did not identify specific concerns related to the genotoxicity of decanedioic acid (Gooderham et al., 2020). No reproductive or developmental toxicity effects were reported in female rats administered the structural relative adipic acid (FEMA 2011) by gavage at doses up to 288 mg/kg bw/day from gestation days 6-15 (Morgareidge, 1973). In developmental toxicity studies in female rats and female rabbits, the structural relative nonanedioic acid (CAS 123-99-9) was provided in the diet at levels of 140 and 200 mg/kg bw/day, respectively, through pregnancy. No reproductive or developmental effects were observed (Mingrone et al., 1983). In 90- and 180-day dietary studies, no toxicologically significant clinical observations were reported for male and female Wistar rats or male and female New Zealand rabbits provided the structural relative nonanedioic acid (CAS 123-99-9) in the diet at levels up to 140 and 280 mg/kg bw/day for rats or 200 mg/kg bw/day and 400 mg/kg bw/day for rabbits, respectively (Mingrone et al., 1983). In a 2-year dietary toxicity study, male and female albino rats were administered the structural relative adipic acid (FEMA 2011) at dietary levels of approximately 75, 750, 2250 and 3750 mg/kg bw/day (Horn et al., 1957). Body weight gains in the top two dose groups were significantly less during the rapid growth period. The no observed adverse effect level (NOAEL) was concluded by the Expert Panel to be 750 mg/kg bw/day based on the slight body weight reductions in the 2250 and 3750 mg/kg bw/day treatment groups. This NOAEL is greater than 650,000 times the daily *per capita* intake of decanedioic acid from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding *trans*-2-dodecenedioic acid (CAS 6402-36-4) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4944) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups (JECFA, 2000; SLR, B1D). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of *trans*-2-dodecenedioic acid from use as a flavor ingredient to be 14 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. *trans*-2-Dodecenedioic acid is anticipated to undergo *beta*-oxidative cleavage and complete metabolism to CO_2 via the fatty acid pathway and the citric acid cycle (Smith et al., 2018). No increases in the frequency of revertant colonies were observed for the structural relative, decanedioic acid (FEMA 4943) in an Ames assay conducted in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and *E. coli* strain WP2 *uvr*A in the presence and absence of S9 metabolic activation (Shimizu et al., 1985). In an Ames assay with the structural relative adipic acid (FEMA 2011), there were no increases in the frequency of revertant colonies in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 as well as in *E. coli* strain WP2 *uvr*A either in the absence and presence of S9 metabolic activation (Kubo et al., 2002; Prival et al., 1991; Shimizu et al., 1985). In an OECD guideline 476 and GLP-compliant *in vitro* mammalian cell gene mutation assay for the same structural relative in V79 Chinese hamster lung cells, there were no significant increases in mutant frequency at the HPRT locus in the presence and absence of S9 metabolic

activation (ECHA, 2009a). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional group therein, the Panel did not identify specific concerns related to the genotoxicity of *trans*-2-dodecenedioic acid (Gooderham et al., 2020). No reproductive or developmental toxicity effects were reported in female rats administered the structural relative adipic acid (FEMA 2011) by gavage at doses up to 288 mg/kg bw/day from gestation days 6-15 (Morgareidge, 1973). In developmental toxicity studies in female rats and female rabbits, the structural relative nonanedioic acid (CAS 123-99-9) was provided in the diet at levels of 140 and 200 mg/kg bw/day, respectively, through pregnancy. No reproductive or developmental effects were observed (Mingrone et al., 1983). In 90- and 180-day dietary studies, no toxicologically significant clinical observations were reported for male and female Wistar rats or male and female New Zealand rabbits administered the structural relative nonanedioic acid (CAS 123-99-9) at doses up to 140 and 280 mg/kg bw/day for rats or 200 mg/kg bw/day and 400 mg/kg bw/day for rabbits, respectively (Mingrone et al., 1983). In a 2-year dietary toxicity study, male and female albino rats were administered the structural relative adipic acid (FEMA 2011) at dietary levels of approximately 75, 750, 2250 and 3750 mg/kg bw/day (Horn et al., 1957). Body weight gains in the top two dose groups were significantly less during the rapid growth period. The NOAEL was concluded by the Expert Panel to be 750 mg/kg bw/day based on the slight body weight reductions in the 2250 and 3750 mg/kg bw/day treatment groups. This NOAEL is greater than 3,200,000 times the daily *per capita* intake of *trans*-2-dodecenedioic acid from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding *cis*-8-decenal (CAS 174155-46-5) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4945) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of unsaturated linear and branched-chain aliphatic, non-conjugated aldehydes, related primary alcohols, carboxylic acids and esters (JECFA, 1999, 2012, 2020; SLR, M1). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of *cis*-8-decenal from use as a flavor ingredient to be 0.007 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. *cis*-8-Decenal is anticipated to be oxidized to the corresponding unsaturated carboxylic acid. The *cis* double bond is isomerized to the *trans* double bond by 3-hydroxyacyl-CoA epimerase before re-entering the fatty acid cycle where it is converted to acetyl-CoA. The acetyl-CoA product then enters the citric acid cycle where it is metabolized to yield CO_2 and water (Smith et al., 2018; Nelson and Cox, 2008). In an OECD 471 guideline and GLP-compliant Ames assay with the structurally related substance 10-undecenal (FEMA 3095), there were no increases in the frequency of revertant colonies in *S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 in the absence or presence of S9 metabolic activation (Bhatia et al., 2010; Sokolowski, 2007a). In an *in vivo* micronucleus assay in male and female NMRI mice, gavage administration at doses up to 2000 mg/kg bw of the same structural relative produced no statistically significant increases in the frequency of micronuclei (Bhatia et al., 2010; Honarvar, 2007). Similar results in the OECD 471 guideline and GLP-compliant Ames assay and the OECD 474 guideline and GLP-compliant *in vivo* mouse micronucleus test were also reported for the structural relative *trans*-4-decen-1-al (FEMA 3264) (Bhatia et al., 2010; Honarvar, 2008; Sokolowski, 2007b). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of *cis*-8-decenal (Gooderham et al., 2020). An OECD 408 guideline and GLP-compliant90-day dietary toxicity study for structural relative 10-undecenal (FEMA 3095) in male and female Sprague-Dawley Crl:CD® (SD) IGS BR rats resulted in a NOAEL of 200 ppm, or approximately 14.3 mg/kg bw/day (Liwska and Watson, 2012), which is greater than 120,000,000 times the anticipated daily *per capita* intake of *cis*-8-decenal from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 2-amino-2-deoxy-poly-D-glucosamine (CAS 9012-76-4) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4946) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of aliphatic poly-hydroxy compounds and derivatives (SLR, B1F). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of 2-amino-2-deoxy-poly-D-glucosamine from use as a flavor ingredient to be 3459 µg/person/day, which is above the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The substance occurs naturally in white button mushrooms and baker's yeast (Christodoulidou et al., 1996; Ghormade et al., 2017; Kannan et al., 2010). Based on the quantitative data, a consumption ratio of 737 could be calculated (Stofberg and Grundschober, 1987). The Expert Panel noted the assay of the material was >91% of the named material with water as the secondary component (6-7%) and considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). It is presumed that 2-amino-2-deoxy-poly-D-glucosamine is not subject to digestion via human digestive enzymes and is not absorbed. The substance is expected to travel intact throughout the upper gastrointestinal tract to the colon, where the material would be subject to fermentation by the endogenous microbiota population. Microbial fermentation would result in the production of normal metabolites of fermentation that include the production of short-chain fatty acids, water, carbon dioxide and methane gas (Lattimer and Haub, 2010). No increases in the frequency of revertant colonies were observed in an Ames assay for 2-amino-2-deoxy-poly-D-glucosamine conducted in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, as well as *E. coli* WP2(pKM101) in either the absence or presence of metabolic activation (FDA, 2011). In another

Ames assay in *S. typhimurium* strains TA97, TA98, TA100, and TA102, 2-amino-2-deoxy-poly-D-glucosamine oligomers did not increase the frequency of revertant colonies in either the absence or presence of S9 metabolic activation (Qin et al., 2006). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 2-amino-2-deoxy-poly-D-glucosamine (Gooderham et al., 2020). In a developmental toxicity study, 2-amino-2-deoxy-poly-D-glucosamine was administered at daily doses of 480 mg/kg bw/day for 4 days to B6C3F1 female mice that were induced to ovulate (Choi et al., 2002). Treatment increased the number of ovulated oocytes and normal oocytes, as well as the *in vivo* and *in vitro* fertilization rates, compared to controls in animals fed a high-fat diet. In a 28-day toxicity study, Wistar rats were administered lobster-derived chitosan (approximately 309 kDa, with a degree of deacetylation of 83%; this material was considered by the Expert Panel to be compositionally equivalent to 2-amino-2-deoxy-poly-D-glucosamine) by gavage at doses of 0, 100, 300, or 1000 mg/kg bw/day (Lagarto et al., 2015). A statistically significant increase in erythrocyte count was reported in females in the 300 and 1000 mg/kg bw/day groups and in males in the 1000 mg/kg bw/day group compared to controls. The authors concluded that the NOAEL was 1000 mg/kg bw/day, noting that the findings of increased erythrocyte count were considered unreliable due to the short-term duration of the study, and no correlated erythrocyte turnover was reported in the long-term study conducted in Sprague-Dawley rats by the National Toxicology Program (NTP). In a 6-month feeding study conducted by the NTP, male and female Sprague-Dawley rats were administered feed containing 0, 1, 3, or 9% 2-amino-2-deoxy-poly-D-glucosamine (approximately 81.6 kDa, with 86.5% deacetylation, considered by the Expert Panel to be low molecular weight chitosan), approximately 450, 1,500, or 5,200 mg/kg bw/day in males and 650, 1,800, or 6,000 mg/kg bw/day in females, respectively (NTP, 2017). The NTP concluded that dietary exposure to 2-amino-2-deoxy-poly-D-glucosamine for 6 months resulted in decreased fat digestion and depletion of some fat-soluble vitamins in male and female rats, and accordingly, reported that "the lowest observed effect level for chitosan was 1% (approximately equivalent to 450 mg/kg) in males and 9% (approximately equivalent to 6,000 mg/kg) in female rats." The Panel reviewed the data and determined that the thymus weight change in the 9% females was a biologically relevant effect. Therefore, the Panel determined that the lowest observed effect level (LOEL) for female rats was 3% (approximately equivalent to 1,800 mg/kg bw/day). These effects are considered as indirect consequences of the recognized fat binding properties of 2-amino-2-deoxy-poly-D-glucosamine, resulting in excretion of dietary fat and reduced absorption of fat-soluble vitamins, and as such were not direct toxic effects of chitosan on organ systems. The effects of 2-amino-2-deoxy-poly-D-glucosamine on fat absorption are considered an expected finding and are not of nutritional or toxicological significance. In a 52-week dietary administration chronic toxicity study, F344 rats were fed the constituent *N*-acetyl-D-glucosamine at concentrations of 1.25%, 2.5% or 5% (approximately 580, 1,159 and 2,323 mg/kg bw/day in males and 647, 1,269 and 2,545 mg/kg bw/day in females, respectively) (Takahashi et al., 2009). Body weights were slightly but statistically significantly decreased in 5% males. The slight suppression of body weights was considered by the authors to relate to reductions in caloric intake due to the high levels of intake of the test article and not a direct toxic effect. The NOAEL was concluded to be 5% in the diet in both studies, equivalent to 2,323 and 2,545 mg/kg bw/day in males and females, respectively. In a carcinogenicity study, F344 rats were fed the structural relative *N*-acetyl-D-glucosamine at concentrations of 2.5%, or 5% in the diet for 104 weeks (approximately 964 and 1,935 mg/kg bw/day in male rats and 1,106 and 2,244 mg/kg bw/day in female rats, respectively) (Takahashi et al., 2009). The NOAEL was concluded to be 5% in the diet, equivalent to 1,935 and 2,244 mg/kg bw/day in males and females, respectively. The NOAEL of 1,935 mg/kg bw/day is greater than 33,000 times the anticipated daily *per capita* intake of 2-amino-2-deoxy-poly-D-glucosamine from use as a flavor ingredient.

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

approximately 89.5 mg/kg bw/day of rebaudioside A (Yamada et al., 1985), which are greater than 78,500 times or 12,700 times the anticipated daily *per capita* intake of glucosylated stevia extract powder 40% rebaudioside A 14% from use as a flavor ingredient, respectively.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 2-hexylpyridine (CAS 1129-69-7) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4948) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of nitrogen containing heterocyclic and heteroaromatic substances (JECFA, 2006, 2012; SLR, D3). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of 2-hexylpyridine from use as a flavor ingredient to be 0.3 µg/person/day, which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). This substance occurs naturally in roasted chicken, lamb, and mutton fats (Van Dongen and Donders, 2021), but only qualitative data is available, and thus no consumption ratio can be calculated. The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that 2-hexylpyridine will undergo metabolism via oxidation of the side chain, and these oxidized products can form glucuronic acid conjugates and be excreted or further oxidized to ultimately result in a carboxylic acid via *beta*-oxidation that would be conjugated with glycine and excreted in the urine (Hawksworth and Scheline, 1975). In an alternative metabolic pathway, oxidation of the pyridine nitrogen would occur, and the corresponding oxide would be expected to be eliminated in the urine (Gorrod and Damani, 1980; Jakoby et al., 1982; Nguyen et al., 1988). In an OECD 471 guideline and GLP-compliant Ames assay in *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537, 2-hexylpyridine did not increase the frequency of revertant colonies either in the absence or presence of S9 metabolic activation (Vashi, 2019a). The Expert Panel reviewed their prior assessment of the genotoxicity data for the structural relative pyridine (FEMA 2966) and determined it sufficient to indicate a lack of genotoxic concern for 2-hexylpyridine (Smith et al., 2011). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 2-hexylpyridine (Gooderham et al., 2020). As described in the Expert Panel's prior assessment of the structural relative pyridine (FEMA 2966), a NOAEL of 5 mg/kg bw/day was determined from NTP studies conducted with F344/N rats and B6C3F1 mice of both sexes (NTP, 2000; Smith et al., 2011). This NOAEL is greater than 1,000,000 times the anticipated daily *per capita* intake of 2-hexylpyridine from use as a flavor ingredient.

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

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding *Stevia rebaudiana* extract with rebaudiosides AM and M and concluded that the use of the

substance as a flavor ingredient is GRAS (FEMA 4950) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of *Stevia rebaudiana* extract with rebaudiosides AM and M from use as a flavor ingredient to be 1384 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This material is derived from the leaves of *Stevia rebaudiana*. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). Metabolic data exist that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Cardoso et al., 1996; Gardana et al., 2003; Geuns et al., 2003; Geuns et al., 2007; Hutapea et al., 1997; Koyama et al., 2003a; Koyama et al., 2003b; Nakayama et al., 1986; Purkayastha et al., 2014; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha and Kwok, 2020; Renwick and Tarka, 2008; Roberts and Renwick, 2008; Roberts et al., 2016; Wheeler et al., 2008; Wingard, 1980). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in *in vitro* mutagenicity assays, *in vivo* studies do not provide evidence of genotoxic effects (Nakajima, 2000; Pezzuto et al., 1985, 1986; Rumelhard et al., 2016; Suttajit et al., 1993; Terai et al, 2002; Williams and Burdock, 2009). Based on the results for the various steviol glycosides, the Expert Panel did not identify specific concerns related to the potential genotoxicity of *Stevia rebaudiana* extract with rebaudioside AM and M (Gooderham et al., 2020). In a 108-week carcinogenicity study for stevioside, no carcinogenic effects were observed (Toyoda et al., 1997). In a 2-year feeding study, male and female rats were administered the equivalent of 0, 50, 150, or 550 mg/kg bw/day of a stevia extract comprised of 74% stevioside and 16% rebaudioside A. The authors considered the NOAEL from this 2-year rat feeding study of a stevia extract to be equal to 550 mg/kg bw/day (Yamada et al., 1985), which is greater than 23,800 times the anticipated daily per capita intake of the anticipated daily per capita intake of *Stevia rebaudiana* extract with rebaudioside AM and M from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding glucosylated steviol glycosides 90% supraglucosylated rebaudioside A and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4951) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of glucosylated steviol glycosides 90% supraglucosylated rebaudioside A from use as a flavor ingredient to be 1384 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This material is derived from the leaves of *Stevia rebaudiana*. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). Metabolic data exist that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Cardoso et al., 1996; Gardana et al., 2003; Geuns et al., 2003; Geuns et al., 2007; Hutapea et al., 1997; Koyama et al., 2003a; Koyama et al., 2003b; Nakayama et al., 1986; Purkayastha et al., 2014; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha and Kwok, 2020; Renwick and Tarka, 2008; Roberts and Renwick, 2008; Roberts et al., 2016; Wheeler et al., 2008; Wingard, 1980). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in *in vitro* mutagenicity assays, *in vivo* studies do not provide evidence of genotoxic effects (Nakajima, 2000; Pezzuto et al., 1985, 1986; Rumelhard et al., 2016; Suttajit et al., 1993; Terai et al, 2002; Williams and Burdock, 2009). Based on the results for the various steviol glycosides, the Expert Panel did not identify specific concerns related to the potential genotoxicity of glucosylated steviol glycosides 90% supraglucosylated rebaudioside A (Gooderham et al., 2020). In a 108-week carcinogenicity study for stevioside, no carcinogenic effects were observed (Toyoda et al., 1997). In a 2-year feeding study, male and female rats were administered the equivalent of 0, 50, 150, or 550 mg/kg bw/day of a stevia extract comprised of 74% stevioside and 16% rebaudioside A. The authors considered the NOAEL from this 2-year rat feeding study of a stevia extract to be equal to 550 mg/kg bw/day, or approximately 89.5 mg/kg bw/day of rebaudioside A (Yamada et al., 1985), which is greater than 23,800 times or 3800 times, respectively, the anticipated daily *per capita* intake of glucosylated steviol glycosides 90% supraglucosylated rebaudioside from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding glucosylated steviol glycosides 91% supraglucosylated rebaudioside D and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4952) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of glycosylated steviol glycosides 91% supraglucosylated rebaudioside D from use as a flavor ingredient to be 692 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This material is derived from the leaves of *Stevia rebaudiana*. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel

evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). Metabolic data exist that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Cardoso et al., 1996; Gardana et al., 2003; Geuns et al., 2003; Geuns et al., 2007; Hutapea et al., 1997; Koyama et al., 2003a; Koyama et al., 2003b; Nakayama et al., 1986; Purkayastha et al., 2014; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha and Kwok, 2020; Renwick and Tarka, 2008; Roberts and Renwick, 2008; Roberts et al., 2016; Wheeler et al., 2008; Wingard, 1980). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in *in vitro* mutagenicity assays, *in vivo* studies do not provide evidence of genotoxic effects (Nakajima, 2000; Pezzuto et al., 1985, 1986; Rumelhard et al., 2016; Suttajit et al., 1993; Terai et al, 2002; Williams and Burdock, 2009). Based on the results for the various steviol glycosides, the Expert Panel did not identify specific concerns related to the potential genotoxicity of glycosylated steviol glycosides 91% supraglucosylated rebaudioside D (Gooderham et al., 2020). In a 108-week carcinogenicity study for stevioside, no carcinogenic effects were observed (Toyoda et al., 1997). In a 2-year feeding study, male and female rats were administered the equivalent of 0, 50, 150, or 550 mg/kg bw/day of a stevia extract comprised of 74% stevioside and 16% rebaudioside A. The authors considered the NOAEL from this 2-year rat feeding study of a stevia extract to be equal to 550 mg/kg bw/day (Yamada et al., 1985), which is greater than 47,600 times the anticipated daily *per capita* intake of glucosylated steviol glycosides 91% supraglucosylated rebaudioside D from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding glucosylated steviol glycosides 58% supraglucosylated stevioside and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4953) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of glucosylated steviol glycosides 58% supraglucosylated stevioside from use as a flavor ingredient to be 2076 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This material is derived from the leaves of *Stevia rebaudiana*. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). Metabolic data exist that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Cardoso et al., 1996; Gardana et al., 2003; Geuns et al., 2003; Geuns et al., 2007; Hutapea et al., 1997; Koyama et al., 2003a; Koyama et al., 2003b; Nakayama et al., 1986; Purkayastha et al., 2014; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha and Kwok, 2020; Renwick and Tarka, 2008; Roberts and Renwick, 2008; Roberts et al., 2016; Wheeler et al., 2008; Wingard, 1980). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in *in vitro* mutagenicity assays, *in vivo* studies do not provide evidence of genotoxic effects (Nakajima, 2000; Pezzuto et al., 1985, 1986; Rumelhard et al., 2016; Suttajit et al., 1993; Terai et al, 2002; Williams and Burdock, 2009). Based on the results for the various steviol glycosides, the Expert Panel did not identify specific concerns related to the potential genotoxicity of glucosylated steviol glycosides 58% supraglucosylated stevioside. (Gooderham et al., 2020). In a 108-week carcinogenicity study for stevioside, no carcinogenic effects were observed (Toyoda et al., 1997). In a 2-year feeding study, male and female rats were administered the equivalent of 0, 50, 150, or 550 mg/kg bw/day of a stevia extract comprised of 74% stevioside and 16% rebaudioside A. The authors considered the NOAEL from this 2-year rat feeding study of a stevia extract to be equal to 550 mg/kg bw/day, or approximately 89.5 mg/kg bw/day of rebaudioside A (Yamada et al., 1985), which is greater than 15,800 times or 2,500 times, respectively, the anticipated daily *per capita* intake of glucosylated steviol glycosides 58% supraglucosylated stevioside from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding blue agave inulin (*Agave tequilana*) (CAS 9005-80-5) and concluded that use of the substance as a flavor adjuvant is GRAS (FEMA 4954) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated individually with the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of blue agave inulin (*Agave tequilana*) from use as a flavor ingredient to be 138 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). Blue agave inulin is isolated from *Agave tequilana*. However, no consumption ratio can be calculated. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. Inulin is classified as a source of dietary fiber, however, at the use levels specified in the GRAS application, its use as a flavor adjuvant is non-nutritive. The Expert Panel concluded that metabolic data exist for a representative member of the principle congeneric group that indicate, in the context of anticipated levels of intake, that the group would be expected to be metabolized primarily by well-established metabolic pathways to innocuous products (Lopez et al., 2003). No increases in the frequency of revertant colonies were observed in an Ames assay for inulin conducted in *S. typhimurium* strains TA98, TA100 and TA102 in the presence and absence of S9 metabolic activation (Márquez-Aguirre et al., 2013). However, this study does not conform to standardized test guidelines, as it did not include at least five *S. typhimurium* tester strains and was not conducted up to a maximum concentration of 5 mg/plate as recommended for non-toxic substances. In *in vivo* chromosomal aberration and micronucleus assays, groups of

male Hsd:ICR mice (4-5 weeks old) received intraperitoneal injections of two commercial blue agave fructans at concentrations of 143, 357.5 or 715 mg/kg bw (Gracia et al., 2013). In the chromosomal aberration test, the number of bone marrow cells with deletions, fragments, translocations or gaps was not significantly increased among the blue agave fructans treated animals compared to the negative controls. In the micronucleus assay, the mean frequency of micronucleated cells in femoral bone marrow was not significantly increased by treatment with the blue agave fructans at any concentration compared to the negative control counts. Given the chemical and physiological similarities of inulins [average degree of polymerization (DP)>10, range 2-60], oligofructose (average DP 4-5, range 2-8) and a commercial preparation of short-chain fructooligosaccharides (FOS), the toxicological studies conducted with FOS are considered to be predictive of the effects of inulin and oligofructose in demonstrating safety (Carabin and Flamm, 1999). No increases in the frequency of revertant colonies were observed in an Ames assay for FOS (average DP 3.5, range 2-4) conducted in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538, as well as in *E. coli* strain WP2 uvrA either in the presence or absence of S9 metabolic activation (Clevenger et al., 1988), FOS were negative in a mouse lymphoma forward mutation assay in L5178Y tk +/- mouse lymphoma cells when tested up to 5000 µg/mL and when tested in an unscheduled DNA synthesis assay in HeLa cells up to 51,200 µg/mL (Clevenger et al., 1988). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of blue agave inulin (*Agave tequilana*) (Gooderham et al., 2020). Administration of 20% short-chain FOS to pregnant female Wistar rats through the diet from gestation day 1-21 showed no adverse effects (Carabin and Flamm, 1999). Reduced body weight gain was noted in the treated females, though this was concluded to be due to reduced caloric value, decreased intake of food or increased diarrhea and/or soft stools in the second and third weeks of the study. Despite the reduction in body weights for treated pregnant females, the fetuses and newborn weights were not affected. In a separate study, no reproductive or developmental effects were reported for Clr CD (SD)BR rats pretreated with a short-chain FOS-supplemented diet at a concentration of 4.75% from post-coital day 0 to 6 in an attempt to avoid the diarrhea observed in the previous study, and 5, 10, or 20% short-chain FOS from days 6-15 (Carabin and Flamm, 1999). In a chronic/carcinogenicity study, male and female Fischer 344 rats were administered diets containing FOS at concentrations of 0, 8,000, 20,000 or 50,000 ppm for 104 weeks (Clevenger et al., 1988). The authors concluded that FOS did not affect the incidence of tumors in F-344 rats and that FOS lacks carcinogenic potential. However, the Panel concluded that an increase in uric acid in the female 8,000 ppm group was a significant effect, and therefore determined the LOAEL to be 8,000 ppm, or 341 mg/kg bw/day. No adverse clinical effects were observed in an acute toxicity study when male Balb/c mice were administered single gavage doses of blue agave fructans at concentrations of 175, 500, 1750 and 5000 mg/kg bw, or when groups of male and female Hsd:ICR mice were administered by gavage one of two different blue agave preparations at concentrations from 17.5-5000 mg/kg bw (Gracia et al., 2013; Márquez-Aguirre et al., 2013). No evidence of toxicity was found when six to seven-week old male Wistar rats were fed a dietary mixture of FOS at 5% or 10% *ad libitum* for six weeks (Carabin and Flamm, 1999). No treatment-related toxicity was noted in a study where male Wistar rats were administered FOS by gavage daily at concentrations of 1500, 3000, or 4500 mg/kg bw/day for six weeks (Carabin and Flamm, 1999). The authors assigned a NOAEL of 4500 mg/kg bw/day which is greater than 1,900,000 times the anticipated daily *per capita* intake of blue agave inulin (*Agave tequilana*) from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding *Emblica officinalis* fruit extract (CAS 90028-28-7) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4955) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of *Emblica officinalis* fruit extract from use as a flavor ingredient to be 346 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). *Emblica officinalis* is known as Indian Gooseberry, the fruits of which are edible. However, no qualitative data are available and thus no consumption ratio can be calculated. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. For a closely related botanical extract of *Emblica officinalis*, no mutagenic potential was reported an Ames assay in *S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 and *E. coli* WP2 *uvr*A tested with concentrations of 5-5000 µg/plate in the presence and absence of S9 metabolic activation (FDA, 2013). In a chronic toxicity study, groups of Sprague-Dawley rats were administered *Emblica officinalis* fruit extract that was standardized to 20% gallic acid by aqueous gavage at concentrations of 300, 600, and 1200 mg/kg bw/day for 270 consecutive days (Jaijoy et al., 2010). A recovery group of male and female rats received 1200 mg/kg bw/day of *Emblica officinalis* fruit extract and were maintained for an additional 28 days without treatment to assess the reversibility of any potential effects. There was a significant decrease in body weights and body weight gains for all of the test group rats on day 270, however, the recovery group at termination showed body weighs comparable to controls. The Expert Panel noted that if the decrease in body weights is not biologically relevant. The NOAEL of 1200 mg/kg bw/day is greater than 208,000 times the anticipated daily per capita intake of *Emblica officinalis* fruit extract from use as a flavor ingredient, and if the LOAEL of 300 mg/kg bw/day is used, it is greater than 52,000 times the daily per capita intake of *Emblica officinalis* fruit extract from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding *Boehmeria nivea* leaf extract (CAS 2246379-81-5) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4956) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor

complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of *Boehmeria nivea* leaf extract from use as a flavor ingredient to be 70 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). Metabolic data exist for a representative member of the principal identified congeneric groups that would predict, at the intake levels proposed, that the groups would be metabolized primarily by well-established detoxication pathways to innocuous products or to be excreted as such (Smith et al., 2018). In an OECD 471 guideline and GLP-compliant Ames assay in *S. typhimurium* strains TA1537, TA1535, TA98, TA100 and TA102, *Boehmeria nivea* leaf extract did not increase the frequency of revertant colonies in either the presence or absence of S9 metabolic activation (Tekale, 2018b). In an Ames assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 the constituent compound, betaine monohydrate (FEMA 4223), did not increase the frequency of revertant colonies in the absence or presence of S9 metabolic activation (Asquith et al., 1989a). An *in vivo* mouse micronucleus study with the constituent compound betaine monohydrate (FEMA 4223) was negative at dose levels up to 2,000 mg/kg bw (Asquith et al., 1989b). In an *in vitro* human lymphocyte assay the constituent compound betaine monohydrate (FEMA 4223) was not clastogenic at concentrations up to 10,000 µg/mL (Asquith et al., 1989c). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of *Boehmeria nivea* leaf extract (Gooderham et al., 2020). No signs of developmental toxicity were observed when rats and rabbits were fed diets containing the constituent compound nonanedioic acid (CAS 123-99-9) at concentrations of either 140 or 200 mg/kg bw/day respectively throughout pregnancy (Mingrone et al., 1983). No toxicologically significant clinical observations were detected in congruent 90- and 180-day dietary studies in Wistar rats when administered the constituent compound nonanedioic acid (CAS 123-99-9) at concentration of 140 and 280 mg/kg bw/day, nor when New Zealand rabbits were administered the same compound at concentrations of 200 and 400 mg/kg bw/day (Mingrone et al., 1983). In a GLP 28-day, single-dose study, no adverse effects were found between treated groups or their respective controls when male and female Balb/c mice were administered 200 mg/kg bw of the constituent compound choline chloride (FEMA 4500) by oral gavage, or when administered 200 mg/kg bw of choline chloride every alternate day via intraperitoneal injection (Mehta et al., 2009). In a series of three studies conducted to evaluate the sub-acute and sub-chronic effects of the constituent compound betaine (FEMA 4223), rats were administered the substance at concentrations of 0, 1147, 2298, or 5771 mg/kw bw/day in the feed. Groups of male and female Sprague-Dawley rats were fed the diets in a dose range-finding study (14 days), a sub-chronic study (90-93 days), and a reversibility study (28 days). No treatment-related toxicity was reported, and follow-up 28 and 90-day studies were conducted to investigate the levels at which triglyceride accumulation appeared in the livers of female rats administered betaine (CAS 107-43-7). Female Sprague-Dawley rats were administered betaine (FEMA 4223) at concentrations of 0, 718, 1071, 1428, or 7143 mg/kg bw/day in the feed. No significant treatment-related adverse effects were observed (Hayes et al., 2003).

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding rebaudioside M 85% (CAS 1220616-44-3) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4957) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of rebaudioside M 85% from use as a flavor ingredient to be 761 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). Metabolic data exist that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Cardoso et al., 1996; Gardana et al., 2003; Geuns et al., 2003; Geuns et al., 2007; Hutapea et al., 1997; Koyama et al., 2003a; Koyama et al., 2003b; Nakayama et al., 1986; Purkayastha et al., 2014; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha and Kwok, 2020; Renwick and Tarka, 2008; Roberts and Renwick, 2008; Roberts et al., 2016; Wheeler et al., 2008; Wingard, 1980). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in *in vitro* mutagenicity assays, *in vivo* studies do not provide evidence of genotoxic effects (Nakajima, 2000a, b; Pezzuto et al., 1985; Pezzuto et al., 1986; Rumelhard et al., 2016; Suttajit et al., 1993; Terai et al., 2002; Williams and Burdock, 2009). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of rebaudioside M 85% (Gooderham et al., 2020). In a 108-week carcinogenicity study for stevioside, no carcinogenic effects were observed (Toyoda et al., 1997). In a 2-year feeding study, male and female F344 rats were administered 0, 50, 150, 550 mg/kg bw/day of a Stevia extract which was comprised of 74% stevioside and 16% rebaudioside A. The authors considered the NOAEL from this 2-year rat feeding study of a stevia extract to be equal to 550 mg/kg bw/day (Yamada et al., 1985), which is greater than 43,300 times the anticipated daily *per capita* intake of rebaudioside M 85% from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 4-formyl-2-methoxyphenyl *l*-menthyl glutarate (CAS 2308574-

23-2) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4958) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of alicyclic ketones, secondary alcohols and related esters (Adams et al., 1996; JECFA, 2006, 2009, 2015; SLR, A5). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of 4-formyl-2-methoxyphenyl *l*-menthyl glutarate from use as a flavor ingredient to be 7 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that 4-formyl-2-methoxyphenyl *l*-menthyl glutarate will be hydrolyzed to menthol (FEMA 2665), glutaric acid and vanillin (FEMA 3107) through the action of hepatic carboxylesterases, which are abundant and non-specifically catalyze the hydrolysis of esters with diverse chemical structures (Smith et al., 2018). No increases in reverse mutations were observed in an OECD 471 guideline-compliant Ames assay for 4-formyl-2-methoxyphenyl *l*-menthyl glutarate in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2uvrA using the pre-incubation method (Fujishima, 2019). The structural relative *l*-monomenthyl glutarate (FEMA 4006) was not mutagenic in an OECD 471 guideline and GLP-compliant bacterial reverse mutation assay in *S. typhimurium* TA1535, TA1537, TA98, TA100, TA102 and *E. coli* WP2 uvrA using plate incorporation and pre-incubation methodologies (Haddouk, 2003). Negative results were observed in the Ames assays for the structurally related substance, vanillin (FEMA 3107), in *S. typhimurium* strains TA92, TA94, TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, TA1538, and TA2637 using the plate incorporation and pre-incubation methodologies (De Flora et al., 1994; Florin et al., 1980; Ishidate et al., 1984; Jones, 1986; Kasamaki et al., 1982; Lawlor, 1991; Marzin, 1979a; Mortelmans et al., 1986; Nagabhushan and Bhide, 1985; Pool and Lin, 1982; Rapson et al., 1980). For the same structural relative, mixed positive and negative results were observed in *in vitro* sister chromatid exchange, chromosomal aberration and micronucleus induction assays conducted in Chinese hamster cells and human lymphocytes, human lymphocytes, and human cell lines, respectively (Jansson et al., 1986; Jansson and Zech, 1987; Sanyal et al., 1997; Sasaki et al., 1987). Vanillin (FEMA 3107) was negative in an unscheduled DNA synthesis assay in rat hepatocytes (Heck et al., 1989) and was negative in bone marrow micronucleus assays in female OF1 mice, male BDF1 mice, and in male MS/Ae mice (Inouye et al., 1988; Marzin, 1979b; Sutou et al., 1999). The structurally related substance, menthol (FEMA 2665), was uniformly negative for mutagenic activity in standard Ames studies conducted in several *S. typhimurium* strains with and without metabolic activation (Andersen and Jensen, 1984; Gomes-Carneiro et al., 1998; Ishidate et al., 1984; Kirkland et al., 2016; Nohmi et al., 1985; Zeiger et al., 1988). Potential genotoxicity was observed in an alkaline elution rat hepatocyte assay, but no sister chromatid exchanges in Chinese hamster ovary (CHO) cells, human lymphocytes or human embryonic lung cells, nor were chromosome aberrations observed in Chinese hamster lung fibroblasts, CHO cells or human lymphocytes (Ishidate et al., 1984; Ivett et al., 1989; Matsuoka et al., 1998; Murthy et al., 1991). Menthol was non-mutagenic in L5178Y mouse lymphoma forward mutation assays, in an *in vitro* comet assay, in *in vivo* single and repeated dose oral gavage studies, in *in vivo* alkaline comet assays, and was negative in a bone marrow micronucleus assay in B6C3F1 mice (Kiffe et al., 2003; Myhr et al., 1991; Olivo, 2016; Shelby et al., 1993; Tennant et al., 1987; Uno et al., 2015). The structural relative glutaric acid was negative in an Ames assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538, in a mouse lymphoma assay conducted in L5178Y/TK cells, and in a bone marrow micronucleus assay in CD-1 mice (Fiume et al., 2012). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 4-formyl-2-methoxyphenyl *l*-menthyl glutarate (Gooderham et al., 2020). In an OECD 407 guideline and GLP-compliant 28-day repeat-dose toxicity study in Sprague Dawley rats, oral administration of a 60-65%/30-35% mixture of the structural relatives *l*-monomenthyl glutarate (FEMA 4006) and dimenthyl glutarate (FEMA 4604) resulted in a NOAEL of 248 mg/kg bw/day, which is 2,480,000 times the anticipated daily *per capita* intake of 4-formyl-2-methoxyphenyl *l*-menthyl glutarate from use as a flavor ingredient (Dhinsa, 2008). Potential short-term and long-term toxicity was evaluated in a series of repeat-dose toxicity studies with vanillin administered to rats (FEMA 3107) (Hagan et al., 1967; Mancebo et al., 2003; OECD SIDS, 2002). Based on a review of these studies, the Expert Panel determined a conservative NOAEL for the structural relative vanillin (FEMA 3107) to be 150 mg/kg bw/day, which is greater than 1,200,000 times the anticipated *per capita* intake of 4-formyl-2-methoxyphenyl *l*-menthyl glutarate from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 9-dodecen-12-olide (CAS 301310-73-6; 79894-05-6) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4959) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of aliphatic, alicyclic, alicyclic-fused and aromatic-fused ring lactones (Adams et al., 1998; JECFA, 1998, 2011; SLR, B1C). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of 9-dodecen-12-olide from use as a flavor ingredient to be 0.1 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). This material is known to be found in Yuzu, a citrus fruit native to Japan; however, quantitative data are unavailable and therefore a consumption ratio cannot be calculated (Van Dongen and Donders, 2021). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that that lactone ring of 9-dodecen-12-olide will undergo hydrolysis followed by conjugation and excretion of the resulting hydroxycarboxylic acid derivative, or *beta*-oxidation of the hydroxy acid to yield short chain polar metabolites that are excreted either unchanged or in conjugated form (Smith et al., 2018). No increases in the frequency of reverse mutations were observed in an Ames assay with 9-dodecen-12-olide in *S. typhimurium* strains TA100 and TA98 in the presence and absence of S9 metabolic activation (Kino, 2019). The structural relative isoambrettolide (FEMA 4145) was non-

mutagenic in an OECD 471 guideline and GLP-compliant Ames assays in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 using the pre-incubation and plate incorporation methods (Forichon, 1997; Poth, 2003). No increases in the frequency of reverse mutations were observed in an OECD 471 guideline and GLP-compliant Ames assay with the structural relative, oxacyclohexadecen-2-one in *S. typhimurium* strain TA1535, TA1537, TA98, TA100, and TA102 using both the plate incorporation and pre-incubation methodologies in the absence and presence of S9 metabolic activation (Sokolowski, 2005). In an OECD 473 guideline and GLP-compliant *in vitro* chromosomal aberration study in human lymphocytes, oxacyclohexadecen-2-one did not induce increases in structural chromosomal aberrations (Schulz, 2005). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 9-dodecen-12-olide (Gooderham et al., 2020). In an OECD 407 guideline and GLP-compliant 28-day study in Sprague Dawley rats, oral administration of the structural relative oxacyclohexadec(10)-en-2-one resulted in a NOAEL of 1000 mg/kg bw/day (ECHA, 2018a). In an OECD 407 guideline and GLP-compliant 28-day study in Crl:DC rats administered oxacyclohexadecen-2-one, the Expert Panel concluded the NOAEL to be 1000 mg/kg bw/day (Leuschner, 2005). In an OECD 408 guideline and GLP-complaint 90-day oral toxicity study in Sprague-Dawley Crl:CD®BR rats, administration of the structural relative oxacyclohexadecen-2-one via carboxymethyl cellulose gavage resulted in a NOAEL of 1000 mg/kg bw/day, which is 500,000,000 times the anticipated daily *per capita* intake of 9-dodecen-12-olide from use as a flavor ingredient (Thomas, 1998). In an OECD 421 guideline and GLP-compliant reproductive and developmental toxicity study in Sprague-Dawley rats, the administration of the structural relative isoambrettolide (FEMA 4145) resulted in a NOAEL of 1000 mg/kg bw/day, which is 500,000,000 times the anticipated daily *per capita* intake of 9-dodecen-12-olide from use as a flavor ingredient (ECHA, 2018b).

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding *trans-alpha*-bergamotene (CAS 13474-59-4) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4960) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. The substance was evaluated individually within the context of the chemical group of aliphatic and aromatic hydrocarbons (Adams et al., 2011; JECFA, 2006, 2015; SLR, A6). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of *trans-alpha*-bergamotene from use as a flavor ingredient to be 138 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). This material occurs naturally in Ashanti pepper, cloves, hops, bergamot oil, lemon peel oil, and lime oil (Van Dongen and Donders, 2021). Based on the quantitative data, a consumption ratio of 75 could be calculated (Stofberg and Grundschober, 1987). The Expert Panel noted the assay of the material was 80-87% of the named material with *trans-beta* bergamotene and sesquisabinene as secondary components (5-8% and 3-5%, respectively) and considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is anticipated that *trans-alpha*-bergamotene will undergo hydroxylation of alkyl ring substituents to yield alcohols that may be excreted in the urine unchanged or in conjugated form. Alternatively, the alcohol metabolites may undergo further oxidation to yield more polar metabolites that may also be excreted in the urine unchanged or in conjugated form. Additionally, the alkene groups present in the substance may form epoxide metabolites that either undergo hydrolysis or conjugation with glutathione (Smith et al., 2018). No evidence of genotoxic potential has been observed in an OECD 471 guideline and GLP-compliant Ames assay or an OECD 487 guideline and GLP-compliant *in vitro* micronucleus assay with *trans-alpha*-bergamotene (Donath, 2019; Schreib, 2019). No evidence of genotoxic potential was observed when the structural relative *beta*-caryophyllene (FEMA 2252) was tested in an Ames assay, *in vitro* mouse lymphoma assay, *in vitro* micronucleus assay, *in vivo* micronucleus assay, and *in vivo* sister chromatid exchange and chromosome aberration assay (Alvarez-Gonzalez et al., 2014; Di Sotto et al., 2008; Di Sotto et al., 2010; Molina-Jasso et al., 2009; Sasaki et al., 1989; Seifried et al., 2006). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of *trans-alpha*-bergamotene (Gooderham et al., 2020). In an OECD 407 guideline-compliant repeated dose 28-day study with female Swiss mice, the administration of the structural relative *beta*-caryophyllene (FEMA 2252) resulted in no adverse clinical effects (da Silva Oliveira et al., 2018). In an OECD 408 guideline and GLP-compliant 90-day dietary toxicity study in Sprague-Dawley rats, the administration of the same structural relative resulted in a NOAEL of 222 mg/kg bw/day in male mice, which is 111,000 times the anticipated daily *per capita* intake of *trans-alpha*-bergamotene from use as a flavor ingredient (Bastaki et al., 2020).

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 4-methyltrideca-2*E*,4-dienal (CAS 2369713-22-2) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4961) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. The substance was evaluated individually within the context of the chemical group of aliphatic linear and branched-chain *alpha*, *beta*-unsaturated aldehydes and related alcohols acids and esters (Adams et al., 2008; JECFA, 2009, 2012; SLR, M1). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of 4-methyltrideca-2*E*,4-dienal from use as a flavor ingredient to be 0.003 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is expected that 4-methyltrideca-2*E*,4-dienal will undergo oxidation to 4-methyltrideca-2*E*,4-dienoic acid, which then undergo *beta*-oxidation and complete metabolism to CO_2 and H_2O. In an alternative pathway, conjugation of the aldehyde with glutathione and subsequent excretion as the mercapturic acid derivative can occur (Smith et al., 2018). The Expert Panel reviewed the extensive literature available for 2,4-alkadienals, including assays conducted by the National Toxicology

Program (NTP) during its investigations of the structural relatives *trans*,*trans*-2,4-decadienal (FEMA 3135) and *trans*, *trans*-2,4-hexadienal (FEMA 3429), and new genotoxicity studies for the structural relative 2-methyl-2-pentenal (FEMA 3194) and determined them sufficient to indicate a lack of genotoxic concern for 4-methyltrideca-2*E*,4-dienal (Adams et al., 2008; Bowen, 2011; EFSA, 2019; Keig-Shevlin, 2016a, b; Kilford, 2016; McKeon and Ciubotaru, 2016; Morris, 2017; NTP, 2011; Whitwell, 2011, 2016a, b). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 4-methyltrideca-2*E*,4-dienal (Gooderham et al., 2020). In a 90-day NTP gavage study with rats and mice, the administrations of the structural relative 2-*trans*,4-*trans*-decadienal (FEMA 3135) resulted in a NOAEL of 100 mg/kg bw/day, which is 2,000,000,000 times the anticipated daily *per capita* intake of 4-methyltrideca-2*E*,4-dienal from use as a flavor ingredient (NTP, 2011). In a series of toxicity studies of the structural relative *trans,trans*-2,4-hexadienal (FEMA 3429), the Expert Panel noted clear carcinogenic effects including increased incidences of forestomach epithelial hyperplasia (NTP, 2003). However, the Expert Panel determined that the effects were due to the high bolus doses administered in the studies, and the strong irritating nature of 2,4-hexadienal. In a subchronic toxicity study of the structural relative *trans*,*trans*-2,4-hexadienal (FEMA 3429) administered to F344/N rats at doses of 7.5, 15, 30, 60, or 120 mg/kg bw/day by gavage 5 days per week for a total of 70 doses over 14 weeks, no mortalities were observed in this study (NTP, 2003). Significant reductions in final mean bodyweights and bodyweight gains were observed in male rats at doses of 30 mg/kg bw/day and above. No other signs of clinical toxicity were observed in treated animals at any dose with the exception of increased salivation in males and females at 30 or 120 mg/kg bw/day during week 4, and only in 120 mg/kg bw/day groups at later times. Increased incidences of mild-to-moderate forestomach epithelial hyperplasia were reported in both males and females at 120 mg/kg bw/day, accompanied by forestomach-localized tissue degeneration and active chronic inflammation. Increased incidences of olfactory epithelial atrophy, osteofibrosis, and excessive exudate of the nose were also reported in males at 120 mg/kg bw/day. There were no biologically significant changes in organ weights at any dose level. Statistically significant but sporadic and non-dose dependent variations in hematological and clinical chemistry parameters were reported but were not considered related to treatment. Based on these findings, the NOEL was determined to be 15 and 60 mg/kg bw/day for male and female rats, respectively. This NOEL is 300,000,000 times the anticipated daily *per capita* intake of 4-methyltrideca-2*E*,4-dienal from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding *Lepidium meyenii* root extract (CAS 828927-86-2) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4962) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of *Lepidium meyenii* root extract from use as a flavor ingredient to be 28 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This material is derived from dried maca roots; however, quantitative data are not available, and a consumption ratio could not be calculated. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). Metabolic data exist for a representative member of the principal identified congeneric groups that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Smith et al., 2018). No increases in the frequency of revertant colonies was observed in an OECD 471 guideline and GLP-compliant Ames assay with *Lepidium meyenii* root extract when incubated with *S. typhimurium* strains TA1537, TA1535, TA98, TA100 and TA102 (Tekale, 2019). In an OECD 487 guideline and GLP-compliant *in vitro* mammalian cell micronucleus assay in human peripheral blood lymphocytes incubated with *Lepidium meyenii* root extract, no statistically significant increases in the induction of micronuclei were observed (Vashi, 2019b). In a 4-strain Ames assay in *S. typhimurium* strains TA97, TA98, TA100 and TA102 with maca root powder, no significant increases in the number of revertants were observed (Yao et al., 2015). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of *Lepidium meyenii* root extract (Gooderham et al., 2020). No reproductive effects were reported for male rats administered maca root powder at concentrations up to 10,000 mg/kg bw/day for 30 successive days (Tian et al., 2007). In a subacute dietary study with Sprague-Dawley rats, the administration of maca root powder resulted in a NOAEL of 6000 mg/kg bw/day (Yang et al., 2010). No signs of toxicity were noted when Sprague-Dawley rats were administered maca root powder in the feed at concentrations up to 6000 mg/kg bw/day for 30 days (Yao et al., 2015). In a 90-day dietary study with male and female Wistar rats, the administration of maca root powder resulted in a NOAEL of 1500 mg/kw bw/day (Tian et al., 2007). The Expert Panel determined the most conservative NOAEL for the related maca root powder to be 1500 mg/kg bw/day, which is 3,000,000 times greater than the anticipated daily *per capita* intake of *Lepidium meyenii* root extract from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding Pandan leaf (*Pandanus amaryllifolius*) distillate extract (CAS 1175005-60-3) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4963) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of Pandan leaf *(Pandanus amaryllifolius)* distillate extract from use as a flavor ingredient

to be 0.7 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This material is derived from the pandan leaf, which has traditionally been used for cooking in southeast Asia as a flavoring in rice cooking, sweets, and beverages. However, quantitative data are not available and a consumption ratio could not be calculated. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. Metabolic data exist for a representative member of the principal identified congeneric groups that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Smith et al., 2018). The Expert Panel reviewed the key constituents of Pandan leaf *(Pandanus amaryllifolius)* distillate extract and noted that the congeneric group intakes were below the respective thresholds of toxicological concern. Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of Pandan leaf *(Pandanus amaryllifolius)* distillate extract (Gooderham et al., 2020).

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

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)isonicotinamide (CAS 1622458-32-5) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4965) (Smith et al., 2005a) in the food categories and at the use levels specified Table 2. The substance was evaluated individually within the context of the chemical group of aliphatic and aromatic amines and related amides (JECFA, 2006, 2008, 2011, 2012, 2017; SLR, A7, C21). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)isonicotinamide from use as a flavor ingredient to be 277

µg/person/day, which is above the threshold of toxicological concern (TTC) for structural class III (90 µg/person/day) (Munro et al., 1996). This material is not known to occur in nature and thus no consumption ratio can be calculated. The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). *In vitro* rat and human microsomal incubations of *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)isonicotinamide showed minor amounts of hydroxylated metabolites (Chen and Castillo, 2011; Guia, 2011). *In vivo* pharmacokinetic, bioavailability and metabolism studies in Sprague-Dawley rats indicated that *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)isonicotinamide is poorly bioavailable, poorly absorbed by the intestinal tract and undergoes limited amounts of metabolic transformation prior to excretion, which occurs predominately in the feces (Levy, 2019; Metabolism Study, 2019a, b, c). *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)isonicotinamide and its secondary component *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)pivalamide were non-mutagenic when tested in Ames assays with *S. typhimurium* TA98 and TA100 only (Samsam, 2012), and when tested with those strains plus TA1535, TA1537 as well as *E. coli* WP2*uvr*A either in the presence or absence of S9 metabolic activation (Dakoulas, 2019a, b). The structural relative *N*-(1((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6] thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)-2,6-dimethylisonicotinamide (FEMA 4899) was non-mutagenic in a series of *in vitro* genotoxicity assays (Karanewsky et al., 2017). The structural relative 3-[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]-2,2-dimethyl-*N*-propylpropanamide (FEMA 4701) similarly showed no evidence of mutagenicity, including no increases in the frequency of revertant colonies or chromosomal aberrations, non-mutagenic *in vitro* and in an OECD 474 guideline and GLP-compliant *in vivo* mammalian erythrocyte micronucleus test (Arthur et al., 2015). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)isonicotinamide (Gooderham et al., 2020). In an OECD 414 guideline and GLP-compliant prenatal developmental toxicity study, administration of the structural relative *N*-(1((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)-2,6-dimethylisonicotinamide (sulfate salt) (FEMA 4899) to pregnant female Sprague Dawley rats by gavage resulted in a NOAEL at the highest tested dose of 1000 mg/kg bw/day, which is 200,000 times the anticipated daily *per capita* intake of *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)isonicotinamide from use as a flavor ingredient (Karanewsky et al., 2017). In a 13-week dietary toxicity study of the same structural relative provided to Sprague-Dawley rats, no adverse effects were observed, resulting in a NOAEL at the highest tested intake of 140 mg/kg bw/day (Karanewsky et al., 2017). In a 28-day repeat-dose toxicity study, the administration of the structural relative *N*-(1((4-amino-2,2-dioxido-1H-benzo[c][1,2,6] thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)-2,6-dimethylisonicotinamide (FEMA 4899) to Sprague Dawley rats resulted in a NOAEL of 100 mg/kg bw/day, which is 20,000 times greater than the anticipated daily *per capita* intake of *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)isonicotinamide from use as a flavor ingredient (Karanewsky et al., 2017). Apart from significantly increased pituitary gland weights relative to body and brain weights, no other significant treatment-related effects were observed in a 28-day dietary toxicity study in male and female Sprague Dawley rats administered the structural relative 3-[(4-amino-2,2-dioxido -1*H*-2,1,3-benzothiadiazin-5-yl)oxy]-2,2-dimethyl-*N*-propylpropanamide (FEMA 4701) at levels of 0, 10, 30 and 100 mg/kg bw/day. In a follow-up 90-day dietary toxicity study of the same structural relative administered to male and female Sprague Dawley rats at levels of 0, 5, 10 or 20 mg/kg bw/day, no significant adverse effects or significant differences in ACTH (adrenocorticotropic hormone), TSH (thyroid stimulating hormone), cortico-sterone, LH (luteinizing hormone) and FSH (follicle stimulating hormone) levels were observed. A NOAEL of 20 mg/kg bw/day was established for the structural relative FEMA 4701 (Arthur et al., 2015), which is 4,000 times greater the anticipated daily *per capita* intake of *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)isonicotinamide from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 4-methylheptan-3-one (CAS 6137-11-7) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4966) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of saturated and unsaturated aliphatic acyclic secondary alcohols, ketones and related esters (JECFA, 1999, 2003, 2017; SLR, A1). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of 4-methylheptan-3-one from use as a flavor ingredient to be 7 µg/person/day, which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). This material is known to occur in black chokeberry (*Aronia melanocarpo*), roasted Malaysian tropical almond nuts (*Terminalia catappa*) and guava fruit *(Psidium guajava* L.) (Idstein and Schreier, 1985; Kraujalyte et al., 2013; Lasekan and Abbas, 2010). However, due to limited quantitative data, a consumption ratio could not be calculated. The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that 4-methylheptan-3-one will be reduced to the corresponding secondary alcohol, followed by glucuronide or sulfate conjugation and urinary elimination (Kamil et al., 1953; Smith et al., 2018). Alternatively, at higher exposure levels, 4-methylheptan-3-one is expected to undergo □-oxidation or □-1 oxidation in the hepatocyte endoplasmic reticulum to the corresponding hydroxymethyl ketones and subsequently to the corresponding ketocarboxylic acids (□-oxidation) or diketones (□-1 oxidation). The carboxylic acids are expected to be conjugated with glucuronic acid and eliminated in the urine. Of the possible metabolites, omega-1 oxidation is expected to yield 4-methylheptan-2,5-dione, a gamma-diketone and a metabolite of toxicological concern based on

available literature (Couri and Milks, 1982; Lehning et al., 2000; O'Donoghue et al., 1984; Opanashuk et al., 2001; Topping et al., 1994). In addition, oxidation of the terminal carbon oxidation proximal to the carbonyl group of the candidate substance is expected to yield 4-methyl-3-keto-heptanoic acid which may be conjugated with glucuronic acid and eliminated in the urine or may undergo decarboxylation to yield 3-methylhexan-2,5-dione, also a γ-diketone. The β-ketoacid metabolites may also enter the ketone body metabolism in extrahepatic tissues by virtue of their structural similarity to acetoacetate. In non-hepatic tissues they can be converted to *beta*-ketoacid-CoA by *beta*-ketoacyl-CoA transferase (thiophorase) and subsequently release acetyl-CoA to extrahepatic energy metabolism in the citric acid cycle and 3-methylpentanoyl-CoA (DiVicenzo et al., 1982; O'Donoghue et al., 1982; O'Donoghue et al., 1984). In an OECD 471 guideline and GLP-compliant Ames assay conducted in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 as well as *E. coli* strain WP2*uvr*A [pKM101], 4-methylheptan-3-one was non-mutagenic in the presence and absence of S9 metabolic activation at concentrations up to 1000 µg/plate (Spruth, 2019). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 4-methylheptan-3-one (Gooderham et al., 2020). In an OECD 414 guideline and GLP-compliant developmental toxicity study, sperm positive female Hsd. Han: WIST rats were administered the structural relative 5-methylheptan-3-one by oral gavage at doses of 0, 80, 300 and 750 mg/kg bw/day during gestation days 5-19 (ECHA, 2016). Clinical signs of toxicity, treatment-related decreases in feed consumption accompanied by decreased bodyweight and bodyweight gain, lower fetal- and placental weight, higher relative placental weight, reduced fetal body weights, fetal skeletal malformations in some fetuses and increased incidence of skeletal variations due to delayed ossification attributed to maternal toxicity, were reported in the high-dose. The NOAEL for maternal and developmental toxicity was determined to be 300 mg/kg bw/day. In a 14-week toxicity study, the administration of the structural relative 3-heptanone (FEMA 2545) was administered to male rats by gavage at doses of 0, 179, 357, 714, 1428 or 2857 mg/kg bw/day for five days per week. resulted in a NOEL of 179 mg/kg bw/day due to evidence of neurotoxicity and central nervous system depression or narcosis at higher doses (O'Donoghue et al., 1984). In a 120-day drinking water study, female Wistar rats were treated with the structural relative 3-heptanone (FEMA 2545) at concentrations of 30 mg/kg bw/day, and at concentrations of 32 or 38 mg/kg bw/day in two preliminary studies. Increased kidney weights relative to bodyweight were observed, though these changes in organ weights were not accompanied with other histopathological changes (Homan and Maronpot, 1977). In a GLP-compliant 90-day toxicity study, the administration of the structural relative 5-methylheptan-3-one (ethyl isoamyl ketone) to adult male Sprague-Dawley rats by gavage at dose levels of 59, 293 and 586 mg/kg bw/day for 5 days/week resulted in a NOAEL of 59 mg/kg bw/day based on neurotoxicity observed at higher doses (Topping, 1984). This NOAEL is 590,000 times greater than the anticipated daily *per capita* intake of 4-methylheptan-3-one from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding *delta*-cadinene (CAS 483-76-1) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4967) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2.The substance was evaluated individually within the context of the chemical group of aliphatic and aromatic hydrocarbons (Adams et al., 2011; JECFA, 2006, 2015; SLR, A6). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of *delta*-cadinene from use as a flavor ingredient to be 15 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The material is known to occur in Mastic (*Pistacia lentiscus*), *Citrus sinensis* x *Poncirus trifoliata* – Troyer Citrange essential oil (γ-Cadinene), Basil essential oil, Rio Red grapefruit juice, *Beta vulgaris* essential oil, Propolis essential oil. Gnaphalium affine (cudweed) oil, Damiana essential oil, and Majorana essential oil (Alcaraz-Meléndez et al., 2004; Caccioni et al., 1998; Chaudhary et al., 2017; Fernandes et al., 2015; Van Dongen and Donders, 2021; Souleles, 1991; Zardi-Bergaoui et al., 2017; Zeng et al., 2011; Zheljazkov et al., 2008). However, a consumption ratio could not be calculated. The Expert Panel noted the assay of the material was 93-95% of the named material with other aliphatic and aromatic hydrocarbons as the secondary component (3%) and considered the specification of the material to be adequately characterized by the purity assays and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that *delta*-cadinene will undergo hydroxylation of alkyl ring substituents to yield hydroxylated species that may be further oxidized and excreted, either unchanged or in conjugated form as glucuronide and sulfate conjugates. Additionally, the alkene groups present may undergo epoxidation and subsequent conjugation with glutathione or hydrolysis (Smith et al., 2018). *delta*-Cadinene was non-mutagenic in an OECD 471 guideline and GLP-compliant Ames assay when tested up to 5 µl/plate (approximately 4 µg/plate based on the specific density of the substance) in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* WP2*uvr*A (pKM 101) either in presence or absence of S9 metabolic activation (Schreib, 2020a). Similar results were observed when the structurally related substances valencene (FEMA 3443) and cadinene (non-isomer specific) were tested in the same strains at concentration up to 5000 µg/plate (Bhalli, 2016c; Bowles and Thompson, 2013). The same structural relatives did not result in significant increases in micronuclei frequency when tested in OECD 487 guideline and GLP-compliant *in vitro* micronucleus assays in human lymphocytes at concentrations up to 103 µg/mL (Bhalli, 2016a, 2017c). No evidence of mutagenicity was observed when the structural relative *β*-caryophyllene (FEMA 2252) was tested in a series of *in vitro* and *in vivo* genotoxicity assays (Di Sotto et al., 2010; Heck et al., 1989; Jagannath, 1984; Molina-Jasso et al., 2009; Sasaki et al., 1987; Seifried et al., 2006). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of *delta*-cadinene (Gooderham et al., 2020). No adverse effects were observed when female Swiss mice were administered the structural relative *β*-caryophyllene (FEMA 2252) at concentrations of 300 mg/kg bw/day or 2000 mg/kg

bw/day (da Silva Oliveira et al., 2018). In an OECD 408 guideline and GLP-compliant 90-day dietary toxicity study, the administration of the structural relative *β*-caryophyllene (FEMA 2252) to Sprague Dawley rats resulted in NOAELs of 222 mg/kg bw/day and 263 mg/kg bw/day for male and female rats, respectively (Bastaki et al., 2020), which is 740,000 times greater than the anticipated daily *per capita* intake of *delta*-cadinene from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding *Stevia rebaudiana* extract with rebaudioside M ≥90% and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4968) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of *Stevia rebaudiana* extract with rebaudioside M ≥90% from use as a flavor ingredient to be 1384 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The material is derived from the leaves of *Stevia rebaudiana*. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). Metabolic data exist that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Cardoso et al., 1996; Gardana et al., 2003; Geuns et al., 2003; Geuns et al., 2007; Hutapea et al., 1997; Koyama et al., 2003a; Koyama et al., 2003b; Nakayama et al., 1986; Purkayastha et al., 2014; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha and Kwok, 2020; Renwick and Tarka, 2008; Roberts and Renwick, 2008; Roberts et al., 2016; Wheeler et al., 2008; Wingard, 1980). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in *in vitro* mutagenicity assays, *in vivo* studies do not provide evidence of genotoxic effects (Nakajima, 2000; Pezzuto et al., 1985, 1986; Rumelhard et al., 2016; Suttajit et al., 1993; Terai et al, 2002; Williams and Burdock, 2009). Based on the results for the various steviol glycosides, the Panel did not identify specific concerns related to the potential genotoxicity of *Stevia rebaudiana* extract with Rebaudioside M ≥90% (Gooderham et al., 2020). In a 108-week carcinogenicity study for stevioside, no carcinogenic effects were observed (Toyoda et al., 1997). In a 2-year feeding study, male and female F344 rats were administered the equivalent of 0, 50, 150, 550 mg/kg bw/day of a stevia extract which was comprised of 74% stevioside and 16% rebaudioside A (Yamada et al., 1985). The authors considered the NOAEL from this 2-year rat feeding study of a stevia extract to be equal to 550 mg/kg bw/day (Yamada et al., 1985), which is greater than 23,800 times the anticipated daily per capita intake of the anticipated daily per capita intake of Stevia rebaudiana extract with Rebaudioside M ≥90% from use as a flavor ingredient, respectively.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding Yerba Mate extract (*Ilex paraguariensis* A. St.-Hil.) (CAS 73296-98-7; 68916-96-1) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4969) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of Yerba Mate extract (*Ilex paraguariensis* A. St.-Hil.) from use as a flavor ingredient to be 761 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and 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 (Gómez-Juaristi et al., 2018; Marques and Farah, 2010; Moura de Oliveira et al., 2017). Yerba Mate extract (*Ilex paraguariensis* A. St.-Hil.) was non-mutagenic at concentrations up to 5000 µg/plate in an OECD 471 guideline and GLP-compliant five-strain Ames assay conducted in *S. typhimurium* strains TA1537, TA1535, TA100, TA98 as well as *E. coli* WP2*uvr*A either in the presence and absence of S9 metabolic activation (Heard, 2019a). The substance also did not result in an increase in the induction of micronuclei in TK6 cells in an OECD 487 guideline and GLP-compliant *in vitro* micronucleus assay (Heard, 2019b). In an OECD 474 and 489 guideline and GLP-compliant *in vivo* combined micronucleus and comet assay in male Sprague Dawley rats at concentrations up to 2000 mg/kg bw/day, no evidence of mutagenicity was observed (Moy, 2020). A related aqueous mate extract (*Ilex paraguariensis*) was non-mutagenic and non-cytotoxic in an Ames assay in *S. typhimurium* TA97 and TA98 at concentrations up to 80,000 µg/plate (Fonseca et al., 2000). *In vitro* and *in vivo* chromosome aberration assays with the same related aqueous mixture resulted in significant increases in the frequency of metaphases with chromosome aberrations at concentrations of 100-750 µg/mL in the absence of S9 metabolic activation in human lymphocytes but was negative when male and female Wistar rats were administered the same aqueous mate extract at 0, 1000, or 2000 mg/kg bw (Fonseca et al., 2000). In a teratogenicity study, the administration of the constituents chlorogenic acid and caffeic acid to pregnant Wistar rats at concentrations up to 5-500 mg/kg bw/day and 40-187.5 mg/kg bw/day, respectively, resulted in NOAELs of the highest concentrations (Chaube and Swinyard, 1976). The Expert Panel determined that the NOAELs established for chlorogenic acid and caffeic acid are 38,400 times greater and 14,000 times greater, respectively, than the anticipated daily *per capita* intake of Yerba Mate extract (*Ilex paraguariensis* A. St.-Hil.) from use as a flavoring with modifying properties. The administration of a related

preparation, dried mate extract (*Ilex paraguariensis*) dissolved in water and administered to male and female Rattus norvergicus Wistar var albinus rats at a concentration of 2000 mg/kg bw/day for 12 weeks did not induce toxic effects (de Andrade et al., 2012). In an eight-week dietary toxicity study, the related preparation of 250 mL of the aqueous extract of *Ilex paraguariensis* was provided to male Wistar rats (8/group) as their only source of drinking water. Edema of the kidney (mainly associated with increased diuresis) and slight blood congestion were observed in treated rats compared to the control group. Increased urogenesis, defined by the authors as visible intensive glomerular filtration, was observed in treated rats as evidenced by tissue staining with Alcian blue. Significantly reduced basal membrane polysaccharides within the glomeruli was observed in the morphometric analysis of the kidneys. Significantly decreased membrane thickness of the capillary tuft and significantly increased glomerular capsule size were observed in treated rats. The authors suggested that the increased urogenesis observed was associated with decreased proteoglycan content in the capillary tuft (Kuropka et al., 2021). In a three-week dietary toxicity study, decreased kidney and adrenal weights were observed in Sprague Dawley rats (5/group) provided approximately 500 mg/kg bw/day of the constituent chlorogenic acid compared to the negative control group (Eklund, 1975). Increased lung γ-tocopherol and pooled α- and γ-tocopherol levels as well as decreased lung lipids were observed in Sprague Dawley rats (8/group) provided approximately 100 mg/kg bw/day of the constituent chlorogenic acid compared to the negative control group in a 28-day dietary toxicity study (Frank et al., 2003). The Expert Panel reviewed the other key constituents of Yerba mate extract (*Ilex paraguariensis* A. St.-Hil) and noted that the congeneric group intakes, with the exception of phenol and phenol derivatives, were below the respective thresholds of toxicological concern.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 2-methyl-1-(2-(5-(*p*-tolyl)-1*H*-imidazol-2-yl)piperidin-1-yl)butan-1-one (CAS 2413115-68-9) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4970) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of aliphatic and aromatic amines and related amides (JECFA, 2006, 2008, 2011, 2012, 2017; SLR, A7, C21). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of 2-methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one from use as a flavor ingredient to be 14 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This material is not known to occur in nature and thus no consumption ratio can be calculated. The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). It is presumed that 2-methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one will be hydroxylated, followed by the subsequent conjugation of some hydroxylated groups primarily with glucuronic acid to conjugated products (Laue and Hostettler, 2019a). In an Ames microplate assay conducted in *S. typhimurium*TA98 and TA100, 2-methyl-1-(2-(5-(*p*-tolyl)-1*H*-imidazol-2-yl)piperidin-1-yl)butan-1-one did not significantly increase the number of revertants at concentrations up to 2.5 mg/mL in the presence and absence of S9 metabolic activation (Laue and Hostettler, 2019b). In an OECD 471 guideline and GLP-compliant Ames assay, 2-methyl-1-(2-(5-(*p*-tolyl)-1*H*-imidazol-2-yl)piperidin-1-yl)butan-1-one was non-mutagenic at concentrations up to 5000 µg/plate in *S. typhimurium* strains TA98, TA1535, TA100, TA1537 as well as *E. coli* WP2*uvr*A either in the presence or absence of S9 metabolic activation (Dakoulas, 2020). In an OECD 487 guideline and GLP-compliant *in vitro* micronucleus assay conducted in human peripheral blood lymphocytes, no significant induction of micronuclei was observed at concentrations of 84-172 µg/mL, 58.8-146 µg/mL and 21.5-50 µg/mL for 4 hours in the absence and presence of S9 metabolic activation and for 24 hours in the absence of S9 metabolic activation, respectively (Xie, 2020). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 2-methyl-1-(2-(5-(*p*-tolyl)-1*H*-imidazol-2-yl)piperidin-1-yl)butan-1-one (Gooderham et al., 2020).

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding *beta*-farnesene (CAS 18794-84-8) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4971) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of aliphatic and aromatic hydrocarbons (Adams et al., 2011; JECFA, 2006, 2015; SLR, A6). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of *beta*-farnesene from use as a flavor ingredient to be 21 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The substance occurs naturally in angelica (*Angelica archangelic* L.), ashanti pepper (*Piper guineense* Schum and Thom), chamomile, citrus fruits, curry (*Bergera koenigii* L.), ginger (*Zingiber* spp), pepper (*Piper nigrum* L.), pistacia palaestina (*Pistacia terebinthus* L.), thyme (*Thymus* species), *Alpinia* species; coriander seed (*Coriandrum sativum* L.), lemon balm (*Melissa officinalis* L.), marula (*Sclerocarya birrea* subsp. Caffra), *Ocimum* species, omija fruit (*Schisandra chinensis* Baillon), passion fruit (*Passiflora* spp), quince, marmelo (*Cydonia oblonga* Mill.), rum, walnut (*Juglans* species) and wine (Van Dongen and Donders, 2021). Based on the quantitative data, a consumption ratio of 5 could be calculated (Stofberg and Grundschober, 1987). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that *beta*-farnesene will undergo hydroxylation of alkyl ring substituents to yield hydroxylated species that may be further oxidized and excreted, either unchanged or in conjugated forms as glucuronide and sulfate conjugates (Adams et al., 2011).

Additionally, the alkene groups present may undergo epoxidation and subsequent conjugation with glutathione or hydrolysis. No increases in the frequency of revertant colonies were observed in an OECD 471 guideline and GLP-compliant Ames assay for *beta*-farnesene conducted in *S. typhimurium* strains TA97a, TA98, TA100, TA1535 and TA1537 and *E. coli* WP2*uvr*A (pKM 101) in the presence and absence of S9 metabolic activation (ECHA, 2009b; Schreib, 2020b). In OECD 473 guideline and GLP-compliant *in vitro* chromosomal aberration assay, farnesene (purity: 96%, isomer not specified) did not induce statistically significant increases in the frequency of aberrant human lymphocytes in the presence of absence of S9 metabolic activation (ECHA, 2009c). In a non-guideline compliant *in vitro* chromosomal aberration assay and *in vitro* micronucleus assay, farnesene did not induce statistically significant increases in the frequency of aberrant cells and micronucleated cells in human lymphocytes incubated with concentrations up to 400 µg/mL of the test substance for 72 hours (Çelik et al., 2014). In an OECD 476 guideline and GLP-compliant mouse lymphoma assay, farnesene (purity: 91.6%, isomer not specified) was non-mutagenic in the presence of absence of S9 metabolic activation in L5178Y TK +/- 3. 7. 2c mouse lymphoma cells (heterozygous at the thymidine kinase locus) (ECHA, 2009d). Farnesene (mixture of isomers including 8.5% (*E*)-β; 6.2% (*Z*)-β; 7.7% (*E*,*Z*)-α; 9.8% (*E*,*E*)-α; 2.2% (*Z*,*E*)-α) was not mutagenic in an OECD guideline 471 and GLP-compliant Ames assay in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* WP2*uvr*A with and without S9 metabolic activation using the plate incorporation method at concentrations up to 5000 µg/plate (Bhalli, 2016b). In an OECD 487 guideline and GLP-compliant *in vitro* micronucleus assay, no statistically significant induction of micronuclei was observed in human peripheral blood lymphocytes treated with farnesene (mixture of isomers including 8.5% (*E*)-β; 6.2% (*Z*)-β; 7.7% (*E*,*Z*)-α; 9.8% (*E*,*E*)-α; 2.2% (*Z*,*E*)-α) in the presence of absence of S9 metabolic activation (Bhalli, 2017a). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of *beta*-farnesene (Gooderham et al., 2020).

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

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 3-mercapto-3-methyl-1-pentyl acetate (CAS 2411762-60-0) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4973) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This substance was evaluated individually within the context of the chemical group of aliphatic and aromatic sulfides and thiols (JECFA, 2000, 2004, 2008, 2011; SLR, C5). The Expert Panel calculated the anticipated *per capita* intake (“eaters only”) of 3-mercapto-3-methyl-1-pentyl acetate from use as a flavor ingredient to be 0.001 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that 3-mercapto-3-methyl-1-pentyl acetate will undergo *S*-methylation to produce the corresponding methyl sulfide followed by *S*-oxidation to yield methyl sulfoxide and methyl sulfone derivatives that are excreted in the urine (Bremer and Greenberg, 1961; Damani, 1987; Hoodi and Damani, 1984; Keith et al., 1983; Rettie et al., 1991; Szumlanski et al., 1988;

Woodson et al., 1982). Alternatively, hydrolysis of the carboxyl ester is expected to yield the corresponding carboxylic acid and alcohol derivatives that will undergo complete oxidation and β-cleavage in the fatty acid pathway, or conjugation followed by excretion in the urine (Anders, 1989; Bosron and Ting-Kai, 1980; Daniel, 1969; Heymann, 1980; Rusoff et al., 1960; Williams, 1959). 3-Mercapto-3-methylpentyl acetate was non-mutagenic in a Ames assay conducted in *S. typhimurium* TA98 and TA100 using the pre-incubation method in a dose-range assay at concentrations up to 5000 µg/plate in both strains in the presence and absence of S9, and in the main assay at concentrations up to 5000 µg/plate in both strains in the presence of S9, at concentrations up to 1500 µg/plate in TA98 in the absence of S9 and at concentrations up to 500 µg/plate in TA100 in the absence of S9 metabolic activation (Kino, 2020b). The structural relative 3-mercapto-3-methyl butanol (FEMA 3854) was non-mutagenic at concentrations up to 5000 µg/plate in a GLP-compliant Ames assay conducted in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 with and without S9 metabolic activation using a 60-minute pre-incubation procedure (Jones, 1990). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 3-mercapto-3-methyl-1-pentyl acetate (Gooderham et al., 2020). In a 14-day dietary toxicity study, no toxicologically significant adverse effects were observed when the structural relative 3-mercaptohexyl acetate (FEMA 3851) was administered to Sprague-Dawley rats at 0 and 10 mg/kg bw/day (Wnorowski, 1996). No subchronic toxicity data on the material of structural relatives were available for consideration.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding germacrene D ≥85% (CAS 23986-74-5) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4974) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The substance was evaluated individually within the context of the chemical group of aliphatic and alicyclic hydrocarbons (JECFA, 2006, 2015; SLR, A6). The Expert Panel calculated the anticipated *per capita* intake (“eaters only”) of germacrene D ≥85% from use as a flavor ingredient to be 14 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The primary constituent, germacrene D, is known to occur naturally in Anise oil, Angelica root oil , Hop oil (*Humulus lupulus*), Anise Hyssop (*Agastache foeniculum* (Pursh) Kuntze), Winter savory (*Satureja montana* L.), Lemon balm (*Melissa officinalis* L.), Lovage leaf, Thymus, other types, German chamomile oil (*Matricaria chamomilla* L.), Ginger (*Zingiber officinale* Roscoe), Curry leaf oil (*Bergera koenigii* L.), Calamintha nepeta oil, Ashanti pepper (*Piper guineense* Schum and Thom), Wormwood oil (*Artemisia absinthium* L.), Citrus oils, *Ocimum basilicum* var., Red sage (Texas sage) (*S. coccinea* Juss. Ex Murr.), Mint oils, Pistacia oils, Moroccan chamomile oil (*Chamaemelum mixtum* L.), Clary sage (*Salvia sclarea* L), Caraway (Van Dongen and Donders, 2021). Based on the quantitative data, a consumption ratio of 7 could be calculated for the primary constituent, germacrene D (Stofberg and Grundschober, 1987). The Expert Panel noted the assay of the material was ≥85% of the named material with *trans*-caryophyllene, other aliphatic and aromatic hydrocarbons and each of the aliphatic and aromatic tertiary alcohols and related esters, and epoxide derivatives as the secondary components (<5%, <4%, <1%, respectively) and considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Expert Panel concluded that metabolic data exist for a representative member of the principal identified congeneric groups that indicate that the group would be predicted to be metabolized primarily by well-established detoxication pathways (Adams et al., 2011). In an OECD 471 guideline and GLP-compliant Ames assay, germacrene D (purity 89%) was non-mutagenic and non-cytotoxic at concentrations up to 5 µg/plate in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 in the presence and absence of S9 metabolic activation using the plate incorporation and pre-incubation methods (Schreib, 2020c). (-)-Germacrene D (purity 45%) was non-mutagenic and non-cytotoxic at concentrations up to 5000 µg/plate in an OECD 471 guideline and GLP-compliant Ames assay conducted in triplicate in *S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP2*uvr*A in the presence and absence of S9 metabolic activation using the plate incorporation method (Sawant, 2017). In an OECD 487 guideline and GLP-compliant *in vitro* micronucleus assay, no significant induction of micronuclei was observed at concentrations up to 86 µg/mL of (-)-germacrene D (purity 45%) incubated with human lymphocytes with 24 hours in the absence of S9 metabolic activation as well as 3 hours with a 21-hour recovery period in the absence and presence of S9 metabolic activation, respectively (Bhalli, 2017b). In an *in vitro* mouse lymphoma assay, the constituent b-caryophyllene (FEMA 2252) was incubated with L5178Y TK +/- cells for 4 hours at 15-140 µg/mL in the presence and absence of S9 metabolic activation. Doubling of mutant frequencies were observed at cytotoxic concentrations and are likely to be false positives, therefore b-caryophyllene (FEMA 2252) was considered to be non-mutagenic in the absence and presence of S9 metabolic activation (Seifried et al., 2006). In an *in vitro* micronucleus assay, no significant differences in micronuclei induction were observed in human lymphocytes treated with up to 100 µg/mL of the constituent b-caryophyllene (FEMA 2252) (Di Sotto et al., 2010). In two additional *in vitro* assays, no evidence of genotoxicity was found for the constituent b-caryophyllene (FEMA 2252) in the UDS assay in rat hepatocytes up to 10 µl/mL (approximately 9 µg/mL based on the specific density of the substance) or in an *in vitro* sister chromatid exchange assay in CHO K-1 hamster cells up to 333 µM (approximately 68 µg/mL) (Sasaki et al., 1989). In *in vivo* micronucleus assays, male mice administered single or repeated gavage doses (three consecutive days) of the constituent b-caryophyllene (FEMA 2252) at dose levels up to 2000 mg/kg bw/day did not exhibit significant increases in micronucleated polychromatic erythrocytes in sampled blood smears (Molina-Jasso et al., 2009). In an *in vivo* sister chromatid exchange and chromosome aberration assay, the constituent b-caryophyllene (FEMA 2252) was orally administered to groups of male Swiss-Webster mice at single doses of 0 (corn oil), 20, 200 or 2000 mg/kg bw. No significant differences in mitotic indices, sister chromatid exchanges as well as the amount and types of chromosome aberrations

were observed in the bone marrow of all treated mice compared to the control group (Alvarez-Gonzalez et al., 2014). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of Germacrene D ≥85% (Gooderham et al., 2020). In an OECD 408 guideline and GLP-compliant 90-day dietary toxicity study, b-caryophyllene (FEMA 2252) was administered to male and female Sprague Dawley rats at concentrations of 0, 222, 456 and 1367 mg/kg bw/day or 0, 263, 1033 and 4278 mg/kg bw/day, respectively. NOAELS of 222 mg/kg bw/day and 263 mg/kg bw/day were established for b-caryophyllene (FEMA 2252) in male and female rats, respectively (Bastaki et al., 2020). In an OECD 407 guideline-compliant repeated dose 28-day study, female Swiss mice were orally administered via a Tween 80 saline vehicle solution 300 mg/kg bw/day or 2000 mg/kw bw/day of the constituent b-caryophyllene (FEMA 2252). No adverse clinical chemistry, hematological, urinalysis, organ weights and histopathological findings up to the highest tested dose were reported (da Silva Oliveira et al., 2018). The Expert Panel assigned a conservative NOAEL for b-caryophyllene (FEMA 2252) of 222 mg/kg bw/day which is greater than 1,110,000 times the anticipated daily *per capita* intake of germacrene D ≥85% from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding *Scutellaria baicalensis* root extract (CAS 94279-99-9) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4975) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. The substance was evaluated individually within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of *Scutellaria baicalensis* root extract from use as a flavor ingredient to be 28 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The material is produced from the roots of the *Scutellaria baicalensis* plant. Though some preparations of this material are consumed as traditional medicine, a consumption ratio could not be calculated. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel concluded that metabolic data exist for a representative member of the principal identified congeneric groups that indicate that constituents of the groups would be predicted to be metabolized primarily by well-established detoxication pathways. In an OECD 471 guideline and GLP-compliant Ames assay, the concentrated extract of *Scutellaria baicalensis* root (purity 93%) was non-mutagenic in *S. typhimurium* strains TA1537, TA1535, TA98, TA100 and TA102 with and without S9 metabolic activation using the plate incorporation method at concentrations up to 5000 µg/plate (Tekale, 2018a). In another OECD 471 guideline and GLP-compliant Ames assay, a related preparation GHX02 (approximately 33% root extract of *Scutellaria baicalensis*, 33% Trichosanthis seeds, 17% *Armeniacae* seeds and 17% *Coptidis rhizoma*) was non-mutagenic at concentrations of 313-5000 µg/plate in *S. typhimurium* TA100, TA1535, TA98, TA1537 and *E. coli* WP2*uvr*A (pKM101) (Ji et al., 2020). In a GLP-compliant *in vitro* chromosome aberration assay, significant increases in the frequency of numerical chromosome aberrations were observed in all tested concentrations, but not in structural chromosome aberrations after CHL cells were incubated with GHX02. The Expert Panel noted that the long-term exposure condition as recommended by the OECD 473 test guideline was not tested in this study, nor did it meet the 300 well-spread metaphases scoring minimum to adequately assess the significant of chromosome aberrations (Ji et al., 2020). No clinical signs of toxicity were observed in an OECD 474 guideline and GLP-compliant *in vivo* micronucleus assay when ICR male mice were administered CXH02 up to concentrations of 5000 mg/kg bw/day (Ji et al., 2020). No statistically significant increases in %tail DNA was observed in left liver lobe samples of Sprague-Dawley rats administered GXH02 in an OECD 489 guideline and GLP-compliant *in vivo* comet assay (Ji et al., 2020). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of *Scutellaria baicalensis* root extract (Gooderham et al., 2020). In an OECD 407 guideline and GLP-compliant repeated dose 28-day dietary toxicity study, no significant treatment-related adverse clinical effects were observed when the concentrated extract of *Scutellaria baicalensis* root (purity 93%) was administered to Wistar rats. The highest concentration tested of 1250 ppm was determined to be the NOAEL, corresponding to a concentrations of 129 mg/kg bw/day in the males and 119 mg/kg bw/day in the females (Shah, 2019). No adverse effects on the respiratory, cardiovascular, and central nervous system were observed when Sprague-Dawley rats and beagle dogs were administered UP446, a 4:1 mixture of *Scutellaria baicalensis* extract and catechin extract obtained from repeated crystallization of an aqueous extract of *Acacia catechu* with not less than 60% baicalin and not less than 10% catechin content, orally at concentrations up to 5000 mg/kg bw/day in rats and up to 1000 mg/kg bw/day in beagle dogs (Yimam et al., 2016). In an OECD 408 guideline and GLP-compliant 90-day repeated dose oral toxicity study, no adverse treatment-related effects were observed when the same related preparation was administered to Sprague Dawley rats. The highest concentration of 1000 mg/kg bw/day was identified as the NOAEL (Yimam et al., 2010). No significant dose-dependent and treatment-related adverse effects were observed when Sprague Dawley rats were administered the same related preparation by gavage mixed in a solution of 0.5% carboxymethylcellulose in distilled water in a GLP-compliant 26-week repeated dose oral toxicity study. The NOAEL was identified as the highest administered concentration of 2000 mg/kg bw/day (Lee et al., 2013). The Expert Panel assigned a conservative NOAEL for *Scutellaria baicalensis* root extract of 119 mg/kg bw/day, which is greater than 238,000 times the anticipated daily *per capita* intake of *Scutellaria baicalensis* root extract (1% propylene glycol solutions of the concentrated product extract) from use as a flavor ingredient. No reproductive or developmental effects were reported for female Sprague-Dawley and New Zealand white rabbits administered UP446 at concentrations up to 1000 mg/kg bw/day by gavage from gestation day 6-18 or 6-17 in rabbits and rats, respectively, in a GLP-compliant study. The authors considered the maternal and fetal NOAEL to be greater than 1000 mg/kg bw/day for rats and rabbits (Yimam et al., 2015a). In another GLP-compliant reproductive and developmental toxicity study in female Sprague-Dawley rats,

the related preparation UP446 was administered at concentrations up to 1000 mg/kg bw/day from gestation day 6 to day 20 of lactation. No significant, treatment related signs of toxicity were reported. The authors considered the maternal and developmental NOAEL to be greater than 1000 mg/kg bw/day for rats (Yimam et al., 2015b). In a GLP-compliant reproductive and embryonic study, a NOAEL of 1000 mg/kg bw/day was determined for male and female Sprague-Dawley rats administered UP446 by gavage at concentrations up to 1000 mg/kg bw/day (Yimam et al., 2015c). Based on its review of available reproductive and developmental toxicity data, the Expert Panel assigned a conservative NOAEL for the related preparation UP446 to be 1000 mg/kg bw/day, which is greater than 2,000,000 times the anticipated daily *per capita* intake of *Scutellaria baicalensis* root extract (1% propylene glycol solution of the concentrated product extract) from use as a flavor ingredient.

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

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 10-hydroxy-4,8-dimethyldec-4-enal (CAS 65210-18-6) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4977) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. The substance was evaluated individually within the context of the chemical group of aliphatic primary alcohols, carboxylic acids, acetals, and esters containing additional oxygenated functional groups (JECFA, 2000; SLR, M1). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of 10-hydroxy-4,8-dimethyldec-4-enal from use as a flavor ingredient to be 0.1 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). This material is not known to occur in nature and thus no consumption ratio can be calculated. The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is anticipated that 10-hydroxy-4,8-dimethyldec-4-enal will oxidized to the corresponding aldehyde and to be further oxidized to the corresponding carboxylic acid (Bosron and Ting-Kai, 1980; Levi and Hodgson, 1989). The acid can then undergo *beta*-oxidative cleavage to carbon dioxide in major metabolic pathways, or may undergo a combination of *omega*-, (*omega*-1) and *beta*-oxidation as well as selective dehydrogenation and hydration to yield polar metabolites that are excreted as glucuronic or sulfate conjugates in the urine

and to a lesser extent, in the feces (Voet and Voet, 1990; Williams, 1959). Alternatively, 10-hydroxy-4,8-dimethyldec-4-enal may be reduced to the corresponding alcohol as a short-lived *in vivo* intermediate (Dilberto et al., 1990). In an Ames assay, 10-hydroxy-4,8-dimethyldec-4-enal was non-mutagenic at concentrations up to 5000 µg/plate in *S. typhimurium* TA98, TA100, TA1535, TA1537 as well as *E. coli* WP2uvrA in the presence or absence of S9 metabolic activation (Kino, 2020c). When tested in the same strains in an OECD 471 guideline and GLP-compliant Ames assay, the structural relative 9-hydroxy-5,9-dimethyldec-4-enal was non-mutagenic up to concentrations of 5000 µg/plate using the plate incorporation and pre-incubation methodologies (Sokolowski, 2013). The structural relative hydroxycitronellal (FEMA 2583) was non-mutagenic in an Ames assay using *S. typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 in the absence and presence of S9 metabolic activation using both the plate incorporation and preincubation methodologies (Wild et al., 1983). No significant induction of micronucleated polychromatic erythrocytes were observed when the same structural relative was provided to NMRI mice (4/dose) at up to 861 mg/kg bw by intraperitoneal administration (Wild et al., 1983). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 10-hydroxy-4,8-dimethyldec-4-enal (Gooderham et al., 2020). In an OECD 407 guideline and GLP-compliant 28-day toxicity study, the administration of the structural relative 9-hydroxy-5,9-dimethyldec-4-enal to Sprague-Dawley rats at concentrations of 0, 50, 200 and 800 mg/kg bw/day resulted in a NOAEL of 800 mg/kg bw/day (Broich, 2014). In a 2-year, chronic dietary toxicity study, the structural relative hydroxycitronellal (FEMA 2583) provided to male and female rats at 50 and 250 mg/kg bw/day resulted in a NOAEL of 250 mg/kg bw/day (Bar and Griepentrog, 1967), which was 125,000,000 times greater than the anticipated daily *per capita* intake of 10-hydroxy-4,8-dimethyldec-4-enal from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the natural flavor complex GRAS application and supporting information regarding rebaudioside B 95% (CAS 58543-17-2) and concluded that use of the substance as a flavor ingredient it is GRAS (FEMA 4978) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. The substance was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of rebaudioside B 95% from use as a flavor ingredient to be 55 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This material is derived from the leaves of *Stevia rebaudiana* leaves. The Expert Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Expert Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavor ingredient (Harman and Hallagan, 2013). Metabolic data exist that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Cardoso et al., 1996; Gardana et al., 2003; Geuns et al., 2003; Geuns et al., 2007; Hutapea et al., 1997; Koyama et al., 2003a; Koyama et al., 2003b; Nakayama et al., 1986; Purkayastha et al., 2014; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha and Kwok, 2020; Renwick and Tarka, 2008; Roberts and Renwick, 2008; Roberts et al., 2016; Wheeler et al., 2008; Wingard, 1980). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in *in vitro* mutagenicity assays, *in vivo* studies do not provide evidence of genotoxic effects (Nakajima, 2000b; Pezzuto et al., 1985; Pezzuto et al., 1986; Rumelhard et al., 2016; Suttajit et al., 1993; Terai et al., 2002; Williams and Burdock, 2009). Based on the results for the various steviol glycosides, the Panel did not identify specific concerns related to the potential genotoxicity of Rebaudioside B 95% (Gooderham et al., 2020). In a 108-week carcinogenicity study for stevioside, no carcinogenic effects were observed (Toyoda et al., 1997). In a 2-year feeding study, male and female rats were administered the equivalent of 0, 50, 150, or 550 mg/kg bw/day of a stevia extract comprised of 74% stevioside and 16% rebaudioside A. The authors considered the NOAEL from this 2-year rat feeding study of a stevia extract to be equal to 550 mg/kg bw/day (Yamada et al., 1985), which is greater than 600,000 times the anticipated daily *per capita* intake of rebaudioside B 95% from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding 2-(furan-2-yl)-4,6-dimethyl-1,3,5-dithiazinane (CAS 142062-38-2) and concluded that the use of the substance as a flavor ingredient is GRAS (FEMA 4979) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. The substance was evaluated individually and within the context of the chemical group sulfur-containing heterocyclic and heteroaromatic derivatives (JECFA, 2003, 2008, 2012, 2015; SLR, D16). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of 2-(furan-2-yl)-4,6-dimethyl-1,3,5-dithiazinane from use as a flavor ingredient to be 0.001 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Expert Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is anticipated that 2-(furan-2-yl)-4,6-dimethyl-1,3,5-dithiazinane will be metabolized similarly to thiazole derivatives. Because of the presence of alkyl substituents, metabolism is expected to be primarily via side-chain oxidation and ring *S*- and *N*-oxidation followed by excretion in the urine unconjugated or as glutathione conjugates after glucuronidation (JECFA, 2003). An *in vitro* hydrolysis study with the structurally related substance 2 or 4-isobutyl-(4 or 2),6-dimethyldihydro-4*H*-1,3,5-dithiazine (FEMA 3781) tested in simulated gastric juice and simulated intestinal fluid indicates that it is not likely that hydrolysis will occur (FEMA, 1989). In an Ames assay, that 2-(furan-2-yl)-4,6-dimethyl-1,3,5-dithiazinane was non-mutagenic at concentrations up to 5,000 µg/plate in *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 in the presence and absence of S9 metabolic activation (Shukla, 2020). Based on these results, as well as the structure of the substance and the arrangement

and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of 2-(furan-2-yl)-4,6-dimethyl-1,3,5-dithiazinane (Gooderham et al., 2020). In an OECD 408 guideline and GLP-compliant 90-day repeat dose toxicity study following a 14-day range finding study, the administration of the structurally related substance 2,4,6-triisobutyl-5,6-dihydro-4*H*-1,3,5-dithiazine (FEMA 4017) to Sprague Dawley rats at concentrations of 0, 140, 1050, or 2100 ppm (equivalent to 0, 9, 68 or 132 mg/kg bw/day and 0, 11, 77 or 154 mg/kg bw/day for males and females, respectively) resulted in a NOAEL of 140 ppm (equivalent to 9 and 11 mg/kg bw/day in males and females, respectively) (Bauter, 2012, 2013). The Expert Panel determined that the most conservative NOAEL of 9 mg/kg bw/day for the structural relative 2,4,6-triisobutyl-5,6-dihydro-4*H*-1,3,5-dithiazine (FEMA 4017) is 540,000,000 times the anticipated daily *per capita* intake of the candidate substance, 2-(furan-2-yl-4,6-dimethyl-1,3,5-dithiazinane, from use as a flavor ingredient.

Using scientific procedures the Expert Panel reviewed the GRAS application and supporting information regarding a mixture of (8*Z*,11*Z*)-heptadeca-8,11-dienal and (*Z*)-heptadec-8-enal (CAS 2415657-73-5) and concluded that the use as a flavor ingredient is GRAS (FEMA 4980) (Smith et al., 2005a) in the food categories and at the use levels specified in Table 2. The substance was evaluated individually and within the context of the chemical group unsaturated linear and branched-chain aliphatic, non-conjugated aldehydes, related primary alcohols, carboxylic acids and esters (JECFA, 1999, 2004, 2007, 2012). The Expert Panel calculated the anticipated *per capita* intake ("eaters only") of the mixture of (8*Z*,11*Z*)-heptadeca-8,11-dienal and (*Z*)-heptadec-8-enal from use as flavor ingredient to be 1 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Expert Panel noted the assay of the material was >95% mixture of aldehydes containing 63-70% (8*Z*,11*Z*)-heptadeca-8,11-dienal, 19-29% (*Z*)-heptadec-8-enal as well as up to 10% of other linear and branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, carboxylic acids and related esters and saturated aliphatic, acyclic, branched-chain primary alcohols, aldehydes, carboxylic acids and related esters, and considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Expert Panel concluded that metabolic data exist for a representative member of the principal identified congeneric groups that indicate that the group would be predicted to be metabolized primarily by well-established detoxication pathways (Abumrad et al., 1984; Beedham, 1988; Borgstrom, 1974; Bosron and Ting-Kai, 1980; Dawson et al., 1964; Dhopshwarkar and Mead, 1973; Eckfeldt and Yonetani, 1982; Feldman and Weiner, 1972; Gaillard and Derache, 1965; Gibson et al., 1982; Harris et al., 1980; Levi and Hodgson, 1989; Masoro, 1977; Voet and Voet, 1990; Wakil and Barnes, 1971; Williams, 1959). The candidate substance, a mixture of (8*Z*,11*Z*)-heptadeca-8,11-dienal and (*Z*)-heptadec-8-enal, was non-mutagenic in an OECD 471 guideline and GLP-compliant Ames assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 as well as *E. coli* WP2*uvr*A at concentrations up to 5000 µg/plate either with or without S9 metabolic activation (Sokolowski, 2020). The structural relative 10-undecenal (FEMA 3095) was similarly non-mutagenic in an OECD 471 guideline and GLP-compliant Ames assay in *S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 (Bhatia et al., 2010; Sokolowski, 2020). No significant induction of chromosome aberrations was observed when the same structural relative was tested in a GLP-compliant *in vitro* chromosome aberration assay in Chinese hamster lung cells (CHL/IU) (MHLW, 2014). The structural relative 10-undecenal (FEMA 3095) was also negative in an *in vivo* micronucleus test in NMRI mice at doses up to 2000 mg/kg bw (Bhatia et al., 2010; Honarvar et al., 2007a). In an OECD 471 guideline and GLP-compliant Ames assay, a related preparation, a reaction mass of (9*E*)-9-undecenal and (9*Z*)-9-undecenal and undec-10-enal (purity: 91.9% sum of three isomers), was non-mutagenic in *S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvr*A in the absence and presence of S9 using the plate incorporation method (Verspeek-Rip, 2014). No significant induction of micronuclei in human lymphocytes or induction of gene mutations at the HPRT locus of CHO V79 cells were observed when the same related preparation was tested in an OECD 487 guideline and GLP-compliant *in vitro* micronucleus assay and in an OECD 476 guideline and GLP-compliant *in vitro* mammalian cell gene mutation test (ECHA, 2018c). The constituent oleic acid (FEMA 2815) was non-mutagenic at concentrations up to 5000 µg/plate in an Ames assay conducted in *S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP2uvrA in the absence and presence of S9 (Mortelmans et al., 1986; Shimizu et al., 1985). No significant induction of micronuclei was observed in an OECD 487 guideline and GLP -compliant *in vitro* micronucleus assay in human lymphocytes tested with concentrations of up to 80 µg/mL in a 4-hr exposure group and 40-100 µg/mL in a 24-hr exposure group of the constituent oleic acid (FEMA 2815) (Morris, 2014b). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Expert Panel did not identify specific concerns related to the genotoxicity of a mixture of (8*Z*,11*Z*)-heptadeca-8,11-dienal and (*Z*)-heptadec-8-enal (Gooderham et al., 2020). In an OECD 422 guideline and GLP-compliant combined repeat dose and reproductive/development toxicity study, the administration of the related preparation of a reaction mass of (9*E*)-9-undecenal and (9*Z*)-9-undecenal and undec-10-enal to Sprague-Dawley rats by gavage resulted in a NOAEL of 1000 mg/kg bw/day (ECHA, 2018d), which is 50,000,000 times greater than the anticipated daily *per capita* intake of a mixture of (8*Z*,11*Z*)-heptadeca-8,11-dienal and (*Z*)-heptadec-8-enal from use as a flavor ingredient. In an OECD 407 guideline and GLP-compliant 28-day toxicity study, the administration of the structural relative 10-undecenal (FEMA 3095) administered to Wistar rats at concentrations up to 1000 mg/kg bw/day resulted in a NOAEL of 1000 mg/kg bw/day (ECHA, 2015). In an OECD 408 guideline and GLP-compliant 90-day dietary toxicity study, the administration of the structural relative 10-undecenal (FEMA 3095) to Sprague-Dawley Crl:CD® (SD) IGS BR rats in the diet resulted in a NOAEL of 200 ppm, or approximately 14.3 mg/kg bw/day, which is 715,000 times greater than the anticipated daily *per capita* intake of the mixture of (8*Z*,11*Z*)-heptadeca-8,11-dienal and (*Z*)-heptadec-8-enal from use as a flavor ingredient (Liwska and Watson, 2012).

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