

GRAS 28

FLAVORING SUBSTANCES

[About FEMA GRAS Program](#)

FEMA EXPERT PANEL: S.M. COHEN, S. FUKUSHIMA, N.J. GOODERHAM, F.P. GUENGERICH, S.S. HECHT, I.M.C.M. RIETJENS, R.L. SMITH

28. GRAS FLAVORING SUBSTANCES: This list of substances will appear in the 28th 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](#).

DISCLAIMER: The user of this list agrees that its use of this document and the information contained therein is at the user’s sole risk and that FEMA shall have no liability to any person for any loss or damage arising out of the use of this document. This document and the information contained herein is subject to change. It is the responsibility of the user to ensure the information is up to date.

STATEMENT REGARDING GENERALLY RECOGNIZED AS SAFE STATUS OF EUGENYL

METHYL ETHER (METHYL EUGENOL): The FEMA GRAS status of methyl eugenol (CAS NO. 93-15-2; FEMA No. 2475) 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 methyl eugenol, including recent studies, the Expert Panel concluded that additional data are required to support the continuation of its GRAS status. Such data should clarify the relevance to humans of DNA adducts formed by methyl eugenol. Until such data are available for review by the Expert Panel, the flavor ingredient methyl eugenol has been removed from the FEMA GRAS list.

The Expert Panel also considered the FEMA GRAS status of herbs, spices, and essential oils that contain naturally-occurring methyl eugenol, including basil, pimento, allspice, etc. and their extractives. The Panel concluded that these flavorings continue to meet the criteria for FEMA GRAS under their conditions of intended use as flavorings.

TABLE 1: Primary Names & Synonyms

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

FEMA NO.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4817	S-[(Methylthio)methyl]thioacetate 3,5-Dithiahexan-2-one Methylthiomethyl acetyl sulfide
4818	trans-1-Ethyl-2-methylpropyl 2-butenolate 1-Ethyl-2-methylpropyl (2E)-2-butenic acid ester
4819	Erythritol (2R,3S)-ref-1,2,3,4-Butanetetrol (2R,3S)-Butane-1,2,3,4-tetrol meso-Erythritol Mesoerythritol
4820	Purified Damar Gum Purified <i>Shorea javanica</i> Gum
4821	gamma-Aminobutyric acid:Linoleic acid conjugates GABA:Linoleic acid conjugates
4822	2,6-Dipropyl-5,6-dihydro-2H-thiopyran-3-carboxaldehyde 3,6-Dihydro-2,6-dipropyl-2H-thiopyran-5-carboxaldehyde
4823	Allyl 1-propenyl disulfide Allyl propenyl disulfide 1-Propenyl 2-propenyl disulfide
4824	2-(5-Isopropyl-2-methyl-tetrahydrothiophen-2-yl)-ethyl acetate Tetrahydro-2-methyl-5-(1-methylethyl)-2-thiopheneethanol acetate
4825	E-6-Nonenal trans-6-Nonenal
4826	3-Phenylpropyl 2-(4-hydroxy-3-methoxyphenyl)acetate 3-Phenylpropyl homovanillate
4827	1-(4-Methyl-3-cyclohexen-1-yl)-ethanone 1-Methyl-4-acetyl-1-cyclohexene 1-(4-Methylcyclohex-3-enyl)ethanone 4-Methyl-3-cyclohexen-1-yl methyl ketone
4828	1,1-Propanedithioacetate S,S'-propane-1,1-diyl diethanethioate Propane-1,1-dithioacetate Ethanedithioic acid S,S'-propylidene ester 1,1-Propanedithiol, diacetate
4829	2-Pyrrolidone alpha-Pyrrolidone gamma-Aminobutyrolactam Butyrolactam
4830	7,8-Dihydroxyflavone 7,8-Dihydroxy-2-phenyl-4H-1-benzopyran-4-one 7,8-Dihydroxy-2-phenyl-4-benzopyrone 7,8-Dihydroxy-2-phenyl-4H-chromen-4-one
4831	Katemfe fruit extract <i>Thaumatococcus daniellii</i> fruit extract
4832	2-(3-Benzoyloxypropyl)pyridine 2-[3-(Phenylmethoxy)propyl]-pyridine
4833	(2S)-3',7-Dihydroxy-8-methyl-4'-methoxyflavan (S)-2-(3-Hydroxy-4-methoxyphenyl)-8-methylchroman-7-ol (2S)-7,3'-Dihydroxy-4'-methoxy-8-methylflavane
4834	(R)-5-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-7-methylchroman-2-one (4R)-4-(4-Hydroxy-3-methoxyphenyl)-5,7-dimethyl-3,4-dihydro-2H-1-benzopyran-2-one

FEMA NO.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4835	2,4-Dihydroxy-N-[(4-hydroxy-3-methoxyphenyl)methyl] benzamide 2,4-Dihydroxybenzoic acid vanillylamide
4836	10% solution of 3,4-dimethyl-2,3-dihydrothiophene-2-thiol
4837	Chrysanthemum parthenium extract Feverfew extract Common pellitory extract Motherwort extract <i>Tanacetum parthenium</i> extract
4838	Valencene 80 extract
4839	Mixture of 3- and 4-butyl-2-thiophenecarboxaldehyde
4840	(±)-Tetrahydronootkatone (±)-Octahydro-4,4a-dimethyl-6-(1-methylethyl)-2(1H)-naphthalenone (±)-6-Isopropyl-4,4a-dimethyl-decalin-2-one
4841	cis-5-Dodecenyl acetate (Z)-5-Dodecen-1-ol acetate cis-Dodec-5-en-1-yl acetate
4842	2,4,5-Trithiaoctane 1-(Methylthiomethyl)-2-propylidysulfane
4843	3-(Allyldithio)butan-2-one 3-(Allyldisulfanyl)butan-2-one 3-(2-Propen-1-ylidithio)-2-butanone
4844	(2E,4E)-2,4-Decadien-1-ol acetate trans, trans-2,4-decadien-1-yl acetate
4845	Glucosylated stevia extract
4846	Grapefruit essence oil (Citrus paradisi Macf.) <i>Citrus paradisi</i> Macf. essence oil
4847	Grapefruit oil, terpeneless (Citrus paradisi Macf.) <i>Citrus paradisi</i> Macf. Oil, terpeneless
4848	Lemon terpenes <i>Citrus limon</i> (L.) Burm. f., terpenes
4849	Lime terpenes <i>Citrus aurantifolia</i> Swingle, terpenes <i>Citrus medica</i> var. <i>acida</i> , terpenes <i>Citrus latifolia</i> , terpenes
4850	Orange terpenes <i>Citrus sinensis</i> (L.) Osbeck., terpenes
4851	Grapefruit terpenes <i>Citrus paradisi</i> Macf., terpenes
4852	Lemon essence oil (Citrus limon (L.) Burm. f.) <i>Citrus limon</i> (L.) Burm. f. essence oil

TABLE 1 Continued: Primary Names & Synonyms

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

FEMA NO.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4853	Petitgrain oil terpeneless <i>Citrus aurantium</i> L. oil terpeneless
4854	Tangelo oil (<i>Citrus paradisi</i> Macf. x <i>Citrus tangerine</i> hort. ex Tanaka) <i>Citrus paradisi</i> Macf. x <i>Citrus tangerine</i> hort. ex Tanaka oil <i>Citrus x tangelo</i> oil
4855	Clementine oil (<i>Citrus clementina</i> hort. ex Tanaka) <i>Citrus clementina</i> hort. ex Tanaka oil
4856	Blood orange oil (<i>Citrus sinensis</i> (L.) Osbeck 'Blood orange') <i>Citrus sinensis</i> (L.) Osbeck 'Blood orange' oil
4857	Iyokan oil (<i>Citrus iyo</i>) <i>Citrus iyo</i> oil
4858	Hassaku oil (<i>Citrus hassaku</i> hort. ex Tanaka) <i>Citrus hassaku</i> hort. ex Tanaka oil
4859	Sikuwasya oil (<i>Citrus depressa</i>) <i>Citrus depressa</i> oil Shiikuwasha oil
4860	Natsumikan oil (<i>Citrus natsudaikai</i>) <i>Citrus natsudaikai</i> oil
4861	Mikan oil (<i>Citrus unshiu</i>) <i>Citrus unshiu</i> oil Satsuma mandarin oil
4862	Yuzu oil (<i>Citrus junos</i> (Sieb.) c. Tanaka) <i>Citrus junos</i> Siebold ex Tanaka oil
4863	Sudachi oil (<i>Citrus sudachi</i> hort. ex Shirai) <i>Citrus sudachi</i> hort. ex Shirai oil
4864	Kabosu oil (<i>Citrus sphaerocarpa</i>) <i>Citrus sphaerocarpa</i> oil
4865	Ponkan oil (<i>Citrus reticulata</i> Blanco 'Ponkan') <i>Citrus reticulata</i> Blanco 'Ponkan' oil
4866	Orange essence water phase (<i>Citrus sinensis</i> (L.) Osbeck) Orange aroma water phase
4867	(3<i>S</i>,5<i>R</i>,8<i>S</i>)-3,8-Dimethyl-5-prop-1-en-2-yl-3,4,5,6,7,8-hexahydro-2H-azulen-1-one (-)-Guaia-1(5),11-dien-2-one
4868	4-(4-Methyl-3-penten-1-yl)-2(5<i>H</i>)-furanone

FEMA NO.	SUBSTANCE PRIMARY NAMES AND SYNONYMS
4869	4-(<i>l</i>-Menthoxyl)-2-butanone 4-[(1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-2-Isopropyl-5-methylcyclohexyl]-oxybutan-2-one
4870	2-Ethyl-4-methyl-1,3-dithiolane
4871	2-Phenoxyethyl 2-(4-hydroxy-3-methoxyphenyl)acetate
4872	3-(3-Hydroxy-4-methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one Hesperetin dihydrochalcone
4873	Watermint, <i>Mentha aquatica</i> L., extract Marsh mint extract Hairy mint extract Smartweed extract Pepperwort extract Wild mint extract
4876	Enzyme modified stevia, stevioside 20%
4877	(<i>E</i>)-3-(3,4-Dimethoxyphenyl)-<i>N</i>-[2-(4-methoxyphenyl)ethyl]-acrylamide 4-methoxyphenylethylamine 3,4-dimethoxycinnamic amide
4878	<i>Cordyceps sinensis</i> fermentation product

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 judgements that the substances are generally recognized as safe (GRAS).

	S-[(Methylthio)methyl]thioacetate	trans-1-Ethyl-2-methylpropyl 2-butenate	Erythritol	Purified Damar Gum	gamma-Aminobutyric acid; Linoleic acid conjugates	2,6-Dipropyl-5,6-dihydro-2H-thiopyran-3-carboxaldehyde	Allyl 1-propenyl disulfide	2-(5-Isopropyl-2-methyl-tetrahydrothiophen-2-yl)-ethyl acetate	E-6-Nonenal	3-Phenylpropyl 2-(4-hydroxy-3-methoxyphenyl)acetate
FEMA No.	FEMA No. 4817	4818	4819	4820	4821	4822	4823	4824	4825	4826
BAKED GOODS	0.5/1	0.4/4			0.02/0.5		1/4	0.3/1	0.001/0.01	
BEVERAGES, NON-ALCOHOLIC		0.2/2	5000/12500	100/200	0.01/0.25	0.05/5	0.1/0.5	0.1/0.5	0.00001/0.0001	3/15
BEVERAGES, ALCOHOLIC		0.2/2		100/200	0.0002/0.005	0.03/10		0.3/2	0.00001/0.0001	3/15
BREAKFAST CEREALS		0.4/4			0.02/0.5		1/4	0.3/1	0.001/0.01	
CHEESES	0.5/1	0.1/0.5			0.02/0.5		1/4		0.001/0.01	
CHEWING GUM		0.5/5			0.02/0.5	10/100		1/5	0.0001/0.001	25/100
CONDIMENTS AND RELISHES					0.01/0.25		1/4			5/40
CONFECTIONS AND FROSTINGS		0.4/4			0.01/0.25	0.3/30		0.5/2	0.0001/0.001	
EGG PRODUCTS					0.01/0.25				0.0001/0.001	
FATS AND OILS	0.5/1				0.02/0.5		1/4	0.3/1	0.01/0.1	
FISH PRODUCTS					0.01/0.25		1/4		0.0001/0.001	
FROZEN DAIRY		0.5/5			0.01/0.5	0.5/50		0.1/0.5	0.0001/0.001	
FRUIT ICES		0.2/2	5000/12500		0.01/0.25	0.05/5		0.1/0.5	0.0001/0.001	
GELATINS AND PUDDINGS		0.2/2			0.01/0.25	0.2/10		0.1/0.5	0.0001/0.001	
GRANULATED SUGAR										
GRAVIES	0.3/1				0.01/0.25		1/4		0.001/0.01	
HARD CANDY		0.4/4			0.02/0.5	0.5/50		0.5/2	0.001/0.01	5/20
IMITATION DAIRY					0.02/0.5	0.05/5			0.001/0.01	
INSTANT COFFEE AND TEA		0.1/1	5000/12500		0.0002/0.005	0.05/5	0.01/0.1	0.2/1	0.00001/0.0001	2/15
JAMS AND JELLIES		1/5			0.01/0.25	0.5/20		0.3/1		
MEAT PRODUCTS	0.5/1				0.02/0.5		1/4		0.0001/0.001	5/40
MILK PRODUCTS		0.2/2			0.01/0.25	0.05/5	1/4	0.1/0.5	0.00001/0.0001	2/10
NUT PRODUCTS					0.002/0.05		1/4		0.0001/0.001	
OTHER GRAINS					0.002/0.05		1/4		0.0001/0.001	
POULTRY	0.5/1				0.02/0.5		1/4			
PROCESSED FRUITS		0.4/4	5000/12500		0.01/0.25	0.05/5		0.1/0.5		
PROCESSED VEGETABLES	0.5/1				0.01/0.25		0.5/4			
RECONSTITUTED VEGETABLES					0.01/0.25		0.5/4			
SEASONINGS AND FLAVORS	0.5/1	0.2/2			0.01/0.25	0.5/20	1/4	0.1/0.5	0.1/1.0	50/300
SNACK FOODS	0.5/2	0.2/2			0.01/0.25		1/4	0.1/0.5	0.0001/0.001	5/40
SOFT CANDY		0.4/4			0.01/0.25	0.2/5		0.5/2	0.0001/0.001	
SOUPS	0.2/1				0.01/0.25		1/4		0.0001/0.001	5/20
SUGAR SUBSTITUTES					0.005/0.15					
SWEET SAUCES		0.2/2			0.005/0.15	0.2/10	0.5/2			

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 judgements that the substances are generally recognized as safe (GRAS).

	1-(4-Methyl-3-cyclohexen-1-yl)-ethanone	1,1-Propanedithioacetate	2-Pyrrolidone	7:8-Dihydroxyflavone	Katemfe fruit extract	2-(3-Benzoyloxypropyl)pyridine	(2S)-3:7-Dihydroxy-8-methyl-4-methoxyflavan	(R)-5-Hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-7-methylchroman-2-one	2,4-Dihydroxy-N-[(4-hydroxy-3-methoxyphenyl)methyl] benzamide	10% Solution of 3,4-dimethyl-2,3-dihydrothiophene-2-thiol	Chrysanthemum parthenium extract
CATEGORY	4827	4828	4829	4830	4831	4832	4833	4834	4835	4836	4837
BAKED GOODS	0.5/1.5	0.1/0.5	5/20		4/10	1/10				0.04/0.4	
BEVERAGES, NON-ALCOHOLIC	0.05/0.25		5/20	5/15	4/10	0.1/1	30/50	15/20	10/100	0.01/0.05	30/60
BEVERAGES, ALCOHOLIC	0.5/2.5		5/20	5/15	4/10		30/50	15/20		0.03/0.15	30/60
BREAKFAST CEREALS	0.5/2.5	0.1/0.2	5/20		4/10				10/100		
CHEESES	0.2/2.5	0.1/0.3	5/20		4/10	1/10				0.01/1	
CHEWING GUM	0.5/2.5		50/200	100/1000	4/10		30/50	15/20		0.03/0.3	300/1000
CONDIMENTS AND RELISHES	0.2/2.5	0.2/3	5/20	10/30	4/10					0.01/1	50/200
CONFECTIONS AND FROSTINGS	0.5/2.5		10/40		4/10		30/50	15/20		0.03/0.3	
EGG PRODUCTS	0.05/0.25		5/20		4/10	0.2/2					
FATS AND OILS	0.5/2.5		5/20							0.01/0.5	
FISH PRODUCTS	0.05/0.15		5/20		4/10	0.5/5					50/200
FROZEN DAIRY	0.5/2.5		5/20		4/10	0.1/1					
FRUIT ICES	0.5/2.5		5/20	5/15	4/10					0.04/0.4	50/200
GELATINS AND PUDDINGS	0.5/1.5		5/20		4/10					0.03/0.3	
GRANULATED SUGAR	0.25/0.85		40/160								
GRAVIES	0.05/0.5	0.3/3	5/20	10/30	4/10	1/10				0.01/1	50/200
HARD CANDY	0.5/2.5		10/40	50/200	4/10					0.04/0.4	250/500
IMITATION DAIRY	0.5/2.5		5/20		4/10	0.5/5					
INSTANT COFFEE AND TEA	0.05/0.25		5/20	5/15	4/10						
JAMS AND JELLIES	0.5/1.5		10/40		4/10					0.04/0.4	50/200
MEAT PRODUCTS	0.05/0.15	0.5/2	5/20	10/30	4/10	0.5/5				0.01/1	
MILK PRODUCTS	0.25/0.85		5/20		4/10	0.2/2			10/100		
NUT PRODUCTS	0.05/0.25		5/20		4/10	0.1/1					
OTHER GRAINS	0.5/2.5		5/20		4/10						
POULTRY	0.05/0.25		5/20	10/30	4/10					0.01/1	
PROCESSED FRUITS	0.5/2.5		5/20		4/10						50/200
PROCESSED VEGETABLES	0.2/2	0.2/1	5/20		4/10	0.1/1				0.01/1	
RECONSTITUTED VEGETABLES	0.05/0.15	0.2/1	5/20		4/10	0.1/1					
SEASONINGS AND FLAVORS	0.05/0.5	0.1/2	5/20	30/100	4/10	1/10				0.01/1	400/800
SNACK FOODS	0.05/0.5	0.1/2	5/20	50/200	4/10	1/10				0.01/1	400/800
SOFT CANDY	0.5/2.5		10/40	50/200	4/10					0.04/0.4	250/500
SOUPS	0.25/2	0.3/1	5/20	10/20	4/10	0.5/5				0.01/1	
SUGAR SUBSTITUTES	0.5/1.5		10/40								
SWEET SAUCES	0.5/1.5		5/20		4/10						

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 judgements that the substances are generally recognized as safe (GRAS).

	Valencene 80 extract	Mixture of 3- and 4-butyl-2-thiophene-carboxaldehyde	(±)-Tetrahydronootkatone	cis-5-Dodecetyl acetate	2,4,5-Trithiooctane	3-(Allyldithio)butan-2-one	(2E,4E)-2,4-Decadien-1-ol acetate	Glucosylated Stevia Extract	Grapefruit essence oil (Citrus paradisi Macf.)	Grapefruit essence oil terpenes(Citrus paradisi Macf.)	Lemon terpenes
CATEGORY	4838	4839	4840	4841	4842	4843	4844	4845	4846	4847	4848
BAKED GOODS	0.9/0.9				0.1/0.5	0.1/8		30/100	363/5000	45/1000	366/5000
BEVERAGES, NON-ALCOHOLIC	0.6/0.6	0.2/5	0.2/5	0.05/5			0.1/5	30/100	78/500	11/275	70/500
BEVERAGES, ALCOHOLIC	0.9/0.9	0.5/10	0.5/5	0.15/10			0.3/15	30/100	91/500	16/100	81/1000
BREAKFAST CEREALS	0.9/0.9				0.01/0.05			30/100	133/1000	28/200	102/1000
CHEESES					0.01/2	0.03/3		30/100	200/1000	40/200	200/1000
CHEWING GUM	20/1000	1/20	1/10	0.5/25			1/40	30/100	1341/20000	253/5000	1355/20000
CONDIMENTS AND RELISHES					0.1/2	0.2/3		30/100	88/500	9/100	68/500
CONFECTIONS AND FROSTINGS	0.9/0.9	0.6/10	0.6/5	0.25/10			0.5/20	30/100	385/5000	55/1000	393/5000
EGG PRODUCTS					0.03/0.3	0.1/0.5			1000/5000	200/1000	1000/5000
FATS AND OILS		0.5/10	0.5/2	0.2/10	0.03/0.3	0.1/0.5	0.5/20		41/500	10/100	47/500
FISH PRODUCTS									51/180	0.2/2	41/180
FROZEN DAIRY	0.9/0.9	0.2/5	0.2/1	0.05/5			0.1/10	30/100	142/1000	26/200	172/1000
FRUIT ICES		0.2/5	0.2/5	0.05/5			0.1/5	30/100	110/1000	21/200	136/1000
GELATINS AND PUDDINGS	0.9/0.9							30/100	238/1000	25/200	238/2000
GRANULATED SUGAR									100/500	10/30	100/500
GRAVIES					0.1/2	0.1/2.5		30/100	200/1000	40/200	200/1000
HARD CANDY		0.6/10	0.6/5	0.25/10			0.5/25	30/100	359/5000	59/1000	392/5000
IMITATION DAIRY						0.1/1		30/100	153/500	38/180	253/900
INSTANT COFFEE AND TEA		0.3/5	0.3/5	0.2/5			0.2/10	30/100	75/500	20/100	113/1000
JAMS AND JELLIES		0.5/10	0.5/2	0.2/10			0.5/15	30/100	375/5000	75/1000	372/5000
MEAT PRODUCTS					0.1/5	0.1/3			2/20	2/6	2/20
MILK PRODUCTS	0.9/0.9							50/100	92/500	26/150	177/750
NUT PRODUCTS								30/100	100/500	20/100	100/500
OTHER GRAINS								30/100	100/500	20/100	50/500
POULTRY					0.1/5	0.05/0.5			26/100	0.2/2	30/100
PROCESSED FRUITS		0.2/5	0.2/5	0.1/5		0.1/5	0.2/10	30/100	200/1000	44/210	327/1050
PROCESSED VEGETABLES					0.1/2			30/100	100/500	20/100	100/500
RECONSTITUTED VEGETABLES								30/100			
SEASONINGS AND FLAVORS		0.5/10	0.05/2	0.2/5	0.1/5	0.01/8	0.4/10	30/100	351/5000	340/5000	1735/5000
SNACK FOODS					0.1/5	0.2/2		30/100	117/1000	15/200	101/1000
SOFT CANDY		0.6/10	0.6/3	0.25/5			0.5/10	30/100	342/5000	50/1000	331/5000
SOUPS					0.1/2	0.1/1		10/50	50/250	10/50	26/250
SUGAR SUBSTITUTES									100/500	20/100	100/500
SWEET SAUCES								30/100	253/2000	28/200	354/5000

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 judgements that the substances are generally recognized as safe (GRAS).

	Lime terpenes	Orange terpenes	Grapefruit terpenes	Lemon essence oil (Citrus limon(L.) Burm. f.)	Petitgrain oil terpeness	Tangelo oil (Citrus paradisi Macf. x Citrus tangerine hort. ex Tanaka)	Clementine oil (Citrus clementina hort. ex Tanaka)	Blood orange oil (Citrus sinensis (L.) Osbeck, 'Blood orange')	Iyokan oil (Citrus iyo)	Hassaku oil (Citrus hassaku)
CATEGORY	4849	4850	4851	4852	4853	4854	4855	4856	4857	4858
BAKED GOODS	440/5000	470/5000	564/5000	291/5000	60/1000	491/5000	516/5000	501/5000		125/300
BEVERAGES, NON-ALCOHOLIC	81/750	80/1550	98/500	53/500	31/500	72/500	70/500	102/2400	34/64	14/60
BEVERAGES, ALCOHOLIC	93/1000	93/1000	115/1000	93/1000	36/500	92/500	114/1000	90/1000	37/74	16/36
BREAKFAST CEREALS	104/1000	101/1000	133/1000	122/1000	200/1000	133/1000	133/1000	100/1000		50/100
CHEESES	200/1000	100/1000	200/1000	200/1000	200/1000	200/1000	200/1000	200/1000		60/275
CHEWING GUM	2240/20000	1943/20000	1504/20000	1530/20000	1070/20000	1524/20000	1484/20000	1829/20000	300/1000	125/350
CONDIMENTS AND RELISHES	90/500	71/500	93/500	108/500	48/500	88/500	92/500	49/500	100/200	20/50
CONFECTIONS AND FROSTINGS	474/5000	489/5000	600/5000	322/5000	116/1000	495/5000	528/5000	470/5000		2/20
EGG PRODUCTS	1000/5000	1000/5000	1000/5000	1000/5000	200/1000	1000/5000	1000/5000	1000/5000		
FATS AND OILS	47/500	43/500	43/500	38/500	51/500	41/500	42/500	43/500	100/200	60/125
FISH PRODUCTS	34/180	38/180	55/180	55/180	0.2/1	51/180	53/180	55/180		30/80
FROZEN DAIRY	205/1000	215/1000	215/1000	123/1000	70/1000	160/1000	198/1000	150/1000		12/35
FRUIT ICES	164/1000	166/1000	200/1000	106/1000	85/1000	148/1000	170/1000	138/1000	63/123	20/43
GELATINS AND PUDDINGS	303/2000	323/2000	323/2000	220/2000	70/1000	237/1000	234/2000	228/2000	88/168	28/59
GRANULATED SUGAR	100/500	100/500	100/500	100/500		100/500	100/500	100/500		
GRAVIES	200/1000	200/1000	200/1000	121/1000	100/1000	200/1000	200/1000	73/1000		
HARD CANDY	542/5000	507/5000	550/5000	370/5000	99/1000	359/5000	407/5000	416/5000	192/312	70/135
IMITATION DAIRY	253/900	190/900	253/900	153/500	140/500	173/540	193/660	193/660		11/35
INSTANT COFFEE AND TEA	100/500	113/1000	113/1000	88/1000	45/500	80/500	93/1000	98/1000		
JAMS AND JELLIES	463/5000	475/5000	475/5000	326/5000	93/36526	388/5000	418/5000	352/5000	88/168	34/90
MEAT PRODUCTS	2/20	10/50	10/50	18/50	0.2/1	2/20	5/25	15/50		30/80
MILK PRODUCTS	179/750	181/788	233/750	113/500	84/500	150/500	183/550	183/550		
NUT PRODUCTS	100/500	50/500	100/500	100/500	100/500	100/500	100/500	100/500		
OTHER GRAINS	100/500	100/500	100/500	100/500	100/500	100/500	100/500	100/500		
POULTRY	26/100	30/100	30/100	30/100	0.2/1	26/100	28/100	30/100		
PROCESSED FRUITS	307/1050	333/1050	333/1050	217/1000	137/1000	223/1000	257/1000	263/1000		
PROCESSED VEGETABLES	100/500	100/500	100/500	100/500	100/500	100/500	100/500	100/500		
RECONSTITUTED VEGETABLES										
SEASONINGS AND FLAVORS	1727/5000	1738/5000	2600/5000	600/5000	501/5000	2600/5000	2600/5000	2600/5000	24/45	30/80
SNACK FOODS	163/1000	100/1000	133/1000	133/1000	101/1000	117/1000	127/1000	174/1000	100/300	75/150
SOFT CANDY	477/5000	449/5000	476/5000	304/5000	95/1000	472/5000	562/5000	418/5000	188/368	70/169
SOUPS	27/250	29/250	50/250	28/250	50/250	50/250	50/250	50/250		20/50
SUGAR SUBSTITUTES	100/500	50/500	100/500	100/500	100/500	100/500	100/500	100/500		
SWEET SAUCES	440/5000	440/5000	440/5000	264/5000	117/1000	265/2000	328/3500	270/5000	100/200	35/125

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 judgements that the substances are generally recognized as safe (GRAS).

	Sikuwasya oil (<i>Citrus depressa</i>)	Natsumikan oil (<i>Citrus natsudaida</i>)	Mikan oil (<i>Citrus unshiu</i>)	Yuzu oil (<i>Citrus junos</i> (Sieb.) c. Tanaka)	Sudachi oil (<i>Citrus sudachi</i> hort. ex Shirai)	Kabosu oil (<i>Citrus sphaerocarpa</i>)	Ponkan oil (<i>Citrus reticulata</i> Blanco 'Ponkan')	Orange essence water phase (<i>Citrus sinensis</i> (L.) Osbeck)	(3S,5R,8S)-3,8-Dimethyl-5-prop-1-en-2-yl-3,4,5,6,7,8-hexahydro-2H-azulen-1-one	4-(4-Methyl-3-penten-1-yl)-2(5H)-furanone
CATEGORY	4859	4860	4861	4862	4863	4864	4865	4866	4867	4868
BAKED GOODS		400/860	50/200	60/184	2/2		463/746	556/10000	0.001/0.02	0.0001/0.001
BEVERAGES, NON-ALCOHOLIC	20/40	113/276	24/55	14/45	12/31	11/24	59/110	537/5000	0.0001/0.005	0.00001/0.0001
BEVERAGES, ALCOHOLIC		106/160	24/44	25/71	11/24	13/23	61/140	802/10000	0.0001/0.005	0.00001/0.0001
BREAKFAST CEREALS			50/200	50/200				40/200		0.0001/0.001
CHEESES			30/60	33/170				40/200		0.001/0.01
CHEWING GUM		844/1608	100/200	384/1150			360/1100	1498/8000	0.001/0.02	0.0001/0.001
CONDIMENTS AND RELISHES			30/60	37/100				250/5000		
CONFECTIONS AND FROSTINGS		440/800		8/9			560/880	356/2000	0.0003/0.005	0.0001/0.001
EGG PRODUCTS								200/1000	0.0003/0.005	0.0001/0.001
FATS AND OILS			30/60	30/150					0.02/0.2	0.001/0.01
FISH PRODUCTS			30/60	18/70					0.0003/0.005	0.0001/0.001
FROZEN DAIRY		175/400	30/60	18/65			219/440	334/5000	0.0002/0.003	0.0001/0.001
FRUIT ICES		240/400	25/45	16/57	3/10	5/5	280/440	334/5000	0.0002/0.003	0.00001/0.0001
GELATINS AND PUDDINGS		313/883	45/75	24/64	9/30	15/15	239/440	168/1000	0.0003/0.002	0.0001/0.001
GRANULATED SUGAR										
GRAVIES								40/200	0.001/0.01	0.001/0.01
HARD CANDY		342/1978	55/145	64/154	9/30	15/15	318/1965	952/8000	0.001/0.01	0.0001/0.001
IMITATION DAIRY		360/600	30/60	19/98			420/660	550/2000	0.001/0.01	0.0001/0.001
INSTANT COFFEE AND TEA		120/200					140/220	300/500	0.0001/0.001	0.00001/0.0001
JAMS AND JELLIES		300/500	45/75	28/79	3/90	15/15	250/550	256/1250		
MEAT PRODUCTS			30/60	18/70						0.00001/0.0001
MILK PRODUCTS		180/500		15/76			350/550	360/2000	0.001/0.01	0.00001/0.0001
NUT PRODUCTS									0.001/0.01	0.0001/0.001
OTHER GRAINS										0.0001/0.001
POULTRY										
PROCESSED FRUITS		420/700		20/50			490/770	528/5000		0.00001/0.0001
PROCESSED VEGETABLES				20/50				200/2000		
RECONSTITUTED VEGETABLES										
SEASONINGS AND FLAVORS			20/37	25/90	3/10	5/5		1200/10000	0.1/1	0.01/0.1
SNACK FOODS			50/200	47/114				40/200	0.001/0.01	0.0001/0.001
SOFT CANDY		552/1084	55/145	98/284	55/165	15/15	595/1251	313/2000	0.001/0.01	0.0001/0.001
SOUPS			30/60	13/60				50/250	0.0001/0.002	0.0001/0.001
SUGAR SUBSTITUTES										
SWEET SAUCES		300/500	30/60	14/64			350/550	450/5000	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 judgements that the substances are generally recognized as safe (GRAS).

	4-(1-Menthoxy)-2-butanone	2-Ethyl-4-methyl-1,3-dithiolane	2-Phenoxyethyl 2-(4-hydroxy-3-methoxyphenyl)acetate	3-(3-Hydroxy-4-methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one	Watermint, <i>Mentha aquatica</i> L., extract	Enzyme Modified Stevia, stevioside 20%	(E)-3-(3,4-Dimethoxyphenyl)-N-[2-(4-methoxyphenyl)ethyl]-acrylamide	<i>Cordyceps sinensis</i> fermentation product
CATEGORY	4869	4870	4871	4872	4873	4876	4877	4878
BAKED GOODS		1/2	75/150	5/10	50/100	75/100		30/50
BEVERAGES, NON-ALCOHOLIC	1/5	1/2	10/20	1.5/10		90/120		40/1000
BEVERAGES, ALCOHOLIC	1/5	1/2	10/30	1.5/10		75/100		100/1000
BREAKFAST CEREALS			5/15	5/10		75/100	15/30	
CHEESES		1/2	50/100		100/400	75/100	20/50	
CHEWING GUM	1/10		2000/5000	5/10		75/100		
CONDIMENTS AND RELISHES		1/2	15/50	4/10	200/800	80/110	25/50	
CONFECTIONS AND FROSTINGS			50/200			80/110		
EGG PRODUCTS		1/2	5/10		200/800	80/110		
FATS AND OILS		1/2	50/100		200/800	80/110	20/50	
FISH PRODUCTS		1/2	20/50		50/100	75/100	15/50	
FROZEN DAIRY			30/60	3/10		90/120		
FRUIT ICES			5/10	5/10		75/100		
GELATINS AND PUDDINGS			10/20	3/10		80/110		
GRANULATED SUGAR			5/10					
GRAVIES	1/5	1/2	15/50	2/10	200/800	75/100	20/50	
HARD CANDY			100/300	2/10		80/110		
IMITATION DAIRY			20/50		100/200	90/120		
INSTANT COFFEE AND TEA	1/5		10/20	1.5/10		75/100		
JAMS AND JELLIES			5/10			80/110		
MEAT PRODUCTS		1/2	25/50		100/200	75/100	20/50	
MILK PRODUCTS			20/50	2/10	50/100	90/120		15/100
NUT PRODUCTS			100/250		50/100	75/100		
OTHER GRAINS			5/15			75/100		50/150
POULTRY		1/2	25/50		100/200	75/100	15/50	
PROCESSED FRUITS			5/10	3/10		80/110		
PROCESSED VEGETABLES		1/2	5/10	2/10	50/100	75/100		
RECONSTITUTED VEGETABLES			5/10	2/10	50/100	75/100	20/50	
SEASONINGS AND FLAVORS	1000/5000	1/2	100/200	2/10	50/100	75/100	50/80	
SNACK FOODS		1/2	75/500	6/10	100/400	75/100	50/80	
SOFT CANDY	1/5		50/100	5/10		80/110		
SOUPS	1/5	1/2	35/100	1/10	100/200	75/100	20/50	
SUGAR SUBSTITUTES			5/10					4/10
SWEET SAUCES			15/50	4/10		80/110		

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

Average Usual Use Levels (ppm)/Average Maximum Use Levels (ppm) for flavoring substances previously recognized as FEMA GRAS. Superscript 'a' represents a new use level.

	Cinnamic Acid	Thaumatococin	Neohesperidine dihydrochalcone	Thaumatococin B-Recombinant	(+/-)-(2,6,6-Trimethyl-2-hydroxycyclohexylidene) acetic acid gamma-lactone	Geranic Acid	Polyglycerol Ester of Fatty Acids	Rebaudioside A	N-(2-Methylcyclohexyl)-2,3,4,5,6-pentafluorobenzamide	(2S,5R)-N-[4-(2-Amino-2-oxoethyl)phenyl]-5-methyl-2-(propan-2-yl)cyclohexanecarboxamide
FEMA NO.	2288	3732	3811	3814	4020	4121	4201	4601	4678	4684
GRAS PUBLICATION	3	13	17	17	20	22	22	24	25	25
CATEGORY										
BAKED GOODS	232/384	7 ^a /7 ^a	5/7 ^a	1/1	5 ^a /20 ^a	10/50	6/6	20/30	1 ^a /5 ^a	0 ^a /0 ^a
BEVERAGES, NON-ALCOHOLIC	300/400	7 ^a /7 ^a	5/15	5/7 ^a	5 ^a /20 ^a	3/15	4 ^a /20 ^a	20/30	1/5	10 ^a /50 ^a
BEVERAGES, ALCOHOLIC	570/712	7 ^a /7 ^a	5/15	5/7 ^a	5 ^a /20 ^a		4 ^a /20 ^a	20/30	1 ^a /3 ^a	
BREAKFAST CEREALS		7 ^a /7 ^a	8/20	1/2	5 ^a /20 ^a	5/25	6/20	20/30	1 ^a /5 ^a	
CHEESES		7 ^a /7 ^a	3/4	7 ^a /7 ^a	5 ^a /20 ^a	3/15				0 ^a /0 ^a
CHEWING GUM	224/300	150 ^a /150 ^a	200/300	150/150 ^a	50 ^a /200 ^a	165 ^a /500 ^a		200/200	10/20	400 ^a /800 ^a
CONDIMENTS AND RELISHES		7 ^a /7 ^a	2/3	1/2	5 ^a /20 ^a	5/25	6/200	20/30	1 ^a /25 ^a	0 ^a /0 ^a
CONFECTIONS AND FROSTINGS		7 ^a /7 ^a	3/3	2/5	10 ^a /40 ^a	10/50		20/30	1/5	25 ^a /100 ^a
EGG PRODUCTS		7 ^a /7 ^a	2/3	2/5	5 ^a /20 ^a					
FATS AND OILS	746/1000	7 ^a /7 ^a	4/4		5 ^a /20 ^a	2/10				
FISH PRODUCTS		7 ^a /7 ^a	2/3	5/7 ^a	5 ^a /20 ^a	2/10			1 ^a /2 ^a	
FROZEN DAIRY	192/263	7 ^a /7 ^a	2/8	1/2	5 ^a /20 ^a	3/15		20/30	1/8 ^a	
FRUIT ICES		7 ^a /7 ^a	2/3	2/5	5 ^a /20 ^a	3/15		20/30	1/5	
GELATINS AND PUDDINGS	459/500	7 ^a /7 ^a	3/8	1/2	5 ^a /20 ^a	5/25		20/30	1/5	
GRANULATED SUGAR										
GRAVIES	746/1000	7 ^a /7 ^a	3/4	2/5	5 ^a /20 ^a	15/75	60/400	20/30	1 ^a /25 ^a	0 ^a /0 ^a
HARD CANDY	0.01/0.01	7 ^a /7 ^a	5/15	2/5	10 ^a /40 ^a	100 ^a /400 ^a		20/30	1/5	25 ^a /100 ^a
IMITATION DAIRY		7 ^a /7 ^a	3/10	7 ^a /7 ^a	5 ^a /20 ^a	3/15		20/30	1 ^a /8 ^a	
INSTANT COFFEE AND TEA	224/300	7 ^a /7 ^a	3/6	2/5	5 ^a /20 ^a			20/30	1/5	0 ^a /0 ^a
JAMS AND JELLIES	373/500	7 ^a /7 ^a	2/3	2/5	10 ^a /40 ^a	5/25		20/30	1 ^a /5 ^a	25 ^a /100 ^a
MEAT PRODUCTS		7 ^a /7 ^a	2/3	2/2		2/10		20/75	1 ^a /2 ^a	
MILK PRODUCTS	700 ^a /1000 ^a	7 ^a /7 ^a	3/10	3/6	5 ^a /20 ^a	3/15		20 ^a /30 ^a	1/8 ^a	
NUT PRODUCTS		7 ^a /7 ^a	3/4	5/7 ^a	5 ^a /20 ^a				1 ^a /5 ^a	
OTHER GRAINS		7 ^a /7 ^a	3/4		5 ^a /20 ^a	5/25			1 ^a /5 ^a	
POULTRY		7 ^a /7 ^a	2/3	2/5	5 ^a /20 ^a	2/10		20/75	1 ^a /2 ^a	
PROCESSED FRUITS	37/50	7 ^a /7 ^a	2/3	2/5		2/10		20/30	1/5	
PROCESSED VEGETABLES		7 ^a /7 ^a	2/3	2/5				20/30		
RECONSTITUTED VEGETABLES		7 ^a /7 ^a	2/3	2/5	5 ^a /20 ^a					
SEASONINGS AND FLAVORS		7 ^a /7 ^a	3/4	0.5/1	5 ^a /20 ^a	5/25	2.3/15	20/30	1 ^a /25 ^a	
SNACK FOODS		7 ^a /7 ^a	3/3	1/2	5 ^a /20 ^a	10/50	0.2/40	20/30	1 ^a /25 ^a	0 ^a /0 ^a
SOFT CANDY	249/356	7 ^a /7 ^a	4/10	2/5	10 ^a /40 ^a			20/30	1/5	25 ^a /100 ^a
SOUPS		7 ^a /7 ^a	5/7 ^a	2/5	5 ^a /20 ^a	5/25		20/30	1 ^a /2 ^a	
SUGAR SUBSTITUTES	746/1000		0 ^a /0 ^a	0 ^a /0 ^a						
SWEET SAUCES	746/1000	7 ^a /7 ^a	2/3	2/5	5 ^a /20 ^a	5/25		20/30	1/5	

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

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

Average Usual Use Levels (ppm)/Average Maximum Use Levels (ppm) for flavoring substances previously recognized as FEMA GRAS. Superscript 'a' represents a new use level.

	3-[(4-Amino-2,2-dioxido-1H-2,1,3-benzothiazin-5-yl)oxy]-2,2-dimethyl-N-propylpropanamide	Glucosyl steviol glycosides	4-Amino-5-(3-(isopropylamino)-2,2-dimethyl-3-oxopropoxy)-2-methylquinoline-3-carboxylic acid	Glucosylated <i>Rubus suavisissimus</i> extract, 20-30% glucosylated rubusoside glycosides	(S)-1-(3-((4-Amino-2,2-dioxido-1H-benzof[1,2,6]thiaziazin-5-yl)oxy)methyl)piperidin-1-yl)-3-methylbutan-1-one	2-(4-Methylphenoxy)-N-(1H-pyrazol-3-yl)-N-(thiophen-2-ylmethyl)acetamide	Palmitoylated Green Tea Extract Catechins	Sugar Cane Distillate*
FEMA NO.	4701	4728	4774	4800	4802	4809	4812	4816
GRAS PUBLICATION	25	26	26	27	27	27	27	27
CATEGORY								
BAKED GOODS	10/22	150 ^a /500 ^a	10 ^a /30 ^a		6/6	3 ^a /15 ^a	100/400 ^a	0.01 (2,250)/0.01(2,250)
BEVERAGES, NON-ALCOHOLIC		125/175 ^a	8/30	150/350	2.5/6	1/3		0.016(3,600) ^a /0.016(3,600) ^a
BEVERAGES, ALCOHOLIC	5/22	125/175 ^a	10/30	75/200	2.5/6	2/6		
BREAKFAST CEREALS	15/22	200 ^a /500 ^a	12/30	150/400	6/6	3a/15 ^a	50/600 ^a	
CHEESES		100/133 ^a						
CHEWING GUM	30/300	500 ^a /1500 ^a	30/300	400 ^a /1000 ^a	6/6	75/150		
CONDIMENTS AND RELISHES	3/22	125/200 ^a	8/30		6/6	3 ^a /15 ^a	100/600 ^a	
CONFECTIONS AND FROSTINGS	10/22	50/100	30/300	150 ^a /300 ^a	6/6	5 ^a /30 ^a	50/600 ^a	0.01 (2,250)/0.01(2,250)
EGG PRODUCTS						3 ^a /15 ^a	150 ^a /600 ^a	
FATS AND OILS		125/189 ^a	8/30		3/6	3 ^a /15 ^a	200/2800 ^a	
FISH PRODUCTS	10 ^a /22a						250/600 ^a	
FROZEN DAIRY	5/22	125/133 ^a	10 ^a /30 ^a	200/300	3/6	1/3		0.016(3,600) ^a /0.016(3,600) ^a
FRUIT ICES	5/22	125/133 ^a	10/30	100/300	3/6	1/3		
GELATINS AND PUDDINGS	5/22	125/133 ^a	8/30	150 ^a /300 ^a	3/6	1/3		
GRANULATED SUGAR								
GRAVIES		125/133 ^a	8/30	100/150	3/6	3 ^a /15 ^a	150 ^a /600 ^a	
HARD CANDY	15/75	100/133 ^a	10/30	400 ^a /1000 ^a	3/6	5/15		
IMITATION DAIRY	5 ^a /22 ^a	125/250 ^a	8/30		2.5/6	1/3	150 ^a /600 ^a	0.016(3,600) ^a /0.016(3,600) ^a
INSTANT COFFEE AND TEA	5 ^a /22 ^a	125/175 ^a	8/30	150/350	2.5/6	1/3	150 ^a /500 ^a	
JAMS AND JELLIES	10/22	125 ^a /200 ^a	10/30	150 ^a /300 ^a	6/6	1 ^a /3 ^a		
MEAT PRODUCTS	10 ^a /22 ^a			100/150		3 ^a /15 ^a	250/400 ^a	
MILK PRODUCTS	3/22	133 ^a /225 ^a	8/30	200/300	2.5/6	1/3	150 ^a /400 ^a	0.016(3,600) ^a /0.016(3,600) ^a
NUT PRODUCTS		133 ^a /175 ^a			3/6	1 ^a /3 ^a	50/600 ^a	
OTHER GRAINS		100/133 ^a					150/400 ^a	
POULTRY	10 ^a /22 ^a					3 ^a /15 ^a	250/400 ^a	
PROCESSED FRUITS		133 ^a /200 ^a	10 ^a /30a		3/6	1 ^a /3 ^a		
PROCESSED VEGETABLES		100/133 ^a				3 ^a /15 ^a		
RECONSTITUTED VEGETABLES		133 ^a /133 ^a				3 ^a /15 ^a		
SEASONINGS AND FLAVORS	10 ^a /22 ^a	133 ^a /175 ^a	10 ^a /30 ^a	100/150	3 ^a /6a	3 ^a /15 ^a	750 ^a /1500 ^a	
SNACK FOODS		133 ^a /133 ^a	12/30		6/6	3 ^a /15 ^a	100/600 ^a	0.01 (2,250)/0.01(2,250)
SOFT CANDY	15/75	100/133 ^a	10/30	400 ^a /1000 ^a	6/6	5/15	50/600 ^a	
SOUPS		133 ^a /133 ^a	8/30	100/150	3/6	3 ^a /15 ^a	100/600 ^a	
SUGAR SUBSTITUTES		0 ^a /0 ^a						
SWEET SAUCES	10/22	133 ^a /133 ^a	15/30		3/6	5/15	150 ^a /600 ^a	0.01 (2,250)/0.01(2,250)

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

SUPPLEMENTARY INFORMATION 1: Identity for Natural Flavor Complexes as Evaluated by the Expert Panel

FEMA NO.	FEMA PRIMARY NAME	THE IDENTITY DESCRIPTION AS REVIEWED BY THE FEMA EXPERT PANEL
4728	Glucosyl steviol glycosides	Total steviol glycosides 80-90% inclusive of supraglucosylated steviol glycosides 75-80%; Rebaudioside A 1-6%; stevioside 2-4% and other individual steviol glycosides not further glucosylated each less than 3%. Maltodextrin 3-20%
4820	Purified Damar Gum	Oxygenated triterpenes and sesquiterpenes 34-39% measured as isomers of hydroxydammarone, dammerene diol, oleanonic aldehyde and urosonic aldehyde and acid and polycadene 14-17%.
4831	Katemfe fruit extract	Derived from the Katemfe fruit, Katemfe fruit extract is measured as thaumatin 45-55%, Carbohydrates 13-17%; Ash no more than 35% with less than 8% sodium.
4837	<i>Chrysanthemum parthenium</i> extract	Derived from the aerial parts of the <i>Chrysanthemum parthenium</i> plant, <i>Chrysanthemum parthenium</i> extract is measured as carbohydrate up to 74%; flavanoids 5-6% (luteolin glycosides and apigenin glycosides); sesquiterpene lactones 3-4% (parthenolide); chlorogenic acid derivatives 3-4% (caffeoylquinic acid); amino acids 4-5%; protein 2-3%; fat 1-2%; ash
4838	Valencene 80 extract	Valencene >80% with no less than 15% other sesquiterpene hydrocarbons typically aristolochene, selinenes and cadinenes.
4845	Glucosylated stevia extract	At least 80% steviol glycosides, not more than 10% Rebaudioside A, not more than 4% Rebaudioside C, not more than 5% stevioside, and no individual steviol glycosides further glucosylated ≤3%.
4873	Watermint, <i>Mentha aquatica</i> L., extract	Prepared by extraction of the leaves of <i>Mentha aquatica</i> , watermint extract is measured as 8-12% polyphenols, 1.2-1.4% rosmarinic acid, 5-7% polysaccharides, 20-30% water, 25-30% propylene glycol and 5-7% total protein.
4876	Enzyme modified stevia, stevioside 20%	90-95% steviol glycosides inclusive of supraglucosylated steviol glycosides 64-70%; rebaudioside A 10-13%; stevioside 20-22%, maltodextrin 1-6%, and other individual steviol glycosides not further glucosylated each less than 1%.
4878	<i>Cordyceps sinensis</i> fermentation product	Approximately 25% <i>alpha</i> -glucans; approximately 60-70% maltodextrin and its degradation products with no more than 1.5% protein.

¹FEMA 4846-4866 will be included within "GRAS Affirmation of Citrus Natural Flavor Complexes Used as Flavor Ingredients" publication pending.

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

Since its initial publication of GRAS determinations for flavor ingredients (Hall and Oser, 1965), the FEMA Expert Panel has consistently made available to the public information on its determinations, including 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 28. Comprehensive monographs of the information relevant to the evaluations are also published as part of the FEMA Expert Panel's ongoing GRAS re-evaluation program (see Hallagan and Hall (2009)). For more information on the FEMA GRAS program, please see "About the FEMA GRAS™ Program" on femaflavor.org.

The Panel reviewed the GRAS application and supporting information regarding S-[(methylthio)methyl]thioacetate (CAS 38634-59-2) and concluded that the substance is GRAS (FEMA 4817) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic sulfides and thiols (SLR B5C; JECFA, 2000a, 2004, 2008, 2011). The Panel calculated the anticipated *per capita* intake ("eaters only") of S-[(methylthio)methyl]thioacetate from use as a flavor ingredient to be 0.2 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Cramer et al., 1978; Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that S-[(methylthio)methyl]thioacetate will undergo hydrolysis to acetic acid and (methylthio)methanethiol, followed by S-oxidation and elimination (Parkinson, 1996; Williams et al., 1966). No increases in the number of reverse mutations were observed in the Ames assay for the structurally related substance, S-methyl-2-(acetyloxy)propanethioate (FEMA 3788) in *S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 in either the absence or presence of S-9 metabolic activation (Watanabe and Morimoto, 1989a, b). Based on these results, as well as the structure of the substance and the arrangement and identify of the functional groups therein, the Panel did not identify specific concerns related to the genotoxicity of S-[(methylthio)methyl]thioacetate. A 90-day dietary study in male and female rats resulted in a No-Observed-Adverse-Effect Level (NOAEL) of greater than 6.48 mg/kg bw/day for the structurally related substance, ethyl thioacetate (FEMA 3282) (Shellenberger, 1970). This is greater than 1,940,000 times the anticipated daily *per capita* intake of S-[(methylthio)methyl]thioacetate from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *trans*-1-ethyl-2-methylpropyl 2-butenolate (CAS 1370711-06-0) (Smith et al., 2005a) and concluded that the substance is GRAS (FEMA 4818) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of aliphatic, alicyclic, linear, alpha, beta-unsaturated aldehydes, acids, and related alcohols, acetals and esters (FEMA, 1985; JECFA, 2005, 2009, 2012). The Panel calculated the anticipated *per capita* intake ("eaters only") of *trans*-1-ethyl-2-methylpropyl 2-butenolate from use as a flavor ingredient to be 0.3 µg/person/day, which is below the threshold of toxicological concern for structural class I

(1800 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that *trans*-1-ethyl-2-methylpropyl 2-butenolate will rapidly hydrolyze to produce *trans*-2-butenic acid and 2-methyl-3-pentanol (Fukami and Yokoi, 2012; Hosokawa, 2008). These hydrolysis products are predicted to form conjugates and be excreted in the urine. No increases in the number of reverse mutations were observed in the Ames assay for *trans*-1-ethyl-2-methylpropyl 2-butenolate in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2 *uvrA* in either the absence or presence of S-9 metabolic activation (Thompson, 2013). *trans*-1-Ethyl-2-methylpropyl 2-butenolate did not induce chromosomal aberrations in human peripheral lymphocytes treated for 4 hours with a 20-hour recovery period in the absence and presence of S-9 metabolic activation, or when continuously incubated in human peripheral lymphocytes treated for 24 hours in the absence of S-9 metabolic activation (Bowles, 2014). Based on these results, the Panel did not identify specific concerns related to the genotoxicity of *trans*-1-ethyl-2-methylpropyl 2-butenolate. A 13-week CFW male and female rat study for the structurally related substance *trans*-2-hexenal (FEMA 2560) provided in the diet resulted in a NOAEL of 80 mg/kg bw/day, which is 16,000,000 times the anticipated daily *per capita* intake of *trans*-1-ethyl-2-methylpropyl 2-butenolate from use as a flavor ingredient (Gaunt et al., 1971).

The Panel reviewed the GRAS application and supporting information regarding erythritol (CAS 149-32-6) (Smith et al., 2005a) and concluded that the substance is GRAS (FEMA 4819) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of aliphatic polyhydroxy compounds (SLR B1F; JECFA, 1999). The Panel calculated the anticipated *per capita* intake ("eaters only") of erythritol from anticipated use as a flavor ingredient to be 290 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 cheese, grapes, melons, miso, pears, sake, sherry wine, soy sauce, watermelon, and wine (de Cock, 2012; Shindou and Ishizuka, 1996; Sreenath and Venkatesh, 2008), but only qualitative data is available and, thus, no consumption ratio can be calculated. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Erythritol is rapidly absorbed from the proximal intestine. It is distributed and eliminated within 24 hours (Noda et al., 1996; Noda and Oku, 1992; van Ommen et al., 1996). In humans, erythritol is not metabolized systemically but about 10% is degraded by intestinal microflora. The remaining 90 % of erythritol administered to humans is excreted unchanged in urine (Bornet et al., 1996a, b). No increases in the number of reverse mutations were observed in the Ames assay for erythritol in *Salmonella typhimurium* strains TA98, TA100 and TA1537 and *Escherichia coli* WP2 *uvrA* in either the absence or presence of S-9 metabolic activation. No chromosomal aberrations were observed with concentrations of erythritol up to 10 mmol in Chinese hamster fibroblast cells (Kawamura et al., 1996). In an *in vitro* comet assay, erythritol treatment of L5178Y tk+/-

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

cells resulted in slight increases in the percentage of tail DNA, but the increases were not concentration dependent and were all less than 2-fold when compared to controls, and thus the authors concluded that the results were negative. There were no increases in the numbers of micronucleated polychromatic erythrocytes in an *in vivo* mouse micronucleus assay performed with up to 5000 mg/kg bw erythritol (Chung and Lee, 2013). Based on these results, the Panel did not identify any specific concerns related to the genotoxicity of erythritol. Erythritol was evaluated in a two-generation dietary administration reproductive study in male and female rats. No effects on reproductive performance or fertility, offspring developments, or incidences of abnormalities were observed at doses up to 6.5 g/kg (males) and 16 g/kg (females), which were the highest doses tested (Waalens-Berendsen et al., 1996). A study at a single low dose of erythritol (5 mg/kg) reported rib malformations in pups, but fewer fetal resorptions than control group. However, only limited information was available for the study (Keehr and Hunt, 2000). Erythritol was evaluated in a study wherein pregnant Wistar rats were given up to 6.6 g/kg bw/day during gestational days 0 to 21. No adverse reproductive, embryotoxic, fetotoxic, or teratogenic effects occurred at doses up to 6.6 g/kg bw/day, which was the highest dose tested (Smits-Van Prooije et al., 1996). No toxicologically-related fetal effects were observed in a teratogenicity study in which pregnant KBL:JW rabbits were administered erythritol at doses up to 5 g/kg bw/day during gestational days 6 to 18. Maternal effects were considered to be transient and related to osmotic loading and diuresis due to the high doses of erythritol administered (Shimizu et al., 1996). A two-year toxicity and carcinogenicity study for erythritol was conducted in Wistar rats at 2, 5 or 10% in the diet (ca. 1000, 2500 and 5000 mg/kg bw/day). No toxicologically relevant effects attributable to the test substance were observed in any of the test parameters. There was no evidence of toxicity or carcinogenicity at levels of erythritol up to 10% (5000 mg/kg bw/day) in the diet (Lina et al., 1996). The resulting NOAEL was considered to be 5000 mg/kg bw/day which is greater than 1,030,000 times the anticipated daily *per capita* intake of erythritol from use as a flavor ingredient. Other toxicity studies were reported, including 28-day, 13-week, and 1-year studies in rodents and beagle dogs, and where effects were observed they were attributed to physiological, and not toxicological, responses to the high dose levels of erythritol, which is well-absorbed and rapidly excreted unchanged in the urine (Noda et al., 1996; Noda and Oku, 1992; van Ommen et al., 1996).

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding purified damar gum (CAS 9000-16-2) and concluded that the material is GRAS (FEMA 4820) (Smith et al., 2005a) for use as a flavor adjuvant, specifically as a flavor stabilizer within flavor formulations, in the food categories and at the use levels specified in the GRAS application (see Table 2). This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of purified damar gum from use as a flavor adjuvant to be 7400 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). Purified damar gum is derived from the *Shorea javanica* tree trunk. The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation (see Appendix 1). Metabolic data exists for representative members of each congeneric group of purified damar gum that would predict, at

the levels of intake proposed, metabolism by well-established detoxication pathways to innocuous products (ERINI, 2014; He et al., 2014; Kong et al., 2013; Scheline, 1991; Ukiya et al., 2010; Xie et al., 2012; Zhang et al., 2009; Zhang et al., 2014). No evidence of genotoxic effects was observed with purified damar gum in *S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 in either the presence or absence of metabolic activation in an Ames assay, or in a Chinese hamster ovary cell in a chromosomal aberration assay in the presence and absence of S-9 metabolic activation (King and Harnasch, 1999a). Purified damar gum did not induce genotoxicity in an *in vivo* mouse bone marrow micronucleus assay (King and Harnasch, 1999b). A 90-day male and female rat study with purified damar gum resulted in a NOAEL of 540 and 1000 mg/kg bw/day, respectively (Bisson et al., 2012). The NOAEL of 540 mg/kg bw/day for purified damar gum is greater than 4,300 times the anticipated daily intake from use as a flavor adjuvant.

The Panel reviewed the GRAS application and supporting information regarding *gamma*-aminobutyric acid:linoleic acid enriched conjugates (CAS 1444005-46-2, 1444005-47-3, 1444005-48-4, 1444005-49-5) and concluded that the substance is GRAS (FEMA 4821) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was reviewed individually within the context of the chemical group of aliphatic and aromatic amines and amides (SLR A7; C21; JECFA, 2006, 2008, 2011, 2012). The Panel calculated the anticipated *per capita* intake ("eaters only") of *gamma*-aminobutyric acid:linoleic acid enriched conjugates from anticipated use as a flavor ingredient to be 590 µg/person/day, which is above the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is anticipated that *gamma*-aminobutyric acid:linoleic acid enriched conjugates will undergo oxidative metabolism. The pharmacokinetic parameters of *gamma*-aminobutyric acid:linoleic acid enriched conjugates were determined in single-dose mice studies; elimination half-lives ranged from 2 to approximately 4.5 hours (Boggs, 2014). Based on the structure of the substance and the identity and arrangements of functional groups therein, the Panel did not identify specific concerns related to the potential genotoxicity of *gamma*-aminobutyric acid:linoleic acid enriched conjugates. For the amino component, *gamma*-aminobutyric acid, a 90-day gavage administration toxicity study in Sprague-Dawley male and female rats resulted in a NOAEL of 2500 mg/kg bw/day, which was the highest dose tested (Takeshima et al., 2014). This NOAEL is greater than 250,000 the anticipated daily *per capita* intake of *gamma*-aminobutyric acid:linoleic acid enriched conjugates from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2,6-dipropyl-5,6-dihydro-2*H*-thiopyran-3-carboxaldehyde (CAS 61407-00-9) and concluded that the substance is GRAS (FEMA 4822) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of aliphatic alcohols, aldehydes acids and related esters with thiol or sulfide functions (SLR B5A; JECFA, 2000a, 2004, 2008, 2011). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2,6-dipropyl-

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

5,6-dihydro-2*H*-thiopyran-3-carboxaldehyde from anticipated 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). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. Based on analogy, 2,6-dipropyl-5,6-dihydro-2*H*-thiopyran-3-carboxaldehyde would be expected to undergo oxidation at the aldehyde function to the corresponding carboxylic acid followed by conjugation with glycine and excreted as such. Furthermore, the sulfur center might be expected to oxidize to the sulfoxide and perhaps further to the sulfone. In addition, the propyl side-chains might be predicted to undergo oxidative metabolism (Parkinson, 1996; Rance, 1989). No increases in the number of reverse mutations were observed in the Ames assay for 2,6-dipropyl-5,6-dihydro-2*H*-thiopyran-3-carboxaldehyde in *S. typhimurium* strains TA98, TA100 TA1535 and TA1537 in either the absence or presence of S-9 metabolic activation using both the plate incorporation and pre-incubation methods (Merrill, 2015b). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Panel did not identify specific concerns related to the genotoxicity of 2,6-dipropyl-5,6-dihydro-2*H*-thiopyran-3-carboxaldehyde.

The Panel reviewed the GRAS application and supporting information regarding allyl 1-propenyl disulfide (CAS 33368-82-0) and concluded that the substance is GRAS (FEMA 4823) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic sulfides and thiols (SLR B4; JECFA, 2000a, 2004, 2008, 2011). The Panel calculated the anticipated *per capita* intake ("eaters only") of allyl 1-propenyl disulfide from use as a flavor ingredient to be 0.02 µg/person/day, which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. Allyl 1-propenyl disulfide would be predicted to be reduced to its two sulfhydryl metabolites. These in turn would be expected to undergo methylation of the sulfhydryl groups and possibly further oxidation. The allyl groups may undergo epoxidation followed by interaction with glutathione or hydration followed by oxidation (Germain et al., 2008; Teyssier and Siess, 2000). In an *in vivo* mouse micronucleus induction assay with structurally related substances allyl sulfide (FEMA 2042), allyl disulfide (FEMA 2028) and diallyl trisulfide (FEMA 3265), no induction of micronuclei was reported (Reddy et al., 1993). Based on these results, the structure of the substance and the arrangement and identity of the functional groups therein, the Panel did not identify specific concerns related to the genotoxicity of allyl 1-propenyl disulfide. A 90-day dietary study for a structurally related substance, propyl disulfide (FEMA 3228), was conducted in male and female rats at single doses of 7.29 or 8.17 mg/kg bw/day, respectively. No adverse effects were noted as a result of propyl disulfide in the diet (Posternak et al., 1969). The resulting NOAEL was considered to be greater than 7.29 mg/kg bw/day, which is greater than 21,800,000 times the anticipated daily *per capita* intake of allyl 1-propenyl disulfide from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2-(5-isopropyl-2-methyl-tetrahydrothiophen-2-yl)-ethyl acetate (CAS 1658479-63-0) and concluded that the substance is GRAS (FEMA 4824) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of sulfur-containing heterocyclic compounds (Cohen et al., 2017; SLR D15; JECFA, 2004, 2008, 2012, 2015). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2-(5-isopropyl-2-methyl-tetrahydrothiophen-2-yl)-ethyl acetate from use as a flavor ingredient to be 0.03 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The substance occurs naturally in lemon peel, but only qualitative data is available and, thus, no consumption ratio can be calculated (Cannon et al., 2015). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. 2-(5-isopropyl-2-methyl-tetrahydrothiophen-2-yl)-ethyl acetate is predicted to undergo hydrolysis at the ester moiety, subsequent conjugation of the resulting alcohol with glucuronic acid, and then elimination in the urine (Rance, 1989). Additionally, oxidation of the sulfur to the sulfoxide and sulfone and subsequent excretion in the urine is anticipated (Mozier and Hoffman, 1990). Based on the structure of the substance and the arrangement and identity of the functional groups therein, the Panel did not identify specific concerns related to the genotoxicity of 2-(5-isopropyl-2-methyl-tetrahydrothiophen-2-yl)-ethyl acetate. A 90-day dietary study for a structurally related substance, *alpha*-methyl-*beta*-hydroxypropyl *alpha*-methyl-*beta*-mercaptopropyl sulfide (FEMA 3509), was conducted in male and female rats at a single dose of 2.82 mg/kg bw/day. There were no adverse test substance-related effects observed (Morgareidge et al., 1974). The resulting NOAEL was considered by the authors to be greater than 2.82 mg/kg bw/day, which is greater than 5,640,000 times the anticipated daily *per capita* intake of 2-(5-isopropyl-2-methyl-tetrahydrothiophen-2-yl)-ethyl acetate from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding (*E*)-6-nonenal (CAS 2277-20-5) and concluded that the substance is GRAS (FEMA 4825) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of aliphatic primary alcohols, aldehydes, esters and acids (SLR M1; JECFA, 1999, 2012). The Panel calculated the anticipated *per capita* intake ("eaters only") of (*E*)-6-nonenal from use as a flavor ingredient to be 0.003 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 Rooibos tea (*Aspalathus linearis*), but only qualitative data is available and, thus, no consumption ratio can be calculated (Nijissen, 2017). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. Based on the metabolism of linear and branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids and related esters, it is predicted that (*E*)-6-nonenal will be oxidized to (*E*)-6-nonenic acid which will enter into *beta*-oxidation and ultimately be metabolized to CO₂.

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

that will be expired (Nelson and Cox, 2008). No increases in the number of reverse mutations were observed in the Ames assay for a structurally related substance, *trans*-4-decenal (FEMA 3264) in *S. typhimurium* strains TA102, TA98, TA100 TA1535 and TA1537 in either the absence or presence of S-9 metabolic activation using both the plate incorporation method (Sokolowski, 2007). An *in vivo* mouse micronucleus assay at doses of 500, 1000 and 2000 mg/kg bw administered via gavage showed no increases in micronuclei induction (Honarvar, 2008). A 98-day drinking water study for a structurally related substance, *cis*-3-hexenol (FEMA 2563), was conducted in male and female rats at doses of 310, 1250 and 5000 ppm. There were no adverse test substance-related effects observed (Gaunt et al., 1969). The resulting NOAEL was considered to be 1250 ppm (ca., 120-150 mg/kg bw/day), which is greater than 2,400,000,000 times the anticipated daily *per capita* intake of (*E*)-6-nonenal from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 3-phenylpropyl 2-(4-hydroxy-3-methoxyphenyl)acetate (CAS 105025-99-8) and concluded that the substance is GRAS (FEMA 4826) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of hydroxy- and alkoxy-substituted benzyl derivatives (SLR C18; JECFA, 2002, 2009). The Panel calculated the anticipated *per capita* intake ("eaters only") of 3-phenylpropyl 2-(4-hydroxy-3-methoxyphenyl)acetate from use as a flavor ingredient to be 16 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. It is predicted that the substance will readily undergo hydrolysis to homovanillic acid and 3-phenylpropanol. Homovanillic acid could be excreted in the urine unchanged or undergo conjugation at the phenolic moiety or the acid moiety and be excreted. 3-Phenylpropanol could be conjugated with sulfate or glucuronic acid and excreted, or undergo further oxidative steps and be excreted in the urine (Strand and Scheline, 1975). No increases in the number of reverse mutations were observed in the Ames assay for the structurally related substance, ethyl 2-(4-hydroxy-3-methoxyphenyl)acetate (FEMA 4810) in *S. typhimurium* strains TA98, TA100 TA1535, TA1537 and *E. coli* WP2 *uvrA* in either the absence or presence of S-9 metabolic activation using both the plate incorporation method (Sokolowski, 2014). The structurally related substance Vanillin (FEMA 3107) was reported negative in the Ames assay at doses up to 10,000 µg/plate in the absence and presence of S-9 metabolic activation (Heck et al., 1989; Ishidate et al., 1984; Kasamaki et al., 1982; Mortelmans et al., 1986; Pool and Lin, 1982; Rapson et al., 1980). No induction of micronuclei was observed when mice were dosed with up to 500 mg/kg bw of vanillin. The allowable daily intake (ADI) of 10 mg/kg bw/day of vanillin was established by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) based on a NOAEL of 1000 mg/kg bw per day from a 2-year study in rats (Hagan et al., 1967). The resulting ADI set by JECFA is 37,500 times the anticipated daily *per capita* intake of 3-phenylpropyl 2-(4-hydroxy-3-methoxyphenyl)acetate from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 1-(4-methyl-3-cyclohexen-1-yl)-ethanone (CAS 6090-09-1) and concluded that the substance is GRAS (FEMA 4827) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of aliphatic secondary alcohols, ketones and related substances (SLR C4; JECFA, 1999). The Panel calculated the anticipated *per capita* intake ("eaters only") of 1-(4-methyl-3-cyclohexen-1-yl)-ethanone from use as a flavor ingredient to be 0.4 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 naturally occurs in orange juice (1000 ppm) and the consumption ratio was calculated as 1,424,000 (Nijissen, 2017). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. It is predicted that 1-(4-methyl-3-cyclohexen-1-yl)-ethanone will undergo reduction of the ketone moiety followed by conjugation and elimination (Ferdinandi, 1993). Alternatively, oxidation of the cyclohexene ring followed by hydrolysis of the epoxide and conjugation and elimination in the urine could occur. Based on data for related substances as well as the structure of the substance and the identity and the position of the functional groups therein, the Panel did not identify any specific concerns for the genotoxic potential of the substance. A NOAEL of 200 mg/kg bw/day in a 28-day study in male and female rats for the structurally related substance *p*-menthane-3,8-diol (FEMA 4053) is greater than 28,570,000 times the anticipated daily *per capita* intake of from use of 1-(4-methyl-3-cyclohexen-1-yl)-ethanone from use as a flavor ingredient (Braun et al., 2000).

The Panel reviewed the GRAS application and supporting information regarding 1,1-propanedithioacetate (CAS 729602-98-6) and concluded that the substance is GRAS (FEMA 4828) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of dithiols and related substances (SLR D1; JECFA, 2000a, 2004, 2008, 2011). The Panel calculated the anticipated *per capita* intake ("eaters only") of 1,1-propanedithioacetate from use as a flavor ingredient to be 0.04 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. It is predicted that 1,1-propanedithioacetate will undergo hydrolysis to the corresponding acid, acetic acid, which will be metabolized to CO₂ and expired. The other hydrolysis product, 1,1-propanedithiol, will likely undergo S-alkylation and oxidation to produce a polar sulfonate. The other sulfur is anticipated to undergo conjugation with cysteine to form a mixed disulfide that could subsequently be excreted (Maiorino et al., 1996). Based on the structure of the substance and the arrangement and identity of the functional groups therein, the Panel did not identify specific concerns related to the genotoxicity of 1,1-propanedithioacetate. A 90-day dietary study for a structurally related substance, ethyl thioacetate (FEMA 3282), was conducted in male and female rats at a single dose of 6.48 mg/kg bw/day. There were no adverse test substance-related

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

effects observed (Shellenberger, 1970). The resulting NOAEL was considered to be greater than 6.48 mg/kg bw/day, which is 9,720,000 times the anticipated daily *per capita* intake of 1,1-propanedithioacetate from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2-pyrrolidone (CAS 616-45-5) and concluded that the substance is GRAS (FEMA 4829) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of pyridine, pyrrole and quinoline derivatives (SLR D3; JECFA, 2006, 2012). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2-pyrrolidone from use as a flavor ingredient to be 0.2 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 naturally occurs in beer, cocoa, rice, wheaten bread, whisky, wine, malt and taro (*Colocasia esculenta*), but only qualitative data are available and thus no consumption ratio can be calculated (Nijissen, 2017). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. 2-Pyrrolidone is endogenous to the human body. No increases in the number of reverse mutations were observed in the Ames assay for 2-pyrrolidone in *S. typhimurium* strains TA1538, TA98, TA100, TA1535 and TA1537 in either the absence or presence of S-9 metabolic activation (ECHA, 2015). No mutations were observed *in vitro* when 2-pyrrolidone was incubated with CHO cells in the absence and presence of metabolic activation. An *in vitro* human peripheral lymphocyte micronucleus assay with pyrrolidone showed no increases in micronuclei induction (ECHA, 2015). In addition, *in vivo* chromosomal aberration assays in mice showed no indication of genetic damage (ECHA, 2015). A NOAEL of 207 mg/kg bw/day for 2-pyrrolidone administered to male and female Wistar rats is 62,100,000 times the anticipated daily *per capita* intake of 2-pyrrolidone from use as a flavor ingredient (ECHA, 2015).

The Panel reviewed the GRAS application and supporting information regarding 7,8-dihydroxyflavone (CAS 38183-03-8) and concluded that the substance is GRAS (FEMA 4830) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of phenol and phenol derivatives (SLR C12; JECFA, 2001, 2011, 2015). The Panel calculated the anticipated *per capita* intake ("eaters only") of 7,8-dihydroxyflavone 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). It is predicted that 7,8-dihydroxyflavanone would be metabolized along various routes: conjugation of the hydroxyl functions with glucuronic acid and sulfate and excretion of these conjugates; demethylation and ring-opening of the heterocyclic ring function to form the corresponding hydroxyphenylpropionic acid (Day et al., 2000; Donovan et al., 2006; Gee et al., 2000; Manach et al., 2005). No increases in the number of reverse mutations were observed in the Ames assay for 7,8-dihydroxyflavone in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* WP2uvrA (pKM101) in either the absence or presence of S-9 metabolic activation using both the plate incorporation and pre-incubation methods (Merrill, 2015a). Based on these results, as well as the

structure of the substance and the identity and arrangements of the functional groups therein, the Panel did not identify specific concerns related to the genotoxicity of 7,8-dihydroxyflavone. A conservative NOAEL from the 2-year study for quercetin in F344/N rats (NTP, 1992) assigned by the Panel at 40 mg/kg bw/day is greater than 3,400,000 times the anticipated daily *per capita* intake of 7,8-dihydroxyflavone from use as a flavor ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding Katemfe extract (CAS 90131-57-0) and concluded that the material is GRAS (FEMA 4831) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of Katemfe extract from anticipated use as a flavor ingredient is 220 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 fruit arils of the Katemfe plant (*Thaumatococcus daniellii*). Katemfe extract is primarily composed of protein, ash, and carbohydrate. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Thaumatin, the principal constituent, would likely be hydrolyzed to its component amino acids that would then be utilized in protein synthesis. Partial reduction of the disulfide bonds resulted in auto-digestion of the protein. One study indicated that the digestibility of thaumatin is comparable to that of egg albumin (Stanworth, 1977). The carbohydrates would enter into standard metabolic pathways and be utilized for energy. The ash is expected to be excreted via the feces (Stanworth, 1977). The principal constituent of Katemfe extract, thaumatin, was not mutagenic in an Ames test in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and *E. coli* strain WP2, in either the presence or absence of S-9 metabolic activation (Higginbotham et al., 1983). Thaumatin was also negative for the induction of dominant-lethal mutations in the gametes of male mice (Tesh et al., 1977). Based on these results the Panel did not identify a specific concern for the genotoxic potential of katemfe extract. In a 13-week study in male and female rats, the principal constituent of Katemfe extract, thaumatin, was administered via the diet and produced NOAELs of 2502 mg/kg bw/day (males) and 2889 mg/kg bw/day (females), which were the highest doses administered (Hawigara et al., 2005). The NOAEL of 2502 mg/kg bw/day is greater than 682,300 times the anticipated daily *per capita* intake of Katemfe extract used as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2-(3-benzyloxypropyl)pyridine (CAS 108715-62-4) and concluded that the substance is GRAS (FEMA 4832) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of pyridine pyrrole, and quinoline derivatives (SLR D2; JECFA, 2009, 2012). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2-(3-benzyloxypropyl)pyridine from anticipated use as a flavor ingredient to be 0.2 µg/person/day, which is below the threshold of toxicological concern for structural class III (90

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. 2-(3-Benzyloxypropyl)pyridine is predicted to undergo side chain oxidation as well as *N*-oxidation or methylation to yield polar metabolites that are conjugated and eliminated in the urine (Cowan et al., 1978; Damani et al., 1980; Damani et al., 1982; Hawksworth and Scheline, 1975; Nguyen et al., 1988). No increases in the number of reverse mutations were observed in the Ames assay for 2-(3-benzyloxypropyl)pyridine in *S. typhimurium* strains TA98 and TA100 in the absence and presence of S-9 metabolic activation (Kawaguchi and Komai, 2015). Based on the results from this initial screening assay, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of 2-(3-benzyloxypropyl)pyridine. A NOAEL of 196 mg/kg bw/day for a structurally related substance, dibenzyl ether (Burdock and Ford, 1992) administered to male and female rats is 58,800,000 times the anticipated daily *per capita* intake of 2-(3-benzyloxypropyl)pyridine from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2-(3-(2*S*)-3',7-dihydroxy-8-methyl-4'-methoxyflavan (CAS 87733-81-1) and concluded that the substance is GRAS (FEMA 4833) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of phenol and phenol derivatives (SLR C12; JECFA, 2001, 2011, 2015). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2-(3-(2*S*)-3',7-dihydroxy-8-methyl-4'-methoxyflavan from anticipated use as a flavor ingredient to be 7 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). *In vitro* rat and human hepatocyte studies provided evidence that (2*S*)-3',7-dihydroxy-8-methyl-4'-methoxyflavan is likely to be rapidly metabolized *in vivo*, primarily by conversion to the glucuronic acid conjugate (Kandel, 2015). It is anticipated that this would be followed by excretion in the urine. No increases in the number of reverse mutations in the Ames assay were observed for (2*S*)-3',7-dihydroxy-8-methyl-4'-methoxyflavan in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* WP2uvrA (pKM101) in either the absence or presence of S-9 metabolic activation using both the plate incorporation and pre-incubation methods (Soltesova, 2015). Marginal increases in micronucleus production were observed in Chinese hamster ovary (CHO) cells incubated with (2*S*)-3',7-dihydroxy-8-methyl-4'-methoxyflavan in the absence of S-9 metabolic activation (Zhao, 2015). No increase in micronucleated polychromatic erythrocytes were observed in femoral bone marrow of CD-1 mice of both sexes (Pant, 2015). Based on the results from these data, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of 2-(3-(2*S*)-3',7-dihydroxy-8-methyl-4'-methoxyflavan.

The Panel reviewed the GRAS application and supporting information regarding (*R*)-5-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-7-methylchroman-2-one (CAS 1793064-68-2) and concluded that the substance is GRAS (FEMA 4834) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of phenol and phenol derivatives (SLR C12; JECFA, 2001, 2011, 2015). The Panel calculated the anticipated *per capita* intake from use as a flavor ingredient to be 3 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). *In vitro* rat and human hepatocyte studies provided evidence that (*R*)-5-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-7-methylchroman-2-one is likely to be rapidly metabolized *in vivo*, primarily by conversion to the glucuronic acid conjugate (Kandel, 2015). It is anticipated that this would be followed by excretion in the urine. No increases in the number of reverse mutations in the Ames assay were observed for (*R*)-5-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-7-methylchroman-2-one in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* WP2uvrA (pKM101) in either the absence or presence of S-9 metabolic activation using both the plate incorporation and pre-incubation methods (Soltesova, 2015). No increases in micronucleus production were observed in Chinese hamster ovary (CHO) cells incubated with (*R*)-5-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-7-methylchroman-2-one in the absence or presence of S-9 metabolic activation (Zhao, 2015). Based on the results from these data, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of (*R*)-5-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-7-methylchroman-2-one.

The Panel reviewed the GRAS application and supporting information regarding 2,4-dihydroxy-*N*-[(4-hydroxy-3-methoxyphenyl)methyl]benzamide (CAS 877207-36-8) and concluded that the substance is GRAS (FEMA 4835) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was reviewed individually within the context of the chemical group of aliphatic and aromatic amines and amides (SLR A7; C21; JECFA, 2006, 2008, 2011, 2012). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2,4-dihydroxy-*N*-[(4-hydroxy-3-methoxyphenyl)methyl]benzamide from anticipated use as a flavor ingredient to be 7 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). 2,4-Dihydroxy-*N*-[(4-hydroxy-3-methoxyphenyl)methyl]benzamide is predicted to undergo conjugation with sulfate or glucuronic acid, and the conjugation products will be eliminated in the urine (Nelson

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

and Cox, 2008). No increases in the number of reverse mutations were observed in the Ames assay for 2,4-dihydroxy-*N*-[(4-hydroxy-3-methoxyphenyl)methyl]benzamide in *S. typhimurium* strains TA97a, TA98, TA100 and TA1535 and *E. coli* strain WP2uvrA in the absence and presence of S-9 metabolic activation (Sokolowski, 2015). Based on the results from this assay, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of 2,4-dihydroxy-*N*-[(4-hydroxy-3-methoxyphenyl)methyl]benzamide. A NOAEL of 8 mg/kg bw/day for a structurally related substance, *N*-(4-hydroxy-3-methoxybenzyl)nonanamide (CAS 244-46-4; FEMA 2787) administered to male and female rats (Posternak, 1963) is 80,000 times the anticipated daily *per capita* intake of 2,4-dihydroxy-*N*-[(4-hydroxy-3-methoxyphenyl)methyl]benzamide from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 10% solution of 3,4-dimethyl-2,3-dihydrothiophene-2-thiol (CAS 137363-86-1) and concluded that the substance is GRAS (FEMA 4836) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was reviewed individually within the context of the chemical group of sulfur containing heterocyclic compounds (SLR D15; JECFA, 2003, 2008, 2012, 2015). The Panel calculated the anticipated *per capita* intake ("eaters only") of 10% solution of 3,4-dimethyl-2,3-dihydrothiophene-2-thiol from use as a flavor ingredient to be 0.2 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Panel noted that due to the instability of the neat material, the substance is used as a flavor ingredient as a 10% solution in a food grade solvent. 10% Solution of 3,4-dimethyl-2,3-dihydrothiophene-2-thiol is predicted to undergo S-oxidation on the ring sulfur, as well as conjugation with glutathione on the thiol moiety. Hydroxylation of a methyl group followed by conjugation could also occur. In all cases, formation of polar metabolites would result in excretion in the urine (Dansette et al., 1992). No increases in the number of reverse mutations were observed in the Ames assay for 10% Solution of 3,4-dimethyl-2,3-dihydrothiophene-2-thiol in *S. typhimurium* strains TA97a, TA98, TA100 and TA1535 and *E. coli* strain WP2uvrA in the absence and presence of S-9 metabolic activation (Swartz, 2016). Based on the results from this assay, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of 10% solution of 3,4-dimethyl-2,3-dihydrothiophene-2-thiol. A NOAEL of greater than 0.29 mg/kg bw/day for a structurally related substance, 2-thienylsulfide (FEMA 3323), administered to male and female rats (Morgareidge and Oser, 1970) is greater than 96,000 times the anticipated daily *per capita* intake of 10% solution of 3,4-dimethyl-2,3-dihydrothiophene-2-thiol from use as a flavor ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding *Chrysanthemum parthenium* extract and concluded that the material is GRAS (FEMA 4837) for use as a flavor ingredient

in the food categories and at the use levels specified in the GRAS application (see Table 2). This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of *Chrysanthemum parthenium* extract from use as a flavor ingredient to be 4 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Panel considered the identity description to be adequate for FEMA GRAS evaluation (see Appendix 1). Metabolic data exist for representative members of each congeneric group of *C. parthenium* extract that would predict metabolism by well-established detoxication pathways to innocuous products. No increases in the occurrence of reverse mutations were observed in an Ames test in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and *E. coli* strain WP2, in either the presence or absence of S-9 metabolic activation (Merrill, 2016). A conservative NOAEL from the 2-year study for quercetin in F344/N rats (NTP, 1992) assigned by the Panel at 40 mg/kg bw/day is greater than 666,000 times the anticipated daily *per capita* intake of *Chrysanthemum parthenium* extract used as a flavor ingredient.

The Panel reviewed the flavor complex GRAS application and supporting information regarding valencene 80 extract and concluded that the material is GRAS (FEMA 4838) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see 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; Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of valencene 80 extract from use as a flavor ingredient to be 47 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 produced by bacterial fermentation. The Panel considered the identity description to be adequate for FEMA GRAS evaluation (see Appendix 1). Metabolic data exist for representative members of each congeneric group of valencene 80 extract that would predict metabolism by well-established detoxication pathways to innocuous products (Adams et al., 2011). No increases in the occurrence of reverse mutations for a structurally related substance *d*-limonene (FEMA 2633) were observed in an Ames test in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and/or TA102, UTH8413 or UTH8414, in either the presence or absence of S-9 metabolic activation (Connor et al., 1985; Florin et al., 1980; Haworth et al., 1983; Heck et al., 1989; Müller et al., 1993). *d*-Limonene was also negative in a chromosomal aberration study in CHO cells, a sister chromatid exchange assay in CHO cells, and a mouse lymphoma forward mutation assay in L5178Y cells, either in the presence or absence of S-9 metabolic activation (Anderson et al., 1990; Heck et al., 1989; Kauderer et al., 1991; Myhr et al., 1990; Sasaki et al., 1989). Based on the results for the structurally related substance, as well as the structures of the components within valencene 80 extract, the Panel did not identify specific concerns related to the genotoxic potential of valencene 80 extract. The structurally related substance *d*-limonene (FEMA 2633) was administered via gavage to F344/N rats for 13 weeks. Findings included significantly increased relative kidney and relative liver weights in high dose rats; hyaline droplet formation in the kidneys, granular casts and multiple cortical changes, classified as chronic nephrosis. There were no histopathological changes noted in the livers of treated rats.

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

The NOAEL for nephrotoxicity was reported to be 5 mg/kg bw/day (NTP, 1990; Webb et al., 1989). This NOAEL is greater than 6,000 times the anticipated daily *per capita* intake of valencene 80 extract from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding mixture of 3- and 4-butyl-2-thiophenecarbaldehyde (CAS 163460-99-9 & 163461-01-6) and concluded that the mixture is GRAS (FEMA 4839) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of sulfur-containing heterocyclic compounds (SLR D15; Cohen et al., 2017; JECFA, 2002, 2008, 2012, 2014). The Panel calculated the anticipated *per capita* intake ("eaters only") of the mixture of 3- and 4-butyl-2-thiophenecarbaldehyde from use as a flavor ingredient to be 0.4 µg/person/day, which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. The mixture of 3- and 4-butyl-2-thiophenecarbaldehyde is predicted to undergo S-oxidation and side-chain C-oxidation, and these metabolites would either be excreted or undergo conjugation and excretion (Dansette et al., 1992). No increases in the number of reverse mutations were observed in the Ames assay for 5-methyl-2-thiophene carboxaldehyde (FEMA 3209), a structurally related substance, in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 in the absence and presence of S-9 metabolic activation (Beevers, 2009). 5-methyl-2-thiophene carboxaldehyde was reported to induce weak induction of micronuclei in an human peripheral blood lymphocytes in the presence of S-9 but not in the absence (Lloyd, 2011). In a combined *in vivo* rat micronucleus induction and comet assay, no evidence of either micronuclei induction or DNA damage in the liver (Beevers, 2012). Based on the results from this series of *in vitro* and *in vivo* assays on a structurally related substance, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of mixture of 3- and 4-butyl-2-thiophenecarbaldehyde. A NOAEL of 7.5 mg/kg bw/day for a structurally related substance, 5-ethyl-2-thiophenecarbaldehyde, administered to male and female rats (Bauter, 2013) is 1,125,000 times the anticipated daily *per capita* intake of mixture of 3- and 4-butyl-2-thiophenecarbaldehyde from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding (±)-tetrahydronootkatone (CAS 38427-80-4) and concluded that the substance is GRAS (FEMA 4840) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of monocyclic and bicyclic secondary alcohols, ketones and related esters (SLR A5; Adams et al., 1996; JECFA, 2006, 2009, 2015). The Panel calculated the anticipated *per capita* intake ("eaters only") of (±)-tetrahydronootkatone 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). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. (±)-

Tetrahydronootkatone is predicted to undergo ring and side-chain oxidation by cytochrome P450s, and these metabolites would either be excreted or undergo conjugation and excretion (Dansette et al., 1992). No increases in the number of reverse mutations were observed in the Ames assay for the structurally related substance nootkatone (FEMA 3166) in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 in the absence and presence of S-9 metabolic activation. Nootkatone was not reported to induce increases of micronuclei in an human peripheral blood lymphocytes in the presence of S-9, but did in the absence S-9 (Lloyd, 2011). In a combined *in vivo* rat micronucleus induction and comet assay, no evidence of either micronuclei induction or DNA damage in the liver was found (Beevers, 2012). Based on the results from these of *in vitro* assays on a structurally related substance, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of (±)-tetrahydronootkatone. In a 28-day gavage study, 10 mg/kg bw/day of the structurally related substance nootkatone was administered to male and female rats (Jones et al., 2004). The resulting NOAEL was considered by the authors to be greater than 10 mg/kg bw/day, which is greater than 2,000,000 times the anticipated daily *per capita* intake of (±)-tetrahydronootkatone from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *cis*-5-dodecenyl acetate (CAS 16676-96-3) and concluded that the substance is GRAS (FEMA 4841) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of linear and branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids and related esters (SLR M1; JECFA, 2000b, 2007, 2012, 2014). The Panel calculated the anticipated *per capita* intake ("eaters only") of *cis*-5-dodecenyl acetate from use as a flavor ingredient to be 0.4 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. *cis*-5-Dodecenyl acetate is predicted to undergo hydrolysis by carboxylesterases or other esterases to acetate and the corresponding unsaturated alcohol, *cis*-5-dodecenol. The alcohol is expected to enter the fatty acid *beta*-oxidation pathway (Nelson and Cox, 2008). No increases in the number of reverse mutations were observed in the Ames assay for the structurally related substance *cis*-3-hexen-1-ol (FEMA 2563) in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* WPuvrA in the absence and presence of S-9 metabolic activation (Bhalli and Phil, 2014a). *cis*-3-Hexen-1-ol was reported to induce no increases of micronuclei in an human peripheral blood lymphocytes in the presence of S-9 but not in the absence (Bhalli and Phil, 2014b). Based on the results from these of *in vitro* assays on a structurally related substance, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of *cis*-5-dodecenyl acetate. A NOAEL of 125 mg/kg bw/day for a structurally related substance, *cis*-3-hexen-1-ol administered to male and female rats (Gaunt et al., 1969) is greater than 18,750,000 times the anticipated daily *per capita* intake of *cis*-5-dodecenyl acetate from use as a flavor ingredient.

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

The Panel reviewed the GRAS application and supporting information regarding 2,4,5-trithiooctane (CAS 911212-28-7) and concluded that the substance is GRAS (FEMA 4842) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic sulfides and thiols (SLR B4; JECFA, 2000a, 2004, 2008, 2011). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2,4,5-trithiooctane from use as a flavor ingredient to be 0.07 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. 2,4,5-Trithiooctane is predicted to undergo reductive cleavage of the disulfide bond followed by oxidative metabolism by cytochrome P450 and flavin-containing monooxygenases to sulfoxides and sulfones (Waring, 1996; Cotgreave et al., 1989; Wells et al., 1993; Williams et al., 1966). Based on the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of 2,4,5-trithiooctane. A NOAEL of greater than 1.9 mg/kg bw/day for a structurally related substance, 3,5-dimethyl-1,2,4-trithiolane (FEMA 3541) administered to male and female rats (BIBRA, 1976) is greater than 1,628,000 times the anticipated daily *per capita* intake of 2,4,5-trithiooctane from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 3-(allyldithio)-butan-2-one (CAS 1838169-65-5) and concluded that the substance is GRAS (FEMA 4843) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic sulfides and thiols (SLR B4; JECFA, 2000a, 2004, 2008, 2011). The Panel calculated the anticipated *per capita* intake ("eaters only") of 3-(allyldithio)-butan-2-one from use as a flavor ingredient to be 0.07 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. 3-(Allyldithio)-butan-2-one (CAS 1838169-65-5) is predicted to undergo reductive cleavage of the disulfide bond followed by oxidative metabolism by cytochrome P450 and flavin-containing monooxygenases to sulfoxides and sulfones (Cotgreave et al., 1989; Waring, 1996; Wells et al., 1993; Williams et al., 1966). No increases in the number of reverse mutations were observed in the Ames assay for a structurally related substance allyl disulfide (FEMA 2028) in *S. typhimurium* strain TA100 in the absence and presence of S-9 metabolic activation (Beevers, 2009; Eder et al., 1980). Equivocal results were obtained in an *in vitro* cytogenetic assay in CHO cells where sister chromatid exchanges and chromosomal aberrations were observed but showed no concentration dependence (Musk et al., 1996) and negative results were obtained from an *in vivo* mouse micronucleus assay (Marks et al., 1992). Using a second structurally related substance, diallyl trisulfide (FEMA 3265) in an *in vivo* mouse micronucleus assay showed no increases in the frequency of micronucleated polychromatic erythrocytes in bone marrow cells (Marks et al., 1992). Based on the results

from these *in vitro* assays on structurally related substances and on the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of 3-(allyldithio)-butan-2-one. A NOAEL of greater than 1.89 mg/kg bw/day for a structurally related substance, 3-mercapto-2-pentanone (FEMA 3300) administered to male and female rats is greater than 1,620,000 times the anticipated daily *per capita* intake of 3-(allyldithio)-butan-2-one from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding (2*E*,4*E*)-2,4-decadiena-1-ol, acetate (CAS 118026-67-8) and concluded that the substance is GRAS (FEMA 4844) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of aliphatic, linear, alpha, beta-unsaturated aldehydes, acids and related alcohols, acids and esters (SLR M1; JECFA, 2004, 2007). The Panel calculated the anticipated *per capita* intake ("eaters only") of (2*E*,4*E*)-2,4-decadiena-1-ol, acetate from use as a flavor ingredient to be 0.3 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. (2*E*,4*E*)-2,4-Decadiena-1-ol, acetate is predicted to undergo hydrolysis by carboxylesterases or other esterases to acetate and the corresponding unsaturated alcohol, (2*E*,4*E*)-2,4-decadiena-1-ol. The alcohol is expected to enter the fatty acid *beta*-oxidation pathway (Nelson and Cox, 2008). No increases in the number of reverse mutations were observed in the Ames assay for a structurally related substance 2,4-decadienal (FEMA 3135) in *S. typhimurium* strains TA97, TA98, TA100, TA102, TA104 and TA1535 in the absence and presence of S-9 metabolic activation (Chan, 2011). Equivocal results were reported for the *in vivo* rat micronucleus assay (Chan, 2011). 2,4-Decadienal was reported to induce no increases of micronuclei in the bone marrow of rats (Lloyd, 2011). Based on the results from these *in vitro* and *in vivo* assays, the Panel did not identify a specific concern for the genotoxic potential of (2*E*,4*E*)-2,4-decadien-1-ol, acetate. In a 14-week study in male and female B6C3F1 mice, a structurally related substance, *trans,trans*-2,4-decadien-1-ol (FEMA 3135) was administered at doses of 50, 100, 200, 400, or 800 mg/kg bw/day (Chan, 2011) with effects of epithelial erosion or ulceration of the forestomach in males of the mid- and highest dose groups. In a 14-week study, a structurally related substance *trans,trans*-2,4-decadien-1-ol (FEMA 3135) administered to male and female rats at doses of 45, 133, 400, 1,200, and 3,600 mg/kg bw/day (Chan, 2011) resulted in a NOAEL of 100 mg/kg bw/day, which is 20,400,000 times the anticipated daily *per capita* intake of (2*E*,4*E*)-2,4-decadiena-1-ol, acetate from use as a flavor ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding glucosylated stevia extract (CAS 1225018-62-1) and concluded that the material is GRAS (FEMA 4845) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

glucosylated stevia extract from use as a flavor ingredient to be 370 µg/person/day. Glucosylated stevia extract is derived from the leaves of *Stevia rebaudiana*. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient. (Harman and Hallagan, 2013). Metabolic data exist for representative members of each congeneric group that would predict, at the intake levels proposed, metabolism by well-established detoxication pathways to innocuous products (Gardana et al., 2003; Geuns et al., 2003; Geuns et al., 2007; Geuns and Pietta, 2004; Hutapea et al., 1997; Koyama et al., 2003a; Koyama et al., 2003b; Nakayama et al., 1986; Renwick and Tarka, 2008; Roberts and Renwick, 2008; Simonetti et al., 2004; Wheeler et al., 2008; Wingard et al., 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; Rummelhard et al., 2016; Suttajit et al., 1993; Terai et al., 2002; Toyoda et al., 1997; 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 glucosylated stevia extract. 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 14,500 times the anticipated daily *per capita* intake of the stevia extract enzymatically modified from use as a flavor ingredient.

The Panel reviewed the natural flavor complex GRAS applications and supporting information regarding Grapefruit essence oil (*Citrus paradisi* Macf.), Grapefruit oil, terpeneless (*Citrus paradisi* Macf.), Lemon terpenes, Lime terpenes, Orange terpenes, Grapefruit terpenes, Lemon essence oil (*Citrus limon* (L.) Burm. f.), Petitgrain oil terpeneless, Tangelo oil (*Citrus paradisi* Macf. x *Citrus tangerine* hort. ex Tanaka), Clementine oil (*Citrus clementina* Hort. ex Tan), Blood orange oil (*Citrus sinensis* (L.) Osbeck 'Blood orange'), lyokan oil (*Citrus iyo*), Hassaku oil (*Citrus hassaku* hort. ex Tanaka), Sikuwasya oil (*Citrus depressa*), Natsumikan oil (*Citrus natsudaïdaï*), Mikan oil (*Citrus unshiu*), Yuzu oil (*Citrus junos* (Sieb.) c. Tanaka), Sudachi oil (*Citrus sudachi* hort. ex Shirai), Kabosu oil (*Citrus sphaerocarpa*), Ponkan oil (*Citrus reticulata* Blanco 'Ponkan'), and Orange essence water phase (*Citrus sinensis* (L.) Osbeck) and concluded that the substances are GRAS for use as flavor ingredients in the food categories and at the use levels specified in the GRAS applications (FEMA 4846-4866, respectively) (see Table 2). These materials were evaluated within the context of the revised procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b; Cohen et al., 2017, submitted for publication; Cohen et al., 2017, manuscript in preparation). These citrus ingredients are derived from commonly consumed fruits. The Panel considered the identity descriptions of each material to be adequate for FEMA GRAS evaluation. These citrus flavor ingredients were evaluated using a rigorous procedure that considers the chemical composition, anticipated *per capita* intake, metabolic fate and toxicity of the identified constituents and potential toxicity and genotoxicity of unidentified constituents.

The Panel reviewed the GRAS application and supporting information regarding (3*S*,5*R*,8*S*)-3,8-dimethyl-5-prop-1-en-2-yl-3,4,5,6,7,8-hexahydro-2*H*-azulen-1-one (CAS 18374-76-0) and concluded that the substance is GRAS (FEMA 4867) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of monocyclic and bicyclic secondary alcohols, ketones and related esters (SLR A5; Adams et al., 1996; JECFA, 2006, 2009, 2015). The Panel calculated the anticipated *per capita* intake ("eaters only") of (3*S*,5*R*,8*S*)-3,8-dimethyl-5-prop-1-en-2-yl-3,4,5,6,7,8-hexahydro-2*H*-azulen-1-one from use as a flavor ingredient to be 0.001 µg/person/day, which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. (3*S*,5*R*,8*S*)-3,8-Dimethyl-5-prop-1-en-2-yl-3,4,5,6,7,8-hexahydro-2*H*-azulen-1-one is predicted to follow a similar metabolic pathway as other lipophilic ketones or those with sterically hindered functional groups. Specifically, this is anticipated to occur via oxidation at a ring position by nonspecific cytochrome P-450 mixed function oxidases, followed by conjugation and excretion in the urine. In an alternative pathway, reduction of the ketone functional group followed by conjugation and excretion in the urine would possibly occur (Asakawa et al., 1986; Nelson et al., 1992). No increase in reverse mutations was observed in the Ames assay regarding (3*S*,5*R*,8*S*)-3,8-dimethyl-5-prop-1-en-2-yl-3,4,5,6,7,8-hexahydro-2*H*-azulen-1-one on *S. typhimurium* strains TA98 and TA100 in the absence or presence of S-9 metabolic (Kawaguchi, 2015b). No increases in the number of reverse mutations were observed in the Ames assay for the structurally related substance nootkatone (FEMA 3166) in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 in the absence and presence of S-9 metabolic activation (Marzin, 1998). Nootkatone was reported to induce no increases of micronuclei in human peripheral blood lymphocytes in the presence of S-9 but not in its absence (Stone, 2011). Based on the results from these assays on the substance itself and a structurally related substance, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of (3*S*,5*R*,8*S*)-3,8-dimethyl-5-prop-1-en-2-yl-3,4,5,6,7,8-hexahydro-2*H*-azulen-1-one. In a 28-day gavage study, 10 mg/kg bw/day of the structurally related substance nootkatone was administered to male and female rats (Jones et al., 2004). The resulting NOAEL was considered by the authors to be greater than 10 mg/kg bw/day is greater than 600,000,000 times the anticipated daily *per capita* intake of regarding (3*S*,5*R*,8*S*)-3,8-dimethyl-5-prop-1-en-2-yl-3,4,5,6,7,8-hexahydro-2*H*-azulen-1-one from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 4-(4-methyl-3-penten-1-yl)-2(5*H*)-furanone (CAS 61315-75-1) and concluded that the substance is GRAS (FEMA 4868) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of tetrahydrofuran and furanone derivatives (SLR D9; JECFA, 2006). The Panel calculated the anticipated *per capita* intake ("eaters only") of 4-(4-methyl-3-penten-1-yl)-

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

2(5*H*)-furanone 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 Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral data provided for FEMA GRAS evaluation. 4-(4-Methyl-3-penten-1-yl)-2(5*H*)-furanone is predicted to follow a similar metabolic pathway as other *alpha,beta*-unsaturated lactones. Specifically, this is anticipated to hydrolyze to the corresponding ring-opened *alpha,beta*-unsaturated hydroxycarboxylic acid and undergo condensation with acetyl-CoA and biotransformation in the *beta*-oxidation pathway. Minor amounts of the lactone are expected to form conjugates with glutathione followed by excretion in the urine as the mercapturic acid conjugate (Boyland and Chasseaud, 1970; Chasseaud, 1979; Fry et al., 1993; Köppel and Tenczer, 1991; Nelson and Cox, 2008). No increase in reverse mutations was observed in the Ames assay for 4-(4-methyl-3-penten-1-yl)-2(5*H*)-furanone on *S. typhimurium* strains TA 98 and TA100 in the absence or presence of S-9 metabolic activation (Kawaguchi, 2015a). No increases in the number of reverse mutations were observed in the Ames assay for the structurally related substances *gamma*-heptalactone, *gamma*-nonalactone, and *gamma*-undecalactone (FEMA 2539, 2781 and 3091, respectively) in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 in the absence and presence of S-9 metabolic activation (Fujita and Sasaki, 1987; Heck et al., 1989; Ishidate et al., 1984). In a standard mouse lymphoma assay, *gamma*-nonalactone showed a weak mutagenic response at high concentrations when in the presence of S-9, but the authors noted that effects on the osmolality or pH may have contributed to the result. *gamma*-Heptalactone did not induce an increase in unscheduled DNA synthesis (Heck et al., 1989). No increases in the incidence of micronucleated polychromatic erythrocytes were observed in ddY mice treated with *gamma*-undecalactone by intraperitoneal injection (Hayashi et al., 1988). Based on the results from these *in vitro* and *in vivo* assays on structurally related substances and the substance itself, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of 4-(4-methyl-3-penten-1-yl)-2(5*H*)-furanone. In a 90-day dietary study, male and female rats were given 14.6 mg/kg bw/day of the structurally related substance *gamma*-undecalactone. Necropsy and histopathological examinations revealed no evidence of toxicity (Oser et al., 1965). The resulting NOAEL of greater than 14.6 mg/kg bw/day is greater than 876,000,000 times the anticipated daily *per capita* intake of 4-(4-methyl-3-penten-1-yl)-2(5*H*)-furanone from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 4-(*l*-menthoxy)-2-butanone (CAS 886449-15-6) and concluded that the substance is GRAS (FEMA 4869) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of aliphatic and aromatic ethers (SLR D12; JECFA, 2004, 2012). The Panel calculated the anticipated *per capita* intake ("eaters only") of 4-(*l*-menthoxy)-2-butanone from use as a flavor ingredient to be 4 µg/person/day, which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity and assay and supporting spectral

data provided for FEMA GRAS evaluation. 4-(*l*-Menthoxy)-2-butanone is predicted to undergo oxidation at a ring position by nonspecific cytochrome P-450 mixed function oxidases, followed by conjugation and excretion in the urine based on data available for the structural relative, menthol (FEMA 2665) (Heck, 2010). 4-(*l*-Menthoxy)-2-butanone gave no increases in mutant frequencies relative to vehicle control when tested in an Ames assay in *S. typhimurium* strains TA98 and TA100 in the presence and absence of S-9 metabolic activation (Tomi and Kawaguchi, 2014). Based on the results from these assays, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of 4-(*l*-menthoxy)-2-butanone. In a 91-day study, CD rats were administered diets containing the structurally related substance 3-(*l*-menthoxy)propane-1,2-diol (FEMA 3784) at 30, 200 and 1000 mg/kg bw/day. A NOAEL of 30 mg/kg bw/day in males and 200 mg/kg bw/day in females was reported by the authors based on effects identified during histopathological examination at higher doses (Wolfe, 1992). The NOAEL of 30 mg/kg bw/day is greater than 450,000 times greater than the anticipated daily *per capita* intake of 4-(*l*-menthoxy)-2-butanone from use as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2-ethyl-4-methyl-1,3-dithiolane (CAS 17564-27-1) and concluded that it is GRAS (FEMA 4870) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic sulfides and thiols (SLR A8; JECFA, 2000a, 2004, 2008, 2011). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2-ethyl-4-methyl-1,3-dithiolane from use as a flavor ingredient to be 0.1 µg/person/day, which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). The substance occurs naturally in onions, garlic, chives, and beef, but only qualitative data is available and, thus, no consumption ratio can be calculated (Takahashi and Shibamoto, 2008). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. 2-ethyl-4-methyl-1,3-dithiolane is predicted to undergo S-oxidation to yield the corresponding monocyclic sulfoxide, which is considered a major metabolic pathway (Grosa et al., 1991). Further oxidation to the corresponding monocyclic cyclic sulfone (*S,S'*-dioxide) is predicted to occur at a slower rate (Cashman et al., 1990). The monosulfoxides are predicted to be the main urinary metabolite produced. Based on the structure of the substance as well as the arrangement and identity of the functional groups therein, the Panel did not identify specific concerns related to the genotoxicity of 2-ethyl-4-methyl-1,3-dithiolane. A 91-day gavage study for a structurally related substance, 2-methyl-1,3-dithiolane (FEMA 3705), was conducted in male and female rats at a single dose calculated to be 7 mg/kg bw/day. There were no adverse test substance-related effects observed (Griffiths et al., 1979). The resulting NOAEL is greater than 7 mg/kg bw/day, which is greater than 4,200,000 times the anticipated daily *per capita* intake of 2-ethyl-4-methyl-1,3-dithiolane from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2-phenoxyethyl 2-(4-hydroxy-3-methoxyphenyl)acetate (CAS 1962956-83-7) and concluded that the substance is GRAS (FEMA 4871) (Smith et al.,

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of hydroxy- and alkoxy-substituted benzyl derivatives (SLR C9; JECFA, 2001). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2-phenoxyethyl 2-(4-hydroxy-3-methoxyphenyl)acetate from use as a flavor ingredient to be 236 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. 2-phenoxyethyl 2-(4-hydroxy-3-methoxyphenyl)acetate is predicted to undergo hydrolysis to form the corresponding 4-hydroxy-3-methoxyphenyl acetic acid, which would form a glycine conjugate and be excreted in the urine. The 2-phenoxyethanol (FEMA 4620) would likely undergo glucuronic acid conjugation of sulfation and be excreted primarily in the urine (Strand and Scheline, 1975; Wong and Sourkes, 1966). Based on the structure of the substance and the arrangement and identity of the functional groups therein, the Panel did not identify specific concerns related to the genotoxicity of 2-phenoxyethyl 2-(4-hydroxy-3-methoxyphenyl)acetate. A two-year dietary study for a structurally related substance, vanillin (FEMA 3107), was conducted in male and female rats at doses of 250, 500, or 1000 mg/kg bw/day. There were no adverse test substance-related effects observed (Hagan et al., 1967). In a 13-week study, vanillin was administered to Sprague Dawley rats by oral gavage at doses of 80, 240, and 400 mg/kg bw/day (Mancebo et al., 2003). The NOAEL for vanillin concluded upon by the authors to be 400 mg/kg bw/day, which is greater than 101,000 times the anticipated daily *per capita* intake of 2-phenoxyethyl 2-(4-hydroxy-3-methoxyphenyl)acetate from use as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding 3-(3-hydroxy-4-methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one (CAS 35400-60-3) and concluded that the substance is GRAS (FEMA 4872) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of phenol and phenol derivatives (SLR C12; JECFA, 2001, 2011, 2015). The Panel calculated the anticipated *per capita* intake ("eaters only") of 3-(3-hydroxy-4-methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one from anticipated use as a flavor ingredient to be 7 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). 3-(3-hydroxy-4-methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one is predicted to undergo metabolism forming sulfate and glucuronide conjugates and/or methylated through the respective action of sulfotransferases (SULT), uridine-50-diphosphate glucuronosyltransferases (UGTs) and catechol-O-methyltransferases (COMT) (Borges et al., 2013; Donovan et al., 2006). Upon entry into the blood stream, the metabolites are further transformed in phase II metabolic processes in the liver (Marin et al., 2015). Metabolites not absorbed in the small

intestine undergo further metabolism by micro flora in the large intestine and colon (Borges et al., 2013). The microflora cleave conjugate moieties with the resultant aglycones undergoing ring fission leading to phenolic acid and cinnamic acid derivatives. These metabolites are absorbed and ultimately excreted in the urine in excess of those flavonoid metabolites in the circulatory system via the small intestine (Donovan et al., 2006). Any unabsorbed metabolites are ultimately excreted in feces (Marin et al., 2015). An Ames assay of 3-(3-hydroxy-4-methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one using *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* WP2 showed no increase in revertant colony numbers as compared with control counts with and without metabolic activation (Leuschner, 2016). Based on this assay, the structure of the substance and the arrangement and identity of the functional groups therein, the Panel did not identify specific concerns related to the genotoxicity of 3-(3-hydroxy-4-methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one. A 13-week dietary study for turmeric oleoresin (containing approximately 79-85% curcumin) was conducted in male and female rats at dose levels of 2.5% and 5% (Lilja et al., 1983). The resulting NOAEL was considered to be 1300 mg/kg bw/day, which corresponds to 1027 mg/kg bw/day of curcumin. The dose of 1027 mg/kg bw/day is greater than 8,800,000 times the anticipated daily *per capita* intake of 3-(3-hydroxy-4-methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one from use as a flavor ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding watermint, *Mentha aquatica* L., extract (CAS 90063-96-0) and concluded that the material is GRAS (FEMA 4873) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of watermint, *Mentha aquatica* L., extract from use as a flavor ingredient to be 140 µg/person/day. The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation (see Appendix 1). The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). In a metabolic study of rats orally administered 50 mg/kg bw of rosmarinic acid, a principal constituent of watermint extract, orally, the metabolites identified in the plasma were rosmarinic acid, monomethylated rosmarinic acid and m-coumaric acid and those identified in the urine were rosmarinic acid, monomethylated RA, caffeic acid, ferulic acid and m-coumaric acid. In the urine 34 and 37 % of rosmarinic acid and monomethylated rosmarinic acid were excreted as such without conjugation but the remainder were either sulfated or formed glucuronic acid conjugates (Baba et al., 2004). In a Comet assay, male rats were administered 2 or 8 mg/kg bw of rosmarinic acid via intraperitoneal injection. No genotoxicity was observed compared to the controls (Pereira et al., 2005). In an Ames assay, an extract derived from spearmin containing 15.4% rosmarinic acid showed no mutagenic activity in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 at concentrations up to 5000 mg/plate with and without metabolic activation (Lasrado et al., 2015). The same extract, when tested at concentrations up to 5000 µg extract/mL culture did not induce chromosomal aberrations when tested with human peripheral blood lymphocytes, both with and without metabolic activation, in an OECD compliant

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

study (Lasrado et al., 2015). Based on these assays and the composition of the material therein, the Panel did not identify specific concerns related to the genotoxicity of watermint, *Mentha aquatica* L., extract. In a 90-day gavage study in male and female rats, a spearmint extract containing 15.4% rosmarinic acid was administered at dose levels corresponding to 422, 844, or 1948 mg/kg bw/day of dry spearmint extract, producing a NOEL of 422 mg/kg bw/day of dry spearmint extract (Lasrado et al., 2015). This NOEL is greater than 170,000 times the anticipated *per capita* daily intake of watermint, *Mentha aquatica* L., extract from use as a flavor ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding enzyme modified stevia, stevioside 20% (CAS 57817-89-7; 58543-16-1) and concluded that the material is GRAS (FEMA 4876) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). This substance was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of enzyme modified stevia, stevioside 20% from use as a flavor ingredient to be 4400 µg/person/day. The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation (see Appendix 1). The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). The Panel concluded that metabolic data exist for a representative members of the principal 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 detoxication pathways to innocuous products (Gardana et al., 2003; Geuns, 2003; Geuns et al., 2003; Koyama et al., 2003a; Koyama et al., 2003b; Nikiforov et al., 2013; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha et al., 2014; Roberts and Renwick, 2008). Negative results were obtained in Ames assays for rebaudioside A at levels of up to 10 to 50 mg/plate with and without metabolic activation (Rumelhard et al., 2016). Rebaudioside A did not induce chromosome aberrations *in vitro* in Chinese hamster lung fibroblasts with or without metabolic activation at levels of up to 5 mg/mL (Williams and Burdock, 2009). An *in vivo* mouse micronucleus study with rebaudioside A at dose levels up to 2,000 mg/kg bw, administered once daily for 2 days by gavage, was negative (Nakajima, 2000). Based on these assays and the composition of the material therein, the Panel did not identify specific concerns related to the genotoxicity of glucosylated rebaudioside A. A 90-day study of rebaudioside A administered to Sprague-Dawley rats via the diet resulted in a NOEL of 2,000 mg/kg bw/day (Rumelhard et al., 2016). The resulting NOEL of 2000 mg/kg bw/day is 27,200 times the anticipated daily *per capita* intake of enzyme modified stevia, stevioside 20% from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding (*E*)-3-(3,4-dimethoxyphenyl)-*N*-[2-(4-methoxyphenyl)ethyl]-acrylamide (CAS 76733-95-4) and concluded that the substance is GRAS (FEMA 4877) (Smith et al., 2005a) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). The substance was evaluated individually within the context of the chemical group of aliphatic and aromatic amines and amides (SLR A7; C21;

JECFA, 2006, 2008, 2011, 2012). The Panel calculated the anticipated *per capita* intake ("eaters only") of (*E*)-3-(3,4-dimethoxyphenyl)-*N*-[2-(4-methoxyphenyl)ethyl]acrylamide from use as a flavor ingredient to be 240 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient. (Harman and Hallagan, 2013). (*E*)-3-(3,4-dimethoxyphenyl)-*N*-[2-(4-methoxyphenyl)ethyl]-acrylamide is predicted to be metabolized primarily by *O*-demethylation and *O*-demethylation to yield phenolic derivatives that form glucuronic acid and sulfate conjugates, which are then excreted primarily in the urine (Nelson and Cox, 2008). No genotoxic potential was observed when the structurally related substance *N*-2[2-(3,4-dimethoxyphenyl)ethyl]-3,4-dimethoxycinnamic acid amide (FEMA 4310) was incubated with *S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 with or without metabolic activation in two separate experiments using the plate incorporation method and the pre-incubation method (Uhde, 2004). In a standard mouse micronucleus bone marrow assay, groups of 63 male mice were injected intraperitoneally with 175, 350, or 700 mg per kg bw of the structurally related substance, *N*-(heptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide (FEMA 4232). No statistically significant differences were observed in the number of polychromatic erythrocytes with micronuclei between each of the test groups and the negative control (Pucaj, 2004). Based on these assays, the structure of the substance and the arrangement and identity of the functional groups therein, the Panel did not identify specific concerns related to the genotoxicity of (*E*)-3-(3,4-dimethoxyphenyl)-*N*-[2-(4-methoxyphenyl)ethyl]-acrylamide. Toxicity studies for structurally related substances have resulted in NOEL values that are, at minimum, greater than 2000 times the anticipated daily *per capita* intake of (*E*)-3-(3,4-dimethoxyphenyl)-*N*-[2-(4-methoxyphenyl)ethyl]-acrylamide from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *Cordyceps sinensis* fermentation product (CAS 1883732-47-5) and concluded that the material is GRAS (FEMA 4878) for use as a flavor ingredient in the food categories and at the use levels specified in the GRAS application (see Table 2). This material was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of *Cordyceps sinensis* fermentation product from use as a flavor ingredient to be 100 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation (see Appendix 1). The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Metabolic data exists for representative members of each congeneric group of *Cordyceps sinensis* fermentation product that would predict, at the levels of intake proposed, metabolism by well-established detoxication pathways to innocuous products (Miao et al., 2014). *Cordyceps sinensis* fermentation product did not produce any evidence of mutagenicity in an Ames assay in *S. typhimurium* strains

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2 *uvrA* in the absence and presence of S-9 metabolic activation (Wagner, 2016). *Cordyceps sinensis* did not increase the number of micronucleated cells relative to vehicle controls in an *in vitro* micronucleus study in human peripheral blood lymphocytes in the absence and presence of S-9 metabolic activation (Roy, 2016). Based on these assays, and the composition of the material therein, the Panel did not identify specific concerns related to the genotoxicity of *Cordyceps sinensis* fermentation product.

References

Adams, T.B., Gavin, C.L., McGowen, M.M., Waddell, W.J., Cohen, S.M., Feron, V.J., Marnett, L.J., Munro, I.C., Portoghese, P.S., Rietjens, I.M.C.M., Smith, R.L., 2011. The FEMA GRAS assessment of aliphatic and aromatic terpene hydrocarbons used as flavor ingredients. *Food and Chemical Toxicology* 49, 2471-2494.

Adams, T.B., Hallagan, J.B., Putnam, J.M., Gierke, T.L., Doull, J., Munro, I.C., Newberne, P., Portoghese, P.S., Smith, R.L., Wagner, B.M., Weil, C.S., Woods, L.A., Ford, R.A., 1996. The FEMA GRAS assessment of alicyclic substances used as flavour ingredients. *Food and Chemical Toxicology* 34, 763-828.

Anderson, B.E., Zeiger, E., Shelby, M.D., Resnick, M.A., Gulati, D.K., Ivett, J.L., Loveday, K.S., 1990. Chromosome aberration and sister chromatid exchange test results with 42 chemicals. *Environmental and Molecular Mutagenesis* 16, 55-137.

Asakawa, Y., Ishida, T., Toyota, M., Takemoto, T., 1986. Terpenoid biotransformation in mammals. IV. Biotransformation of (+)-longifolene, (-)-caryophyllene, (-)-caryophyllene oxide, (-)-cyclocolorenone, (+)-nootkatone, (-)-elemol, (-)-abietic acid and (+)-dehydroabietic acid in rabbits. *Xenobiotica* 16, 753-767.

Baba, S., Osakabe, N., Natsume, M., Terao, J., 2004. Orally administered rosmarinic acid is present as the conjugated and/or methylated forms in plasma, and is degraded and metabolized to conjugated forms of caffeic acid, ferulic acid and *m*-coumaric acid. *Life Sciences* 75, 165-178.

Bauter, M.R., 2013. 5-Ethylthiophene-2-carbaldehyde: a 90-day oral gavage study in rats, Unpublished report to the International Organization of the Flavor Industry. Product Safety Labs, Dayton, NJ, USA. Provided by IOFI to the FEMA Expert Panel.

Beevers, C., 2009. Reverse mutation in five histidine-requiring strains of *S. typhimurium* for 5-methyl-2-thiophenecarbaldehyde. Unpublished report to the International Organization of the Flavor Industry. Covance Laboratories Ltd., North Yorkshire, England. Provided by IOFI to the FEMA Expert Panel.

Beevers, C., 2012. Combined Comet assay in the liver and a bone marrow micronucleus test in treated rats for 5-methyl-2-thiophenecarbaldehyde, Unpublished report to the International Organization of the Flavor Industry. Covance Laboratories Ltd., North Yorkshire, England. Provided to the FEMA Expert Panel by the International Organization of the Flavor Industry.

Bhalli, J., Phil, M., 2014a. *cis*-3-hexenol (CAS # 928-96-1): Bacterial reverse mutation assay: plate incorporation method with a confirmatory assay. Study no. 8289058. Covance Laboratories Inc., Greenfield, IN, USA. Unpublished report provided by the Research Institute for Fragrance Materials to the FEMA Expert Panel.

Bhalli, J., Phil, M., 2014b. *cis*-3-hexenol (CAS # 928-96-1): *In vitro* micronucleus assay in human peripheral blood lymphocytes. Study no. 8289135 Covance Laboratories Inc., Greenfield, IN, USA. Unpublished report provided by the Research Institute for Fragrance Materials to the FEMA Expert Panel.

BIBRA, 1976. Acute and short term toxicity of TT171, TT172, TT173 and TT174, Unpublished report to FEMA. British Industrial Biological Research Association, England. Provided to the FEMA Expert Panel by FEMA

Bisson, J.-F., Rozan, P., Hidalgo, S., Friedrich, M., 2012. Evaluation of the toxicity of Resinogum DD (RDD), orally administered as a subchronic treatment at three doses during 90 Days, in male and female Wistar rats. *Ethologie Appliquée, Vandoeuvre-lès-Nancy, France*. Unpublished report provided to the FEMA Expert Panel.

Boggs, J.W., 2014. GR-72-7311: A central nervous system behavioral tetrad assessment following oral (gavage) administration in the male CD-1 mouse. Summary toxicokinetics report. WIL Research, Ashland, OH. Unpublished report provided to the FEMA Expert Panel.

Borges, G., Lean, M.E., Roberts, S.A., Crozier, A., 2013. Bioavailability of dietary (poly)Phenols: a study with ileostomists to discriminate between absorption in small and large intestine. *Food & Function* 4, 754-762.

Bornet, F.R.J., Blayo, A., Dauchy, F., Slama, G., 1996a. Gastrointestinal response and plasma and urine determinations in human subjects given erythritol. *Regulatory Toxicology and Pharmacology* 24, S296-S302.

Bornet, F.R.J., Blayo, A., Dauchy, F., Slama, G., 1996b. Plasma and urine kinetics of erythritol after oral ingestion by healthy humans. *Regulatory Toxicology and Pharmacology* 24, S280-S285.

Bowles, A., 2014. *trans*-1-Ethyl-2-methylpropyl-2-butenolate: chromosome aberration test in human lymphocytes *in vitro*. Harlan Laboratories Ltd, Derbyshire, UK. Unpublished report provided to the FEMA Expert Panel.

Boyland, E., Chasseaud, L.F., 1970. The effect of some carbonyl compounds on rat liver glutathione levels. *Biochemical Pharmacology* 19, 1526-1528.

Cannon, R.J., Kazimierski, A., Curto, N.L., Li, J., Trinnaman, L., Jańczuk, A.J., Agyemang, D., Da Costa, N.C., Chen, M.Z., 2015. Identification, synthesis, and characterization of novel sulfur-containing volatile compounds from the in-depth analysis of Lisbon lemon peels (*Citrus limon* L. Burm. f. cv. Lisbon). *Journal of Agricultural and Food Chemistry* 63, 1915-1931.

Cashman, J.R., Olsen, L.D., Bornheim, L.M., 1990. Enantioselective S-oxygenation by flavin-containing and

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

cytochrome P-450 monooxygenases. *Chemical Research in Toxicology* 3, 344-349.

Chan, P.C., 2011. NTP toxicity studies of toxicity studies of 2, 4-decadienal (CAS No. 25152-84-5) administered by gavage to F344/N Rats and B6C3F1 mice. Toxicity report series 76, 1-94.

Chasseaud, L.F., 1979. The role of glutathione and glutathione S-transferases in the metabolism of chemical carcinogens and other electrophilic agents. *Advances in Cancer Research* 29, 175-274.

Chung, Y.S., Lee, M., 2013. Genotoxicity assessment of erythritol by using short-term assays. *Toxicological Research* 29, 249-255.

Cohen, S.M., Fukushima, S., Gooderham, N.J., Guengerich, F.P., Hecht, F.M., Rietjens, I.M., Smith, L.M., Bastaki, M., Harman, C.G., McGowen, M.M., Valerio, L.G., Taylor, S.V., 2017. Safety evaluation of substituted thiophenes used as flavoring ingredients. *Food and Chemical Toxicology*, 40-59.

Cohen, S.M., Fukushima, S., Gooderham, N.J., Hecht, S.S., Marnett, L.J., Rietjens, I., Smith, R.L., Bastaki, M., McGowen, M.M., Harman, C., Taylor, S.V. 2015. GRAS Flavoring Substances 27. *Food Technology* 69(8), 40-59.

Connor, T., Theiss, J., Hanna, H., Monteith, D., Matney, T., 1985. Genotoxicity of organic chemicals frequently found in the air of mobile homes. *Toxicology Letters* 25, 33-40.

Cotgreave, I.A., Atzori, L., Moldeus, P., 1989. Thiol-disulphide exchange: physiological and toxicological aspects. Wiley-Blackwell, New York.

Cowan, D.A., Damani, L.A., Gorrod, J.W., 1978. Metabolic N-oxidation of 3-substituted pyridines: Identification of products by mass spectrometry. *Biological Mass Spectrometry* 5, 551-556.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard - A decision tree approach. *Food and Cosmetics Toxicology* 16, 255-276.

Damani, L.A., Bryan, J., Cowan, D.A., Gorrod, J.W., 1980. The origin of 1-(3-pyridyl-N-oxide)ethanol as a metabolite of 3-acetylpyridine. *Xenobiotica* 10, 645-653.

Damani, L.A., Crooks, P.A., Shaker, M.S., Caldwell, J., D'Souza, J., Smith, R.L., 1982. Species Difference in the metabolic C- and N-oxidation, and N-methylation of [¹⁴C]-pyridine *in vivo*. *Xenobiotica* 12, 527-534.

Dansette, P.M., Thang, D.C., Mansuy, H.E.A.D., 1992. Evidence for thiophene-S-oxide as a primary reactive metabolite of thiophene *in vivo*: Formation of a dihydrothiophene sulfoxide mercapturic acid. *Biochemical and Biophysical Research Communications* 186, 1624-1630.

Day, A.J., Cañada, F.J., Díaz, J.C., Kroon, P.A., Mclauchlan, R., Faulds, C.B., Plumb, G.W., Morgan, M.R., Williamson, G., 2000. Dietary flavonoid and isoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase. *FEBS Letters* 468, 166-170.

de Cock, P., 2012. 2.3 Reduced-calorie bulk sweeteners. 2.3.1. Erythritol, in: H. Mitchell (Ed.), *Sweeteners and Sugar Alternatives in Food Technology*. Blackwell, Oxford, pp. 215-241.

Donovan, J.L., Manach, C., Faulks, R.M., Kroon, P.A., 2006. Absorption and metabolism of dietary plant secondary metabolites. *Plant secondary metabolites: occurrence, structure and role in the human diet*, 303-351.

ECHA, 2015. 2-Pyrrolidone - Exp Key Genetic toxicity *in vitro*, REACH registration dossiers summary information. European Chemicals Agency (ECHA).

Eder, E., Neudecker, T., Lutz, D., Henschler, D., 1980. Mutagenic potential of allyl and allylic compounds. *Biochemical Pharmacology* 29, 993-998.

ERINI, 2014. Feasibility study for fine characterization of purified dammar gum from *Shorea javanica*, Unpublished report. European Research Institute on Natural Ingredients. Provided to the FEMA Expert Panel.

FEMA, 1975a. SLR A7, Scientific literature review of aliphatic amines. National Technical Information Service.

FEMA, 1975b. SLR A8, Scientific literature review of simple aliphatic and aromatic sulfides and thiols. National Technical Information Service.

FEMA, 1976a. SLR B4, Scientific literature review of aliphatic mono-, di- and trisulfides. National Technical Information Service.

FEMA, 1976b. SLR B5C, Scientific literature review of aliphatic thio esters, Washington, D.C.

FEMA, 1976, 1978, 1985. SLR A5, Scientific literature review of alicyclic compounds of carbon, hydrogen and oxygen. National Technical Information Service.

FEMA, 1976, 1979. SLR B1F, Scientific literature review of aliphatic poly-hydroxy compounds and derivatives. National Technical Information Service.

FEMA, 1978a. SLR C21, Scientific literature review of capsaicin and related compounds. National Technical Information Service.

FEMA, 1978b. SLR D1, Scientific literature review of dithiols and related substances. National Technical Information Service.

FEMA, 1978c. SLR D12, Scientific literature review of aliphatic ethers. National Technical Information Service.

FEMA, 1978, 1979, 1983. SLR C4, Scientific literature review of aryl substituted tertiary alcohols and esters. National Technical Information Service.

FEMA, 1978, 1984. SLR C9, Scientific literature review of Benzyl alcohol, benzaldehyde, benzoic acid and related compounds. National Technical Information Service.

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

- FEMA, 1978, 1985. SLR C18, Scientific literature review of vanillin and derivatives. National Technical Information Service.
- FEMA, 1979a. SLR B5A, Scientific literature review of primary alcohols, aldehydes, acids and related esters with thiol or sulfide functions. National Technical Information Service.
- FEMA, 1979b. SLR D3, Scientific literature review of pyrrole and related substances. National Technical Information Service.
- FEMA, 1979c. SLR D9, Scientific literature review of tetrahydrofuran and furanone derivatives. National Technical Information Service.
- FEMA, 1979, 1983, 1985. SLR D2, Scientific literature review of pyridine and related substances. National Technical Information Service.
- FEMA, 1979, 1984. SLR C12, Scientific literature review of phenols. National Technical Information Service.
- FEMA, 1985. SLR M1, Scientific literature review of aliphatic primary alcohols, aldehydes, esters and acids. National Technical Information Service.
- FEMA, 1987. SLR D15, Scientific literature review of thiophene derivatives. National Technical Information Service.
- Ferdinandi, E.S., 1993. Excretion of radioactivity and urinary metabolite profile in male beagle dogs following oral administration of ¹⁴C-labeled 3-l-menthoxypropane-1,2-diol, Study No. HPCR-0421 Report No. 38784 ed. Bio-Research Laboratories Ltd., Quebec, Canada. Unpublished report provided to the FEMA Expert Panel.
- Florin, I., Rutberg, L., Curvall, M., Enzell, C.R., 1980. Screening of tobacco smoke constituents for mutagenicity using the ames test. *Toxicology* 15, 219-232.
- Fry, J.R., Fentem, J.H., Salim, A., Tang, S.P.A., Garle, M.J., Whiting, D.A., 1993. Structural requirements for the direct and cytochrome P450-dependent reaction of cyclic α,β -unsaturated carbonyl compounds with glutathione: a study with coumarin and related compounds. *Journal of Pharmacy and Pharmacology* 45, 166-170.
- Fujita, H., Sasaki, M., 1987. Mutagenicity test of food additives with *Salmonella typhimurium* TA97 and TA102 (II). Annual Report of Tokyo Metropolitan Research Laboratory of Public Health 38, 423-430.
- Fukami, T., Yokoi, T., 2012. The emerging role of human esterases. *Drug Metabolism and Pharmacokinetics* 27, 466-477.
- Gardana, C., Simonetti, P., Canzi, E., Zanchi, R., Pietta, P., 2003. Metabolism of stevioside and rebaudioside A from *Stevia rebaudiana* extracts by human microflora. *J Agric Food Chem* 51, 6618-6622.
- Gaunt, I.F., Agrelo, C.E., Colley, J., Lansdown, A.B.G., Grasso, P., 1971. Short-term toxicity of isobornyl acetate in rats. *Food and Cosmetics Toxicology* 9, 355-366.
- Gaunt, I.F., Colley, J., Grasso, P., Lansdown, A.B.G., Gangolli, S.D., 1969. Acute (rat and mouse) and short-term (rat) toxicity studies on cis-3-hexen-1-ol. *Food and Cosmetics Toxicology* 7, 451-459.
- Germain, E., Semon, E., Siess, M.-H., Teyssier, C., 2008. Disposition and metabolism of dipropyl disulphide *in vivo* in rat. *Xenobiotica* 38, 87-97.
- Geuns, J.M., 2003. Stevioside. *Phytochemistry* 64, 913-921.
- Geuns, J.M., Augustijns, P., Mols, R., Buyse, J.G., Driessen, B., 2003. Metabolism of stevioside in pigs and intestinal absorption characteristics of stevioside, rebaudioside A and steviol. *Food and Chemical Toxicology* 41, 1599-1607.
- Geuns, J.M., Buyse, J., Vankeirsbilck, A., Temme, E.H., 2007. Metabolism of stevioside by healthy subjects. *Experimental Biology and Medicine* 232, 164-173.
- Geuns, J.M., Pietta, P., 2004. Stevioside metabolism by human volunteers. Laboratory of Functional Biology, ITB Istituto di Tecnologie Biomediche, Segrate, Italy. Unpublished report provided to the FEMA Expert Panel.
- Griffiths, P.J., Giessinger, M., Fouillet, X., 1979. Report on the oral toxicity (LD50) and three month toxicity (91 days) of TT 184. Batelle Geneva, Switzerland. Unpublished report provided to the FEMA Expert Panel.
- Grosa, G., Caputo, O., Ceruti, M., Biglino, G., Franzone, J.S., Cravanzola, C., 1991. Metabolism of 7-(1,3-dithiolan-2-ylmethyl)-1,3-dimethylxanthine by rat liver microsomes. Diastereoselective metabolism of the 1,3-dithiolane ring. *Drug Metabolism and Disposition* 19, 454-457.
- Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.A., Brouwer, J.B., 1967. Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. *Food and Cosmetics Toxicology* 5, 141-157.
- Hall, R., Oser, B., 1965. III GRAS Substances: recent progress in the consideration of flavoring ingredients under the food additives amendment. *Food Technology* 19, 151 - 156.
- Hallagan, J.B., Hall, R.L., 2009. Under the conditions of intended use – new developments in the FEMA GRAS program and the safety assessment of flavor ingredients. *Food and Chemical Toxicology* 47, 267-278.
- Harman, C.L., Hallagan, J.B., 2013. Sensory testing for flavorings with modifying properties. *Food Technology* 67, 44-47.
- Hawksworth, G., Scheline, R.R., 1975. Metabolism in the rat of some pyrazine derivatives having flavour importance in foods. *Xenobiotica* 5, 389-399.
- Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., Zeiger, E., 1983. *Salmonella* mutagenicity test results for 250 chemicals. *Environmental Mutagenesis* 5, 3-49.
- Hayashi, M., Kishi, M., Sofuni, T., Ishidate, M., Jr., 1988. Micronucleus tests in mice on 39 food additives and eight

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

miscellaneous chemicals. Food and Chemical Toxicology 26, 487-500.

He, C., Zhou, D., Li, J., Han, H., Ji, G., Yang, L., Wang, Z., 2014. Identification of 20(S)-protopanaxatriol metabolites in rats by ultra-performance liquid chromatography coupled with electrospray ionization quadrupole time-of-flight tandem mass spectrometry and nuclear magnetic resonance spectroscopy. Journal of Pharmaceutical and Biomedical Analysis 88, 497-508.

Heck, J.D., 2010. A review and assessment of menthol employed as a cigarette flavoring ingredient. Food and Chemical Toxicology 48 Suppl 2, S1-38.

Heck, J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B.C., Curran, R.D., 1989. An evaluation of food flavouring ingredients in a genetic toxicity screening battery. The Toxicologist 9, 257.

Higginbotham, J., Snodin, D., Eaton, K., Daniel, J., 1983. Safety evaluation of thaumatin (talin protein). Food and Chemical Toxicology 21, 815-823.

Honarvar, N., 2008. Micronucleus assay in bone marrow cells of the mouse with decenal 4-trans (code 76150), RCC Cytotest Cell Research, Rossdorf, Germany. Unpublished report provided to the FEMA Expert Panel.

Hosokawa, M., 2008. Structure and catalytic properties of carboxylesterase isozymes involved in metabolic activation of prodrugs. Molecules 13, 412-431.

Hutapea, A.M., Tuoskulkao, C., Buddhasukh, D., Wilairat, P., Glinsukon, T., 1997. Digestion of stevioside, a natural sweetener, by various digestive enzymes. Journal of Clinical Biochemistry and Nutrition 23, 177-186.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans World Health Organization International Agency for Research on Cancer, 1999. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. World Health Organization.

Ishidate, M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A., 1984. Primary mutagenicity screening of food additives currently used in Japan. Food and Chemical Toxicology 22, 623-636.

JECFA, 1999. Safety evaluation of certain food additives (fifty-first meeting of Joint FAO/WHO Expert Committee on Food Additives). WHO Food Additives Series No. 42.

JECFA, 2000a. Evaluation of certain food additives and contaminants (fifty-first report of Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 891.

JECFA, 2000b. Linear and branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids, and related esters (fifty-first report of Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 891.

JECFA, 2001. Safety evaluation of certain food additives and contaminants (fifty-fifth report of the Joint FAO/WHO Expert

Committee on Food Additives). WHO Food Additive Series No. 48.

JECFA, 2002. Evaluation of certain food additives (Fifty ninth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 913.

JECFA, 2003. Sulfur-containing heterocyclic compounds. WHO Food Additives Series No. 50.

JECFA, 2004. Evaluation of certain food additives and contaminants (Sixty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 922.

JECFA, 2005. Evaluation of certain food additives and contaminants (Sixty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 928.

JECFA, 2006. Safety evaluation of certain food additives and contaminants (sixty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Food Additive Series No. 54.

JECFA, 2007. Evaluation of certain food additives (Sixty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 947.

JECFA, 2008. Simple Aliphatic and Aromatic Sulfides and Thiols (addendum) (sixty-eighth meeting of Joint FAO/WHO Expert Committee on Food Additives). WHO Food Additive Series No. 59, 175-236.

JECFA, 2009. Safety evaluation of certain food additives and contaminants (sixty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives). WHO Food Additive Series No. 60.

JECFA, 2011. Evaluation of certain food additives (Seventy-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 960.

JECFA, 2012. Evaluation of certain food additives (Seventy-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 974.

JECFA, 2014. Evaluation of certain food additives and contaminants (Seventy-ninth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series 990.

JECFA, 2015. Safety evaluation of certain food additives (seventy-ninth report of the Joint FAO/WHO Committee on Food Additives). WHO Food Additive Series No. 70.

Jones, L.J., McKenzie, J., Brooks, P.N., 2004. Nookatone, Verbenone: twenty-eight day repeated dose, single dose level oral toxicity study in the rat. SafePharm Laboratories, Derbyshire, UK. Unpublished report provided to the FEMA Expert Panel.

Kandel, S., 2015. Metabolite characterization of neoflavonoid in rat and human hepatocytes, XenoTech, LLC, Lenexa, KS. Unpublished report provided to the FEMA Expert Panel.

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

- Kasamaki, A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T., Urasawa, S., 1982. Genotoxicity of flavoring agents. *Mutation Research Letters* 105, 387-392.
- Kauderer, B., Zamith, H., Paumgarten, F.J.R., Speit, G., Holden, H.E., 1991. Evaluation of the mutagenicity of β -myrcene in mammalian cells *in vitro*. *Environmental and Molecular Mutagenesis* 18, 28-34.
- Kawaguchi, R., 2015a. Reverse mutation assay "Ames Test" using *Salmonella typhimurium*. Test material 4-(4-methyl-3-penten-1-yl)-2(5H)-furanone. Unpublished report provided to the FEMA Expert Panel.
- Kawaguchi, R., 2015b. Reverse mutation assay "Ames Test" using *Salmonella typhimurium*. Test material Rotundone. Unpublished report provided to the FEMA Expert Panel.
- Kawamura, Y., Saito, Y., Imamura, M., Modderman, J.P., 1996. Mutagenicity studies on erythritol in bacterial reversion assay systems and in Chinese hamster fibroblast cells. *Regulatory Toxicology and Pharmacology* 24, S261-S263.
- Keehr, K.A., Hunt, C.D., 2000. Dietary boron and erythritol affect reproduction and fetal development in rats. *Proceedings of the North Dakota Academy of Science*.
- King, M.T., Harnasch, D., 1999a. Mutagenicity of Resinogum DD (purified damar gum RD 447) in the *Salmonella typhimurium*/mammalian microsome reverse mutation assay (Ames-Test). Freiburger Labor für Mutagenitätsprüfung der King & Harnasch GmbH, Kirchzarten, Germany. Unpublished report provided to the FEMA Expert Panel.
- King, M.T., Harnasch, D., 1999b. Mutagenicity of Resinogum DD (purified damar gum RD 447) with the micronucleus test in bone marrow cells of mice (NMRI). Freiburger Labor für Mutagenitätsprüfung der King & Harnasch GmbH, Kirchzarten, Germany. Unpublished report provided to the FEMA Expert Panel.
- Kong, L.T., Wang, Q., Xiao, B.X., Liao, Y.H., He, X.X., Ye, L.H., Liu, X.M., Chang, Q., 2013. Different pharmacokinetics of the two structurally similar dammarane sapogenins, protopanaxatriol and protopanaxadiol, in rats. *Fitoterapia* 86, 48-53.
- Köppel, C., Tenczer, J., 1991. Mass spectral characterization of urinary metabolites of d,l-kawain. *Journal of Chromatography B: Biomedical Sciences and Applications* 562, 207-211.
- Koyama, E., Kitazawa, K., Ohori, Y., Izawa, O., Kakegawa, K., Fujino, A., Ui, M., 2003a. *In vitro* metabolism of the glycosidic sweeteners, stevia mixture and enzymatically modified stevia in human intestinal microflora. *Food and Chemical Toxicology* 41, 359-374.
- Koyama, E., Sakai, N., Ohori, Y., Kitazawa, K., Izawa, O., Kakegawa, K., Fujino, A., Ui, M., 2003b. Absorption and metabolism of glycosidic sweeteners of stevia mixture and their aglycone, steviol, in rats and humans. *Food and Chemical Toxicology* 41, 875-883.
- Lasrado, J.A., Trinker, D., Ceddia, M.A., Herrlinger, K.A., 2015. The safety of a dry spearmint extract *in vitro* and *in vivo*. *Regulatory Toxicology and Pharmacology* 71, 213-224.
- Leuschner, P.J., 2016. Mutagenicity study of 3-(3-hydroxy-4-methoxy-phenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one in the *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay (*in vitro*). LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG, Hamburg, Germany. Unpublished report provided to the FEMA Expert Panel.
- Lilja, H.S., Hagopian, M., Esber, H.J., Fleischman, R.W., Russfield, A.B., Tiedemann, K.M., 1983. Report on the subchronic toxicity by dosed feed of turmeric oleoresin (C60015) in Fischer 344 rats and B6C3F1 mice. EG&G Mason Research Institute. Unpublished report provided to the FEMA Expert Panel.
- Lina, B., Bos-Kuijpers, M., Til, H., Bär, A., 1996. Chronic toxicity and carcinogenicity study of erythritol in rats. *Regulatory Toxicology and Pharmacology* 24, S264-S279.
- Lloyd, M., 2011. Induction of micronuclei in cultured human peripheral blood lymphocytes for 5-methyl-2-thiophenecarbaldehyde. Covance Laboratories Ltd., North Yorkshire, England. Unpublished report provided to the FEMA Expert Panel by the International Organization of the Flavor Industry.
- Lock, E.A., Hard, G.C., 2004. Chemically induced renal tubule tumors in the laboratory rat and mouse: review of the NCI/NTP database and categorization of renal carcinogens based on mechanistic information. *Critical Reviews in Toxicology* 34, 211-299.
- Maiorino, R.M., Xu, Z.F., Aposhian, H.V., 1996. Determination and metabolism of dithiol chelating agents. XXII. *Journal of Pharmacology and Experimental Therapeutics* 277, 375-384.
- Manach, C., Williamson, G., Morand, C., Scalbert, A., Rémésy, C., 2005. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *The American Journal of Clinical Nutrition* 81, 230S-242S.
- Mancebo, A., Trapero, Y.M., González, Y., González, B.O., Fuentes, D., Hernández, O., Hernández, J., González, C., Hernández, Y., Arteaga, M.E., Subirós, N., Bada, A.M., 2003. Repeated dose oral toxicity (13 weeks) of 4-hydroxy-3-methoxy-benzaldehyde (vanillin) to Sprague Dawley rats. *Toxicology Letters* 144, S57.
- Marin, L., Miguelez, E.M., Villar, C.J., Lombo, F., 2015. Bioavailability of dietary polyphenols and gut microbiota metabolism: antimicrobial properties. *BioMedical Research International* 2015, 1-18.
- Marks, H.S., Anderson, J.L., Stoewsand, G.S., 1992. Inhibition of benzo[a]pyrene-induced bone marrow micronuclei formation by diallyl thioethers in mice. *Journal of Toxicology and Environmental Health* 37, 1-9.
- Marzin, D., 1998. Recherche de mutagenicite sur *Salmonella typhimurium* His- selon la method de B.N. Ames sur le produit ST14C97. Unpublished report provided to the FEMA Expert Panel.

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

- Merrill, D., 2015a. 7,8-Dihydroxyflavone: Bacterial Reverse Mutation Test (Ames Test). Product Safety Labs, Dayton, NJ. Unpublished report provided to the FEMA Expert Panel.
- Merrill, D., 2015b. RD38313: Bacterial Reverse Mutation Test (Ames Test). Product Safety Labs, Dayton, NJ. Unpublished report provided to the FEMA Expert Panel.
- Merrill, D., 2016. Chrysanthemum parthenium extract, CAS# 89997-65-9. Bacterial Reverse Mutation Test (Ames Test). Product Safety Labs, Dayton, NJ. Unpublished report provided to the FEMA Expert Panel.
- Miao, M., Li, R., Jiang, B., Cui, S.W., Lu, K., Zhang, T., 2014. Structure and digestibility of endosperm water-soluble alpha-glucans from different sugary maize mutants. *Food Chemistry* 143, 156-162.
- Morgareidge, K., Bailey, D.E., Cox, G.E., 1974. 90-Day feeding studies in rats with compound 14966. Unpublished report provided to the FEMA Expert Panel by FEMA.
- Morgareidge, K., Oser, B.L., 1970. 90-Day feeding studies in rats with 2-thienyldisulfide. Unpublished report provided to the FEMA Expert Panel. by FEMA
- Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., Zeiger, E., 1986. *Salmonella* mutagenicity tests: II. Results from the testing of 270 chemicals. *Environmental Mutagenesis* 8, 56-119.
- Mozier, N., Hoffman, J.L., 1990. Biosynthesis and urinary excretion of methyl sulfonium derivatives of the sulfur mustard analog, 2-chloroethyl ethyl sulfide, and other thioethers. *FASEB Journal* 4, 3329-3333.
- Müller, W., Engelhart, G., Herbold, B., Jäckh, R., Jung, R., 1993. Evaluation of mutagenicity testing with *Salmonella typhimurium* TA102 in three different laboratories. *Environmental Health Perspectives* 101, 33-36.
- Munro, I.C., Ford, R.A., Kennepohl, E., Sprenger, J.G., 1996. Correlation of structural class with no-observed-effect levels: a proposal for establishing a threshold of concern. *Food and Chemical Toxicology* 34, 829-867.
- Musk, S.R.R., Clapham, P., Johnson, I.T., 1996. Cytotoxicity and genotoxicity of diallyl sulfide and diallyl disulfide towards Chinese hamster ovary cells. *Food and Chemical Toxicology* 35, 379-385.
- Myhr, B., McGregor, D., Bowers, L., Riach, C., Brown, A.G., Edwards, I., McBride, D., Martin, R., Caspary, W.J., 1990. L5178Y mouse lymphoma cell mutation assay results with 41 compounds. *Environmental and Molecular Mutagenesis* 16, 138-167.
- Nakajima, M., 2000. Micronucleus test of rebaudioside A in mice. Biosafety Research Center, Japan. Unpublished report provided to the FEMA Expert Panel.
- Nakayama, K., Kasahara, D., Yamamoto, F., 1986. Absorption, distribution, metabolism and excretion of stevioside in rats. *Food Hygiene and Safety Science (Shokuhin Eiseigaku Zasshi)* 27, 1-8.
- National Toxicology Program, 1990. Carcinogenicity and toxicology studies of *d*-limonene in F344/N Rats and B6C3F1. US Department of Health and Human Services.
- National Toxicology Program, 1992. Toxicology and carcinogenesis studies of quercetin (CAS No. 117-39-5) in F344 rats (feed studies). Technical Report Series 409, 1.
- Nelson, D.L., Cox, M.M., 2008. *The Citric Acid Cycle*, Lehninger Principles of Biochemistry, 5th ed. W.H. Freeman, New York.
- Nelson, S.D., McClanahan, R.H., Thomassen, D., Perry Gordon, W., Knebel, N., 1992. Investigations of mechanisms of reactive metabolite formation from (*R*)-(+)-pulegone. *Xenobiotica* 22, 1157-1164.
- Nguyen, P.L., Saint-Jalm, Y., Dutertre-Catella, H., Truhaut, R., Claude, J.R., 1988. Biotransformations of γ -Picoline in the Rat, *Archives of Toxicology*. Springer Science + Business Media, pp. 308-312.
- Nijssen, L.M., 2017. Volatile Compounds in Food: Database, in: H. Maarse, C. Visscher (Eds.), Version 16.3. Triskelion, Zeist, The Netherlands.
- Nikiforov, A.I., Rihner, M.O., Eapen, A.K., Thomas, J.A., 2013. Metabolism and toxicity studies supporting the safety of rebaudioside D. *International Journal of Toxicology* 32, 261-273.
- Noda, K., Nakayama, K., Modderman, J., 1996. Fate of erythritol after single dose oral administration to rats and dogs. *Regulatory Toxicology and Pharmacology* 24, S206-S213.
- Noda, K., Oku, T., 1992. Metabolism and disposition of erythritol after oral administration to rats. *The Journal of Nutrition* 122, 1266-1272.
- Oser, B.L., Carson, S., Oser, M., 1965. Toxicological tests on flavouring matters. *Food and Cosmetics Toxicology* 3, 563-569.
- Pant, K., 2015. *In vivo* micronucleus screening assay in mice. BioReliance Corporation, Rockville, MD. Unpublished report provided to the FEMA Expert Panel.
- Parkinson, A., 1996. Biotransformation of xenobiotics, in: C.D. Klaasen, L.J. Casarett, J. Doull (Eds.), *Casarett & Doull's Toxicology: The Basic Science of Poisons*, 5 ed. McGraw-Hill Education, New York.
- Pereira, P., Tysca, D., Oliveira, P., da Silva Brum, L.F., Picada, J.N., Ardenghi, P., 2005. Neurobehavioral and genotoxic aspects of rosmarinic acid. *Pharmacological Research* 52, 199-203.
- Pezzuto, J.M., Compadre, C.M., Swanson, S.M., Nanayakkara, D., Kinghorn, A.D., 1985. Metabolically activated steviol, the aglycone of stevioside, is mutagenic. *Proceeding of the National Academy of Science USA* 82, 2478-2482.
- Pezzuto, J.M., Nanayakkara, N.P., Compadre, C.M., Swanson, S.M., Kinghorn, A.D.,

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

- Guenther, T.M., Sparnins, V.L., Lam, L.K., 1986. Characterization of bacterial mutagenicity mediated by 13-hydroxy-ent-kaurenoic acid (steviol) and several structurally-related derivatives and evaluation of potential to induce glutathione S-transferase in mice. *Mutation research* 169, 93-103.
- Pool, B., Lin, P., 1982. Mutagenicity testing in the *Salmonella typhimurium* assay of phenolic compounds and phenolic fractions obtained from smokehouse smoke condensates. *Food and Chemical Toxicology* 20, 383-391.
- Posternak, J.M., 1963. Toxicity Report: Nonanoyl-4-hydroxy-3-methoxybenzylamide, Unpublished report provided to the FEMA Expert Panel.
- Posternak, J.M., Linder, A., Vodoz, C.A., 1969. Summaries of toxicological data. *Food and Cosmetics Toxicology* 7, 405-407.
- Pucaj, K., 2004. Compound: S807 *in vivo* mouse micronucleus test. NuCro-Technics, Scarborough, Ontario, Washington, DC. Unpublished report provided to the FEMA Expert Panel.
- Purkayastha, S., Bhusari, S., Pugh, G., Jr., Teng, X., Kwok, D., Tarka, S.M., 2015. *In vitro* metabolism of rebaudioside E under anaerobic conditions: comparison with rebaudioside A. *Regulatory Toxicology and Pharmacology* 72, 646-657.
- Purkayastha, S., Markosyan, A., Prakash, I., Bhusari, S., Pugh, G., Jr., Lynch, B., Roberts, A., 2016. Steviol glycosides in purified stevia leaf extract sharing the same metabolic fate. *Regulatory Toxicology and Pharmacology* 77, 125-133.
- Purkayastha, S., Pugh, G., Jr., Lynch, B., Roberts, A., Kwok, D., Tarka, S.M., Jr., 2014. *In vitro* metabolism of rebaudioside B, D, and M under anaerobic conditions: comparison with rebaudioside A. *Regulatory Toxicology and Pharmacology* 68, 259-268.
- Rance, D.J., 1989. Sulphur Heterocycles, in: L.A. Damini (Ed.), *Sulphur-containing Drugs and Related Organic Compounds: Chemistry, Biochemistry and Toxicology*. Ellis Horwood Ltd., Chichester, England.
- Rapson, W.H., Nazar, M.A., Butsky, V.V., 1980. Mutagenicity produced by aqueous chlorination of organic compounds. *Bulletin of Environmental Contamination and Toxicology* 24, 590-596.
- Reddy, B.S., Rao, C.V., Rivenson, A., Kelloff, G., 1993. Chemoprevention of colon carcinogenesis by organosulfur compounds. *Cancer Research* 53, 3493-3498.
- Renwick, A.G., Tarka, S.M., 2008. Microbial hydrolysis of steviol glycosides. *Food and Chemical Toxicology* 46, S70-S74.
- Roberts, A., Renwick, A.G., 2008. Comparative toxicokinetics and metabolism of rebaudioside A, stevioside, and steviol in rats. *Food and Chemical Toxicology* 46 Suppl 7, S31-39.
- Roy, S., 2016. *In vitro* mammalian cell micronucleus assay in human peripheral blood lymphocytes (HPBL). BioReliance Corporation, Rockville, MD. Unpublished report provided to the FEMA Expert Panel.
- Rumelhard, M., Hosako, H., Eurlings, I.M., Westerink, W.M., Staska, L.M., van de Wiel, J.A., La Marta, J., 2016. Safety evaluation of rebaudioside A produced by fermentation. *Food and Chemical Toxicology* 89, 73-84.
- Sasaki, Y., Imanishi, H., Ohta, T., Shirasu, Y., 1989. Modifying effects of components of plant essence of the induction of sister-chromatid exchanges in cultured Chinese hamster ovary cells. *Mutation Research Letters* 226, 103-110.
- Scheline, R.R., 1991. *Handbook of Mammalian Metabolism of Plant Compounds*. CRC-Press.
- Shellenberger, T.E., 1970. Subacute toxicity evaluation of ethyl thioacetate in rats. Gulf South Research Institute. Unpublished report provided to the FEMA Expert Panel.
- Shimizu, M., Katoh, M., Imamura, M., Modderman, J., 1996. Teratology study of erythritol in rabbits. *Regulatory Toxicology and Pharmacology* 24, S247-253.
- Shindou, T., Ishizuka, H., 1996. Quantitative determination of erythritol from various natural cheeses by HPLC. *Food Science and Technology International*, Tokyo 2, 82-83.
- Simonetti, P., Gardana, C., Bramati, L., Pietta, P.G., 2004. Bioavailability of stevioside from *Stevia rebaudiana* in human volunteers: preliminary report. Proceedings of the first symposium on the safety of stevioside, KULeuven.
- Smith, R.L., Cohen, S.M., Doull, J., Feron, V.J., Goodman, J.I., Marnett, L.J., Munro, I.C., Portoghese, P.S., Waddell, W.J., Wagner, B.M., Adams, T.B., 2005a. Criteria for the safety evaluation of flavoring substances. *Food and Chemical Toxicology* 43, 1141-1177.
- Smith, R.L., Cohen, S.M., Doull, J., Feron, V.J., Goodman, J.I., Marnett, L.J., Portoghese, P.S., Waddell, W.J., Wagner, B.M., Hall, R.L., Higley, N.A., Lucas-Gavin, C., Adams, T.B., 2005b. A procedure for the safety evaluation of natural flavor complexes used as ingredients in food: essential oils. *Food and Chemical Toxicology* 43, 345-363.
- Smits-Van Prooije, A., Waalkens-Berendsen, D., Bär, A., 1996. Embryotoxicity and teratogenicity study with erythritol in rats. *Regulatory Toxicology and Pharmacology* 24, S232-S236.
- Sokolowski, A., 2007. *Salmonella typhimurium* reverse mutation assay with decenal-4-trans. RCC Cytotest Cell Research, Rossdorf, Germany. Unpublished report provided to the FEMA Expert Panel.
- Sokolowski, A., 2014. Ethylhomovanillate: *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay. RCC Cytotest Cell Research, Rossdorf, Germany. Unpublished report provided to the FEMA Expert Panel.
- Sokolowski, A., 2015. *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay. Harlan/Cytotest Cell Research GmbH (harlan CCR), Rossdorf, Germany. Unpublished report provided to the FEMA Expert Panel.

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

- Soltesova, A., 2015. Bacterial reverse mutation test. Huntingdon Research Centre, Cambridgeshire, UK. Unpublished report provided to the FEMA Expert Panel.
- Sreenath, K., Venkatesh, Y.P., 2008. Analysis of erythritol in foods by polyclonal antibody-based indirect competitive ELISA. *Analytical and Bioanalytical Chemistry* 391, 609-615.
- Stanworth, D.R., 1977. Preliminary Assessment of the Potential Allergenicity of the Sweet Protein, Talin. University of Birmingham, England. Unpublished report provided to the FEMA Expert Panel.
- Stone, V., 2011. Induction of micronuclei in cultured human peripheral blood lymphocytes. Nootkatone. Covance Laboratories Ltd., North Yorkshire, England. Unpublished report provided to the FEMA Expert Panel by the International Organization of the Flavor Industry.
- Strand, L.P., Scheline, R.R., 1975. The metabolism of vanillin and isovanillin in the rat. *Xenobiotica* 5, 49-63.
- Suttajit, M., Vinitketkaumnien, U., Meevatee, U., Buddhasukh, D., 1993. Mutagenicity and human chromosomal effect of stevioside, a sweetener from *Stevia rebaudiana* Bertoni. *Environmental Health Perspectives* 101 Supplement 3, 53-56.
- Swartz, C., 2016. Mutagenicity assessment of 3,4-dimethyl-2,3-dihydrothiophene-2-thiol in a bacterial reverse mutation assay. Integrated Laboratory Systems, Inc., Morrisville, NC, pp. 1-42. Unpublished report provided to the FEMA Expert Panel.
- Takahashi, M., Shibamoto, T., 2008. Chemical compositions and antioxidant/anti-inflammatory activities of steam distillate from freeze-dried onion (*Allium cepa* L.) sprout. *Journal of Agricultural and Food Chemistry* 56, 10462-10467.
- Takeshima, K., Yamatsu, A., Yamashita, Y., Watabe, K., Horie, N., Masuda, K., Kim, M., 2014. Subchronic toxicity evaluation of gamma-aminobutyric acid (GABA) in rats. *Food and Chemical Toxicology* 68, 128-134.
- Terai, T., Ren, H., Mori, G., Yamaguchi, Y., Hayashi, T., 2002. Mutagenicity of steviol and its oxidative derivatives in *Salmonella typhimurium* TM677. *Chemical and Pharmaceutical Bulletin (Tokyo)* 50, 1007-1010.
- Tesh, J.M., Davidson, E.J., Willoughby, C.R., 1977. Talin: test for dominant lethality in the male mouse. Life Science Research, Stock, England. Unpublished report provided to the FEMA Expert Panel.
- Teyssier, C., Siess, M.-H., 2000. Metabolism of dipropyl disulfide by rat liver phase I and phase II enzymes and by isolated perfused rat liver. *Drug Metabolism and Disposition* 28, 648-654.
- Thompson, P.W., 2013. *trans*-1-Ethyl-2-methylpropyl-2-butenolate: reverse mutation assay "Ames Test" using *Salmonella typhimurium* and *Escherichia coli*. Harlan Laboratories Ltd, Shardlow, Derbyshire, UK. Unpublished report provided to the FEMA Expert Panel.
- Tomi, A., Kawaguchi, R., 2014. Reverse Mutation Assay "Ames Test" Using *Salmonella typhimurium*. Test material 4-(1-Methoxy)-2-butanone. Unpublished report provided to the FEMA Expert Panel.
- Toyoda, K., Matsui, H., Shoda, T., Uneyama, C., Takada, K., Takahashi, M., 1997. Assessment of the carcinogenicity of stevioside in F344 rats. *Food and Chemical Toxicology* 35, 597-603.
- Uhde, H., 2004. Mutagenicity study of rubenamin in the *Salmonella typhimurium* reverse mutation assay (*in vitro*). Laboratory of Pharmacology and Toxicology KG, Hamburg, Germany. Unpublished report provided to the FEMA Expert Panel.
- Ukiya, M., Kikuchi, T., Tokuda, H., Tabata, K., Kimura, Y., Arai, T., Ezaki, Y., Oseto, O., Suzuki, T., Akihisa, T., 2010. Antitumor-promoting effects and cytotoxic activities of dammar resin triterpenoids and their derivatives. *Chemistry and Biodiversity* 7, 1871-1884.
- van Ommen, B., de Bie, B., Bär, A., 1996. Disposition of ¹⁴C erythritol in germfree and convention rats. *Regulatory Toxicology and Pharmacology* 24, S198-S205.
- Waalkens-Berendsen, D.H., Smits-van Prooije, A.E., Wijnands, M.V., Bar, A., 1996. Two-generation reproduction study of erythritol in rats. *Regulatory Toxicology and Pharmacology* 24, S237-246.
- Wagner, V.O., 2016. Bacterial reverse mutation assay. BioReliance Corporation, Rockville, MD. Unpublished report provided to the FEMA Expert Panel.
- Waring, R.H., 1996. Sulfur-Sulfur Compounds, Biological Interactions of Sulfur Compounds. Informa UK Limited, pp. 145-173.
- Watanabe, S., Morimoto, Y., 1989a. Mutagenicity study of acetyl lactic acid thiomethyl ester in *Salmonella typhimurium* and *Escherichia coli*. Unpublished report provided to the FEMA Expert Panel.
- Watanabe, S., Morimoto, Y., 1989b. Mutagenicity study of propionyl lactic acid thiomethyl ester in *Salmonella typhimurium* and *Escherichia coli*. Unpublished report provided to the FEMA Expert Panel.
- Webb, D.R., Ridder, G.M., Alden, C.L., 1989. Acute and subchronic nephrotoxicity of *d*-limonene in Fischer 344 rats. *Food and Chemical Toxicology* 27, 639-649.
- Wells, W.W., Yang, Y., Deits, T.T., Gan, Z., 1993. Thioltransferases. *Advances in Enzymology and Related Areas of Molecular Biology* 66, 149-201.
- Wheeler, A., Boileau, A.C., Winkler, P.C., Compton, J.C., Prakash, I., Jiang, X., Mandarino, D.A., 2008. Pharmacokinetics of rebaudioside A and stevioside after single oral doses in healthy men. *Food and Chemical Toxicology* 46 Suppl 7, S54-60.
- Williams, K.I.H., Burstein, S.H., Layne, D.S., 1966. Metabolism of dimethyl sulfide, dimethyl sulfoxide, and

Supplementary Information 2. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 28

dimethyl sulfone in the rabbit. Archives of Biochemistry and Biophysics 117, 84-87.

Williams, L.D., Burdock, G.A., 2009. Genotoxicity studies on a high-purity rebaudioside A preparation. Food and Chemical Toxicology 47, 1831-1836.

Wingard, R.E., Brown, J.P., Enderlin, F.E., Dale, J.A., Hale, R.L., Seitz, C.T., 1980. Intestinal degradation and absorption of the glycosidic sweeteners stevioside and rebaudioside A¹. Birkhauser Verlag 37, 519-520.

Wolfe, G.W., 1992. 91-Day subchronic oral toxicity study in rats with D1156.02. Hazelton Washington, Inc., Vienna, VA. Unpublished report provided to the FEMA Expert Panel.

Wong, K.P., Sourkes, T.L., 1966. Metabolism of vanillin and related substances in the rat. Canadian Journal of Biochemistry 44, 635-644.

Xie, X.L., Wei, M., Kakehashi, A., Yamano, S., Okabe, K., Tajiri, M., Wanibuchi, H., 2012. Dammar resin, a non-mutagen, induces [corrected] oxidative stress and metabolic enzymes in the liver of gpt delta transgenic mouse which is different from a mutagen, 2-amino-3-methylimidazo[4,5-f]quinoline. Mutation Research 748, 29-35.

Yamada, A., Ohgaki, S., Noda, T., Shimizu, M., 1985. Chronic toxicity study of dietary stevia extracts in F344 rats. Food Hygiene and Safety Science (Shokuhin Eiseigaku Zasshi) 26, 169-183.

Zhang, X., Xu, J., Zhang, D., Gu, J., Zhao, Y., 2009. Pharmacokinetics of 20(S)-25-methoxyl-dammarane-3 β , 12 β , 20-triol and its active metabolite after oral and intravenous administration in rat. Xenobiotica 39, 457-464.

Zhang, X., Zhang, J., Li, W., Liu, L., Sun, B., Guo, Z., Shi, C., Zhao, Y., 2014. *In vitro* metabolism of 20(R)-25-methoxyl-dammarane-3, 12, 20-triol from Panax notoginseng in human, monkey, dog, rat, and mouse liver microsomes. PLoS One 9, e94962.

Zhao, Y., 2015. ADME-tox study of subject compound. Eurofins Panlabs, Redmond, WA. Unpublished report provided to the FEMA Expert Panel.