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

FEMA No.[1]	FEMA Primary Name	The Identification Description as Reviewed by the FEMA Expert Panel
4895	Rebaudioside M	Rebaudioside M ≥80%; Rebaudioside D 5-20%; Total steviol glycosides ≥95%.
4907	*Corynebacterium glutamicum* corn syrup fermentation product	Glutamic acid 35-40%; Other amino acids 1-2%; Total nitrogen 6-7%; Aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups 1-2%; Minerals 9-11%
4908	*Corynebacterium stationis* corn syrup fermentation product	Inosine 5´-monophosphate 20-25%; Amino acids 7-8%; Minerals 23-25%; water 28-37%; Other nucleotides 1-2%; Total nitrogen 5-8%
4909	Glucosylated steviol glycosides, 70-80%	Supraglucosylated steviol glycosides 70-80%; Rebaudioside A 14-20%; Steviol glycosides not further glucosylated, each individually, not to exceed 3%; Maltodextrin 3-10%
4910	Glucosylated steviol glycosides, 40%	Supraglucosylated steviol glycosides 30-40%; Rebaudioside A 5-8%; Not more than 4% stevioside; All other individual steviol glycosides not further glucosylated <3%; Maltodextrin 45-60%
4911	Stevia extract stevioside, 70%	Stevioside 70-80%; Rebaudioside A 13-18%; Steviobioside 1-3%; Rebaudioside C 2-3%; Total glycosides (including Rebaudioside D, Rebaudioside B, Rebaudioside F, Dulcoside A, and Rubusoside) <3%
4912	Hibiscus blossom extract	Derived from hibiscus blossom calyces (*Hibiscus sabdariffa* L.) , Hibiscus blossom extract is measured as water 30-60%; ethanol 0-11%; ash content 5-10%; hibiscus acid 12-18%; hydroxycitric acid 2-7%; fructose and glucose 3-5%; phenols 1-3.5%; anthocyanins 0.3-0.6%; volatiles <0.1%
4919	Refined soybean oil extract	Derived from refined soybean oil, refined soybean oil extract is measured as *beta*-Sitosterol 43-45%; Stigmatasterol 27-30%; Campesterol 25-27%; Brassicasterol, trace amounts; Not to exceed Good Manufacturing Practices levels of 50 ppb 3-monochloropropylene (3-MCP) and glycidyl esters
4921	Rebaudioside D 95%	Rebaudioside D ≥95%; Total other steviol glycosides <3.5%
4922	Rebaudioside M 95%	Rebaudioside M ≥95%; Rebaudioside B <2%; Rebaudioside A <1.5%; Total other steviol glycosides <1.5%
4931	Glucosylated steviol glycosides, 90%	Not less than 90% of total steviol glycosides inclusive of supraglucosylated steviol glycosides; Rebaudioside A less than 3%; Stevioside less than 2%; other steviol glycosides not further glucosylated, each individually, less than 2%; Maltodextrin less than 10%
4932	*Chaenomeles speciosa* leaf extract	Derived from the leaves of *Chaenomeles speciosa, Chaenomeles speciosa* leaf extract is measured as not less than 2% polyphenols and ≥95% non-volatile components, including carbohydrate, fat, protein and water

[1] The identity descriptions for FEMA 4923-4925 are included in Cohen et al. (2020).

4933	*Eriobotrya japonica* leaves extract	Derived from the leaves of *Eriobotrya japonica, Eriobotrya japonica* leaves extract is measured as not less than 2% citric acid; Not less than 2.5% triterpene acids; Not less than 93% non-volatile components including carbohydrates, fat, protein, water.
4936	Rebaudioside E ≥85%	Rebaudioside E 85-92%; Rebaudioside D 5-10%; Steviobioside and stevioside, each individually, less than 1%
4937	Rebaudioside I 95%	Not less than 95% Rebaudioside I; Rebaudioside B less than 1%
4940	*beta*-Bisabolene ≥88%	Not less than 88% *beta*-bisabolene with no less than 7% aliphatic and aromatic hydrocarbons, typically identified as *beta*-sesquiphellandrene and *gamma*-bisabolene.
4941	Nootkatone complex	Not less than 60% nootkatone; total mono-, di- and trioxygenated sesquiterpenes up to 95%.
4942	Modified guaiac wood extract	Derived from guaiac wood oil (*Guaiacum* spp.), Modified guaiac wood extract includes not less than 1.25% (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; sesquiterpenes 9-25%; monooxygenated norsesquiterpenes and sesquiterpenes 25-40%; di- and trioxygenated sesquiterpenes 6-15%; triethyl citrate 35-50%.

Supplementary Information. Key Findings of the FEMA Expert Panel Safety Evaluations for GRAS 29

Since its initial publication of GRAS determinations for flavor ingredients (Hall and Oser, 1965), the FEMA Expert Panel has made available information on its determinations, including conditions of intended use for individual flavor ingredients, and the scientific basis and information supporting these determinations. Included herein are the key findings for each of the new GRAS determinations included within GRAS 29. 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 1-(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone (CAS 21145-77-7) and concluded that the substance is GRAS (FEMA 4879) (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 substance was evaluated individually within the context of the chemical group of aromatic substituted secondary alcohols, ketones, and related esters (Adams et al., 2007; JECFA, 2001, 2011, 2017; SLR, C14). The Panel calculated the anticipated *per capita* intake ("eaters only") of 1-(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone from use as a flavor ingredient to be 14 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. It is presumed that 1-(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone will undergo oxidation at multiple positions and the polar metabolites are excreted in the feces and urine (Api et al., 2013; Girkin, 1998; Smith et al., 2018; Yang et al., 2015). No increases in the number of chromosome aberrations in an *in vitro* chromosomal aberration assay in CHO cells without S9 metabolic activation were noted. Statistically significant increases in numerical chromosomal aberrations were observed for this substance in the presence of S9 metabolic activation under conditions of four hours of exposure with a 44-hour recovery period as well as four hours of exposure with a 20-hour recovery period. However, because these data were within historical control ranges and gave no evidence of a dose response, the study authors concluded that 1-(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone is negative for structural and numerical chromosomal aberrations *in vitro* (Api and San, 1999; Curry, 1995). In an *in vivo* micronucleus induction assay, no increases in the occurrence of micro-nucleated polychromatic erythrocytes were observed relative to vehicle controls in male and female ICR mice intraperitoneally injected with 1-(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone (Api and San, 1999; Gudi and Ritter, 1997). 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 1-(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone. A 13-week toxicity study of 1-(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone in Crl:CD(SD)BR (VAF plus) rats resulted in a no observed adverse effect level (NOAEL) of greater than 15 mg/kg bw/day (Api et al., 2004) which is greater than 62,500 times the anticipated daily *per capita* intake of 1-(3,5,5,6,8,8-hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2-(4-ethylphenoxy)-*N*-(l*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide (CAS 2015168-50-8) and concluded that the substance is GRAS (FEMA 4880) (Smith et al., 2005) 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 individually within the context of the chemical group of miscellaneous nitrogen-containing substances (JECFA, 2006, 2009, 2012, 2015; SLR, D19). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2-(4-ethylphenoxy)-*N*-(l*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide for use as a flavor ingredient to be 290 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 that were included within the application and found them satisfactory with regards to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Based on the structural relative, 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide (FEMA 4809), it is presumed that 2-(4-ethylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide will be rapidly hydrolyzed to yield the secondary amine product and 4-ethylphenoxyacetic acid (Smith et al., 2018). In addition to hydrolysis, oxidation at several sites on the substance is likely, and the more polar metabolites are expected to be excreted in the urine or feces either without further reaction or after conjugation (Karanewsky et al., 2015). No increases in the number of reverse mutations were observed in the Ames assay for the structurally related substance, 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide, in *Salmonella typhimurium* (*S. typhimurium*) strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* (*E. coli*) WP2*uvr*A in either the absence or presence of S9 metabolic activation (Karanewsky et al., 2015). For the same structural relative, no genotoxic potential was observed in an *in vitro* chromosomal aberration assay in the presence of S9 metabolic activation. In the absence of S9 metabolic activation positive results were observed. However, in a combined *in vivo* micronucleus/comet assay no increases in polychromatic erythrocytes or DNA damage were observed (Karanewsky et al., 2015). Based on these results, as well as the structure of the substance and the arrangement and identity of the functional groups therein, the Panel did not identify specific concerns related to the genotoxicity of 2-(4-ethylphenoxy)-*N*-(l*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide. A 28-day dietary study for structurally related substance, 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide (FEMA 4809), in male and female rats resulted in a NOAEL of greater than 100 mg/kg

bw/day. A 90-day dietary study for structurally related substance, 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide in male and female rats resulted in a NOAEL of greater than 100 mg/kg bw/day (Karanewsky et al., 2015). This is greater than 20,000 times the anticipated daily *per capita* intake of 2-(4-ethylphenoxy)-*N*-(l*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *N*-(3-hydroxy-4-methoxyphenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide (CAS 1857331-84-0) (Smith et al., 2005a) and concluded that the substance is GRAS (FEMA 4881) 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 (JECFA, 2006, 2008, 2011, 2012, 2017; SLR, A7, C21) . The Panel calculated the anticipated *per capita* intake ("eaters only") of *N*-(3-hydroxy-4-methoxyphenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide from use as a flavor ingredient to be 15 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. Hydrolysis of the amide bond of *N*-(3-hydroxy-4-methoxyphenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide was not detected *in vitro* experiments in simulated gastric juice and only a very low rate was detected in an intestinal matrix (Cheung, 2016a). Amide hydrolysis was also not detected in an *in vitro* study in cryopreserved human hepatocytes (Cheung, 2016b). Based on these results, it is anticipated that *N*-(3-hydroxy-4-methoxyphenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide will undergo metabolism primarily by hydroxylation of the alkyl substituents and ring positions to yield hydroxylated metabolites that are likely excreted as glucuronic acid or sulfate conjugates that are eliminated in the urine. Some *O*-dealkylation to form a catechol species that may be conjugated with glucuronic acid or sulfate, followed by excretion primarily in the urine, could also occur (Smith et al., 2018). No increases in the number of reverse mutations were observed in the Ames assay for *N*-(3-Hydroxy-4-methoxyphenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* stain WP2 uvrA in either the absence or presence of S9 metabolic activation (Hashimoto, 2015). In an *in vivo* mouse micronucleus assay, oral administration of the structurally related substance, *N*-*p*-benzeneacetonitrilementhane carboxamide (4496), did not increase the frequency of micronucleated polychromatic erythrocytes (Pritchard, 2006). Based on these results, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify specific concerns for the genotoxic potential of *N*-(3-hydroxy-4-methoxyphenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide. A 90-day male and female rat study for the structurally related substance *N*-*p*-benzeneacetonitrilementhanecarboxamide (FEMA 4496) provided in the diet resulted in a NOAEL of 100 mg/kg bw/day (Eapen, 2007). This is 400,000 times the anticipated daily *per capita* intake of *N*-(3-hydroxy-4-methoxyphenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *N*-(4-(cyanomethyl)phenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide (CAS 1857331-83-9) (Smith et al., 2005a) and concluded that the substance is GRAS (FEMA 4882) 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 (JECFA, 2006, 2008, 2011, 2012; SLR, A7, C21). The Panel calculated the anticipated *per capita* intake ("eaters only") of *N*-(4-(cyanomethyl)phenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide from use as a flavor ingredient to be 15 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. Based on the lack of amide hydrolysis observed for the structurally related substance, *N*-(3-hydroxy-4-methoxyphenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide (FEMA 4881) in simulated gastric and intestinal matrices (Cheung, 2016a) and cryopreserved human hepatocytes (Cheung, 2016b), very little to no hydrolysis would be predicted for *N*-(4-(cyanomethyl)phenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide. It is predicted that *N*-(4-(cyanomethyl)phenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide will undergo metabolism primarily by hydroxylation of the alkyl substituents and ring positions to yield hydroxylated metabolites that are likely excreted as glucuronic acid or sulfate conjugates that are eliminated in the urine (Smith et al., 2018). No increases in the number of reverse mutations were observed in the Ames assay for of structurally related substance, *N*-(3-hydroxy-4-methoxyphenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide (FEMA 4881), in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2 *uvr*A in either the absence or presence of S9 metabolic activation (Hashimoto, 2015). In an *in vivo* mouse micronucleus assay, oral administration of the structurally related substance, *N*-*p*-benzeneacetonitrilementhanecarboxamide (FEMA 4496), did not increase the frequency of micronucleated polychromatic erythrocytes (Pritchard, 2006). Based on these results, as well as the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify specific concerns for the genotoxic potential of *N*-(4-(cyanomethyl)phenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide. A 90-day male and female rat study for the structurally related substance, *N*-*p*-benzeneacetonitrilementhanecarboxamide (FEMA 4496), provided in the diet resulted in a NOAEL of 100 mg/kg bw/day (Eapen, 2007). This is 400,000 times the anticipated daily *per capita* intake of *N*-(4-(cyanomethyl)phenyl)-2-isopropyl-5,5-dimethylcyclohexanecarboxamide from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *S*-allyl-*L*-cysteine sulfoxide (CAS 556-27-4) and concluded that the substance is GRAS (FEMA 4883) (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 substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic sulfides and thiols (JECFA, 2000, 2004, 2008, 2011; SLR, B5B). The Panel calculated the

anticipated *per capita* intake ("eaters only") of *S*-allyl-*L*-cysteine sulfoxide from use as a flavor ingredient to be 710 µg/person/day, which is above the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). This substance is known to naturally occur in fresh garlic cloves (Ziegler and Sticher, 1988). However, because only qualitative data was available, a consumption ratio could not 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. It is presumed that *S*-allyl-*L*-cysteine sulfoxide will undergo *N*-acetylation followed by excretion in the urine (Amano et al., 2015; Kodera et al., 2002; Smith et al., 2018). 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 *S*-allyl-*L*-cysteine sulfoxide. A 28-day dietary study for structurally related substance, *S*-allyl-*L*-cysteine (FEMA 4322), in male and female Wistar rats resulted in a NOAEL of 500 mg/kg bw/day (Kodera et al., 2002), which is greater than 42,000 times the anticipated daily *per capita* intake of *S*-allyl-*L*-cysteine sulfoxide from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 6-methyl-5-hepten-2-ol (CAS 1569-60-9) (Smith et al., 2005a) and concluded that the substance is GRAS (FEMA 4884) 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 (JECFA, 1999, 2003, 2017; SLR, A1). The Panel calculated the anticipated *per capita* intake ("eaters only") of 6-methyl-5-hepten-2-ol 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 annatto, citrus, macadamia nuts, and tomatoes (Njissen, 2019). 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 predicted that 6-methyl-5-hepten-2-ol will be metabolized primarily by conjugation with glucuronic acid followed by excretion in the urine (Kamil et al., 1953; Smith et al., 2018). No increases in the number of reverse mutations were observed in the Ames assay for structurally related substance, 6-methyl-5-hepten-2-one (FEMA 2707), in *S. typhimurium* strains TA98, TA100, TA1535 or TA1537 in either the absence or presence of S9 metabolic activation. No increase in micronucleated binucleated human peripheral blood lymphocyte cells were observed with concentrations of 6-methyl-5-hepten-2-ol up to 850 µg/mL in the presence or absence of S9 metabolic activation (Roy, 2015). Based on these results, the Panel did not identify any specific concerns related to the genotoxicity of 6-methyl-5-hepten-2-ol. A 90-day oral toxicity study in male and female rat study for the structurally related substance, 6-methyl-5-hepten-2-one (FEMA 2707), resulted in a NOAEL of 50 mg/kg bw/day for both sexes (Kaspers, 2002). This is greater than 10,000 times the anticipated daily *per capita* intake of 6-methyl-5-hepten-2-ol from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *trans*-5-dodecenal (CAS 68820-34-8) and concluded that the substance is GRAS (FEMA 4885) (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 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 (JECFA, 1999, 2012; SLR, M1). The Panel calculated the anticipated *per capita* intake ("eaters only") of *trans*-5-dodecenal 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). This substance occurs naturally in cardamom (1000 ppm) (Njissen, 2019). However, due to limited quantitative data, a consumption ratio could not 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. It is presumed that *trans*-5-dodecenal will oxidize to the corresponding unsaturated carboxylic acid. Because the double bond is at an odd-numbered carbon, the resulting *delta*-3-enoyl-CoA from acetyl-CoA fragmentation must be isomerized by enoyl CoA isomerase to the *trans-delta*-2-enoyl CoA before it can re-enter the fatty acid cycle for complete metabolism to CO_2 and water (Feldman and Weiner, 1972; Eckfeldt and Yonetani, 1982; Nakayasu et al., 1978; Beedham, 1988; Nelson and Cox, 2008). A negative Ames assay was reported for the structurally related substance, 10-undecenal (FEMA 3095), in *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 in the presence and absence of S9 metabolic activation (Bhatia et al., 2010; Sokolowski, 2007a). Negative results for 10-undecenal were also reported in an *in vivo* micronucleus test in male and female NMRI mice (Bhatia et al., 2010; Honarvar, 2007). Similar negative results were reported in the Ames assay using the same *S. typhimurium strains* and *in vivo* mouse micronucleus tests using male and female NMRI mice for another structural relative, *trans*-4-decen-1-al (FEMA 3264) (Bhatia et al., 2010; Sokolowski, 2007b; Honarvar, 2008). 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 *trans*-5-dodecenal. A 90-day dietary study for structurally related substance, 10-undecenal (FEMA 3095), in male and female Sprague-Dawley Crl:CD® (SD) IGS BR rats resulted in a NOAEL of 200 ppm, or approximately 14.3 mg/kg bw/day, (Liwska and Watson, 2012) which is greater than 2,000,000 times the anticipated daily *per capita* intake of *trans*-5-dodecenal from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *cis*-6-dodecenal (CAS 126745-61-7) and concluded that the substance is GRAS (FEMA 4886) (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 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 (JECFA, 1999, 2012; SLR, M1). The Panel calculated the anticipated *per capita* intake ("eaters only") of *cis*-6-dodecenal 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 *cis*-6-dodecenal will be oxidized to the corresponding unsaturated carboxylic acid. The *cis* double bond is isomerized to the *trans* double bond by 3-hydroxyacyl-CoA epimerase before re-

entering the fatty acid cycle where it is converted to acetyl-CoA. The acetyl-CoA product then enters the citric acid cycle where it is metabolized to yield CO_2 and water (Feldman and Weiner, 1972; Eckfeldt and Yonetani, 1982; Nakayasu et al., 1978; Beedham, 1988; Nelson and Cox, 2008). A negative Ames assay was reported for the structurally related substance, 10-undecenal (FEMA 3095), using *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 in the presence and absence of S9 metabolic activation (Bhatia et al., 2010; Sokolowski, 2007a). Negative results for 10-undecenal (FEMA 3095) were also reported in an *in vivo* micronucleus test in male and female NMRI mice (Bhatia et al., 2010; Honarvar, 2007). Similar negative results were reported in the Ames assay using the same *S. typhimurium strains* and *in vivo* mouse micronucleus tests using male and female NMRI mice for another structural relative, *trans*-4-decen-1-al (FEMA 3264) (Bhatia et al., 2010; Sokolowski, 2007b; Honarvar, 2008). 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 *cis*-6-dodecenal. A 90-day dietary study for structurally related substance, 10-undecenal (FEMA 3095), in male and female Sprague-Dawley Crl:CD® (SD) IGS BR rats resulted in a NOAEL of 200 ppm, or approximately 14.3 mg/kg bw/day (Liwska and Watson, 2012), which is greater than 2,000,000 times the anticipated daily *per capita* intake of *cis*-6-dodecenal from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *cis*-9-dodecenal (CAS 56219-03-5) and concluded that the substance is GRAS (FEMA 4887) (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 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 (JECFA, 1999, 2012; SLR, M1). The Panel calculated the anticipated *per capita* intake ("eaters only") of *cis*-9-dodecenal 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 *cis*-9-dodecenal will be oxidized to yield an unsaturated carboxylic acid. Since the double bond is at an odd-numbered carbon, the resulting *delta*-3-enoyl-CoA from acetyl-CoA fragmentation must be isomerized by enoyl-CoA isomerase to *trans-delta*-2-enoyl-CoA before it can re-enter the fatty acid cycle for complete metabolism to CO_2 and water (Feldman and Weiner, 1972; Eckfeldt and Yonetani, 1982; Nakayasu et al., 1978; Beedham, 1988; Nelson and Cox, 2008). A negative Ames assay was reported for the structurally related substance, 10-undecenal (FEMA 3095), using *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 in the presence and absence of S9 metabolic activation (Bhatia et al., 2010; Sokolowski, 2007a). Negative results for 10-undecenal (FEMA 3095) were also reported in an *in vivo* micronucleus test in male and female NMRI mice (Bhatia et al., 2010; Honarvar, 2007). Similar negative results were reported in the Ames assay using the same *S. typhimurium strains* and *in vivo* mouse micronucleus tests using male and female NMRI mice for another structural relative, *trans*-4-decen-1-al (FEMA 3264) (Bhatia et al., 2010; Sokolowski, 2007b; Honarvar, 2008). 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 *cis*-9-dodecenal. A 90-day dietary study for structurally related substance, 10-undecenal (FEMA 3095), in male and female Sprague-Dawley Crl:CD® (SD) IGS BR rats resulted in a NOAEL of 200 ppm, or approximately 14.3 mg/kg bw/day (Liwska and Watson, 2012), which is greater than 2,000,000 times the anticipated daily *per capita* intake of *cis*-9-dodecenal from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding mixture of 5-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-7-methylchroman-2-one and 7-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-5-methylchroman-2-one (CAS 1945993-01-0 and 828265-08-3) and concluded that the substance is GRAS (FEMA 4888) (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 substance was evaluated individually within the context of the chemical group of phenol and phenol derivatives (JECFA, 2001, 2011, 2012; SLR, C12). The Panel calculated the anticipated *per capita* intake ("eaters only") of from use as a flavor ingredient to be 6 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). It is presumed that the will undergo facile enzyme-catalyzed lactone ring-opening, likely followed by excretion or conjugation followed by excretion. Additional metabolic outcomes include hydroxylation, reduction, and conjugation with sulfate or glucuronic acid (Horrigan, 2016). The mixture of 5-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-7-methylchroman-2-one and 7-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-5-methylchroman-2-one was negative for genotoxicity in an Ames assay with *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as *E. coli* strain WP2 *uvr*A (pKM101) in the presence or absence of S9 metabolic activation (Wisher, 2016). In an *in vitro* micronucleus assay in CHO-K1 cells, the mixture did not induce increases in micronucleated cells in the presence or absence of S9 metabolic activation (Diaz et al., 2007; Zhao, 2016). One of the constituents of the mixture, (*R*)-5-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-7-methylchroman-2-one (FEMA 4834), yielded negative results in an Ames assay conducted in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2 *uvr*A (pKM101) in the presence and absence of S9 metabolic activation (Soltesova, 2015). This single component of the mixture also did not induce increases in micronucleated cells in an *in vitro* micronucleus assay conducted in CHO-K1 cells in the presence or absence of S9 metabolic activation (Zhao, 2016).

The Panel reviewed the GRAS application and supporting information regarding methyl propyl sulfide (CAS 3877-15-4) and concluded that the substance is GRAS (FEMA 4889) (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 substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic sulfides and thiols (SLR B4, JECFA 2000, 2004, 2008, 2011). The Panel calculated the

anticipated *per capita* intake ("eaters only") of m from use as a flavor ingredient to be 0.03 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). This substance occurs naturally in beef, chive, durian, Guinea hen, kohlrabi, onion, and cured pork (Njissen, 2019). Due to limited quantitative data, a consumption ratio could not 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. It is presumed that methyl propyl sulfide will undergo S-oxidation to the sulfoxide, and to a lesser extent the sulfone, for excretion in urine (Damani, 1987). 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 methyl propyl sulfide.. A 14-week dietary study for structurally related substance, dimethyl sulfide (FEMA 2746), in male and female Wistar rats resulted in a NOAEL of 250 mg/kg bw/day (Butterworth et al., 1975) which is 500,000,000 times the anticipated daily *per capita* intake of methyl propyl sulfide from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 3-*p*-menthen-7-al (CAS 27841-22-1) and concluded that the substance is GRAS (FEMA 4890) (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 substance was evaluated individually within the context of the chemical group of alicyclic primary alcohols, aldehydes, acids, and related esters (Cohen et al., 2016; JECFA, 2006, 2009, 2015; SLR, A5) . The Panel calculated the anticipated *per capita* intake ("eaters only") of 3-*p*-menthen-7-al from use as a flavor ingredient to be 0.001 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). This material naturally occurs in cumin seeds (Njissen, 2019). 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 3-*p*-menthen-7-al will be oxidized to yield the corresponding carboxylic acid and be excreted in urine unchanged or as a glycine conjugate (Ishida et al., 1989). Mutagenesis was not observed in the Ames assay for this substance conducted in *S. typhimurium* strains TA98 and TA100 in the presence or absence of S9 metabolic activation (Komai, 2016a). The structural relative perillaldehyde (FEMA 3557) induced reverse mutations in an Ames assay in the absence of S9 metabolic activation in *S. typhimurium* strain TA98 but was negative in this strain in the presence of S9 metabolic activation. This structural relative yielded negative results in *S. typhimurium* strains TA100, TA102, TA1535, and TA1537 in the presence and absence of S9 metabolic activation. In an *in vitro* micronucleus assay in human lymphocytes, perillaldehyde (FEMA 3557) did not increase the frequency of micronucleated binuclear cells in the presence and absence of S9 metabolic activation. Perillaldehyde (FEMA 3557) was negative in an hypoxanthine-guanine phosphoribosyltransferase (HPRT) assay in mouse lymphoma cells in the presence and absence S9 metabolic activation. Perillaldehyde (FEMA 3557) did not increase micronucleated cells in the bone marrow of Han Wistar rats and was negative in the comet assay in the duodenum in a comet/micronucleus combined assay. In the same assay for this substance, increased comet tail intensity was observed in the liver at a hepatotoxic dose but these values were within the laboratory's historical control ranges (Hobbs et al., 2016). 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 3-*p*-menthen-7-al (Cohen et al., 2016). A 90-day dietary study of structural relative perillyl alcohol (FEMA 2664) conducted in male and female Fischer 344 rats resulted in a NOAEL of the highest tested dose of 400 mg/kg bw/day (NCI, 1996) which is 20,000,000,000 times the anticipated *per capita* daily intake of 3-*p*-menthen-7-al from use as a flavor ingredient. In a 90-day oral gavage toxicity study in male and female beagle dogs, a NOAEL of 120 mg/kg bw/day was determined for perillyl alcohol (FEMA 2664) (NCI, 1996). This NOAEL is 6,000,000,000 times the anticipated *per capita* daily intake of 3-*p*-menthen-7-al from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding (*E*)-3-methyl-4-dodecenoic acid (CAS 2088117-65-9) and concluded that the substance is GRAS (FEMA 4891) (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 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 (JECFA, 2000, 2007, 2012, 2014; SLR, M1). The Panel calculated the anticipated *per capita* intake ("eaters only") of (*E*)-3-methyl-4-dodecenoic acid from use as a flavor ingredient to be 0.01 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The 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 (*E*)-3-methyl-4-dodecenoic acid will undergo *beta*-oxidative cleavage and complete metabolism to CO_2 via the fatty acid pathway and the citric acid cycle (Williams, 1959; Nelson and Cox, 2008). No increases in the frequency of revertant colonies were observed in the Ames assay for this substance in *S. typhimurium* strains TA98 and TA100 in the presence and absence of S9 metabolic activation (Komai, 2016b). Structural relative, oleic acid (FEMA 2815) did not increase the frequency of revertant colonies in an Ames assay conducted in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as in *E. coli* strain WP2uvrA in the presence and absence of S9 metabolic activation (Shimizu et al., 1985). 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 (*E*)-3-methyl-4-dodecenoic acid. In a 180-day study in male and female Sprague-Dawley rats, oral administration of the structural relative 10-undecenoic acid (FEMA 3247) resulted in a NOAEL at the highest dose of 400 mg/kg bw/day (Tislow et al., 1950). This NOAEL is 2,000,000,000 times the anticipated daily *per capita* intake of (*E*)-3-methyl-4-dodecenoic acid from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *cis*-2-hexylcyclopropaneacetic acid (CAS 4707-61-3) and concluded that the substance is GRAS (FEMA 4892) (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 substance was evaluated individually within the context of the chemical group of aliphatic primary alcohols, aldehydes, esters, and acids (JECFA, 2000, 2007, 2012, 2014; SLR, M1).

The Panel calculated the anticipated *per capita* intake ("eaters only") of *cis*-2-hexylcyclopropaneacetic acid 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). This substance is reported to occurs naturally in *Croton eleuteria*, a medicinal shrub, as well as the essential oil derived from it, cascarilla oil (Lawrence, 1977). However, these are not commonly consumed as food. The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that *cis*-2-hexylcyclopropaneacetic acid will undergo conjugation to create glycine and glucuronide conjugates. This substance could also undergo beta-oxidation to produce cyclopropane carboxylic acid which would lead to the corresponding glycine and glucuronide conjugates. These conjugates can be excreted in urine (Smith et al., 2018). No increases in the frequency of revertant colonies were observed in an Ames assay for this substance conducted in *S. typhimurium* strains TA98 and TA100 in the presence and absence of S9 metabolic activation (Komai, 2016c). In an Ames assay for structural relative oleic acid (FEMA 2815) in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as *E. coli* strain WP2*uvr*A, no increase in the frequency of revertant colonies were observed in the presence and absence of S9 metabolic activation (Shimizu, 1985). 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 *cis*-2-hexylcyclopropaneacetic acid. In a 180-day study in male and female Sprague-Dawley rats, oral administration of the structural relative 10-undecenoic acid (FEMA 3247) resulted in a NOAEL of 400 mg/kg bw/day, which was the highest dose tested (Tislow et al., 1950). This NOAEL is 2,000,000,000 times the anticipated daily *per capita* intake of *cis*-2-hexylcyclopropaneacetic acid from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2-ethoxy-4-(hydroxymethyl)phenol (CAS 4912-58-7) and concluded that the substance is GRAS (FEMA 4893) (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 substance was evaluated individually within the context of the chemical group of hydroxy- and alkoxy-substituted benzyl derivatives (JECFA, 2001, 2006, 2009; SLR, C9). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2-ethoxy-4-(hydroxymethyl)phenol from use as a flavor ingredient to be 21 μg/person/day, which is below the threshold of toxicological concern for structural class I (1800 μg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is presumed that 2-ethoxy-4-(hydroxymethyl)phenol will form glucuronic acid or sulfate conjugates. This substance is also presumed to undergo oxidation to ethyl vanillic acid, forming sulfate or glucuronic acid conjugates that are expelled in urine (Dirscherl and Wirtzfeld, 1964; Sammons and Williams, 1941; Strand and Scheline, 1975; Wong and Sourkes, 1966). Negative results were observed in the Ames assays for the structurally related substance, vanillin (FEMA 3107), in *S. typhimurium* strains TA92, TA94, TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, TA1538, and TA2637 using the plate incorporation and pre-incubation methodologies (De Flora et al., 1994; Florin et al., 1980a; Ishidate et al., 1984; Jones, 1986; Kasamaki et al., 1982; Lawlor, 1991; Marzin, 1979a; Mortelmans et al., 1986; Nagabhushan and Bhide, 1985; Pool and Lin, 1982; Rapson et al., 1980). For the same structural relative, mixed positive and negative results were observed in in vitro sister chromatid exchange, chromosomal aberration and micronucleus induction assays conducted in Chinese hamster cells, human lymphocytes, and human cell lines (Jansson et al., 1986, 1987; Sanyal et al., 1997, Sasaki et al., 1987). Vanillin (FEMA 3107) was negative in an unscheduled DNA synthesis assay in rat hepatocytes (Heck et al., 1989) and was negative in bone marrow micronucleus assays in female OF1 mice, male BDF1 mice, and in male MS/Ae mice (Inouye et al., 1988; Marzin, 1979b; Sutou et al., 1999). 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-ethoxy-4-(hydroxymethyl)phenol. Administration of vanillin (FEMA 3107) to pregnant mice by oral gavage from gestation day 10 until postnatal day 30 showed no adverse effects. NOAEL values of at least 1500 mg/kg bw/day for maternal toxicity and teratogenicity were reported (OECD SIDS, 2002). No reproductive or developmental effects were reported for Crl CD rats administered vanillin (FEMA 3107) at concentrations up to 500 mg/kg bw/day by gavage from 7 days prior to cohabitation, gestation, delivery and 4 days post-parturition (Vollmuth et al., 1990). No significant differences in weekly measurements of body weight changes, food intake and general conditions, as well as, hematology parameters were observed between groups of male Osborne-Mendel rats orally administered the vehicle control, 1000 or 2500 mg/kg bw/day of the structural relative vanillin (FEMA 3107) for one year (Hagan et al., 1967). In a 13-week study in Sprague Dawley rats, oral administration of vanillin (FEMA 3107) resulted in a NOAEL at the highest tested dose level, 400 mg/kg bw/day (Mancebo et al., 2003). In a 13-week study in male and female CD Sprague Dawley rats, dietary administration of the structural relative ethyl vanillin (FEMA 2464) at doses of 500, 1000, and 2000 mg/kg bw/day resulted in a NOAEL of 500 mg/kg bw/day (Hooks et al., 1992) which is 1,428,000 times the daily *per capita* intake of 2-ethoxy-4-(hydroxymethyl)phenol when used as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2-mercapto-3-methyl-1-butanol (CAS 116229-37-9) and concluded that the substance is GRAS (FEMA 4894) (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 substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic sulfides and thiols (JECFA, 2000, 2004, 2008, 2011; SLR, B5B). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2-mercapto-3-methyl-1-butanol from use as a flavor ingredient to be 0.1 μg/person/day, which is below the threshold of toxicological concern for structural class I (1800 μg/person/day) (Munro et al., 1996). This substance occurs naturally in beer (Njissen et al., 2019). However, no consumption ratio could be calculated as no quantitative data was available. 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 thiol group of 2-mercapto-3-methyl-1-butanol undergoes oxidation and results in sulfenic, sulfinic, and sulfonic acids products to be eliminated in the urine. Alternatively, the thiol group could also undergo methylation. Additionally, any hydroxylated products can form

the corresponding carboxylic acid and/or be converted to sulfate or glucuronic acid conjugates and be eliminated in urine (McBain and Menn, 1969; Dutton and Illing, 1972; Maiorino et al., 1988; Richardson et al., 1991; Renwick, 1996). Negative results were observed in an Ames assay for this substance using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as *E.coli* strain WP2 *uvr*A (pKM101) in the presence and absence of S9 metabolic activation (Ogura, 2014). 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-mercapto-3-methyl-1-butanol. A 90-day dietary study for structurally related substance, 3-mercapto-2-butanol (FEMA 3502), in male and female Sprague Dawley Crl:CD® (SD) IGS BR rats resulted in a NOAEL of greater than 0.705 mg/kg bw/day (Cox et al., 1974b) which is 352,500 times the anticipated daily *per capita* intake of 2-mercapto-3-methyl-1-butanol from use as a flavor ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding rebaudioside M (CAS 1220616-44-3) and concluded that the material is GRAS (FEMA 4895) (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 FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015; Smith et al., 2005a). The Panel calculated the anticipated *per capita* intake ("eaters only") of rebaudioside M from use as a flavor ingredient to be 785 µg/person/day. Rebaudioside M is derived from the leaves of *Stevia rebaudiana* (Ohta et al., 2010). 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., 2003a; 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, 2000a, b; Pezzuto et al., 1985; Pezzuto et al., 1986; Rumelhard 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). The NOAEL for structurally related substance, rebaudioside A (FEMA 4601), is greater than 6,800 times the anticipated daily *per capita* intake of the rebaudioside M from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *N*-(2-hydroxy-2-phenylethyl)-2-isopropyl-5,5-dimethylcyclohexane-1-carboxamide (CAS 2186611-08-3) and concluded that the substance is GRAS (FEMA 4896) (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 (JECFA, 2006, 2008, 2011, 2012; SLR, A7, C21). The Panel calculated the anticipated *per capita* intake ("eaters only") of *N*-(2-hydroxy-2-phenylethyl)-2-isopropyl-5,5-dimethylcyclohexane-1-carboxamide from use as a flavor ingredient to be 71 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. It is presumed that *N*-(2-hydroxy-2-phenylethyl)-2-isopropyl-5,5-dimethylcyclohexane-1-carboxamide will undergo metabolism through conjugation of the hydroxyl moiety with glucuronic acid or sulfate followed by excretion in the urine. Additionally, hydroxylation of the alkyl substituents and ring positions would occur to yield hydroxylated metabolites likely to be excreted in the urine as glucuronic acid or sulfate conjugates (James, 1974). No increases in the number of reverse mutations were observed in the Ames assay for *N*-(2-hydroxy-2-phenylethyl)-2-isopropyl-5,5-dimethylcyclohexane-1-carboxamide in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* stain WP2*uvr*A in either the presence or absence of S9 metabolic activation (Hashimoto, 2016). In an *in vitro* micronucleus assay in Chinese hamster lung fibroma cells for *N*-(2-hydroxy-2-phenylethyl)-2-isopropyl-5,5-dimethylcyclohexane-1-carboxamide, there was a significant, concentration dependent increase in the frequency of micronucleated polychromatic erythrocytes in the presence of S9 metabolic activation (Furukuma, 2017). An *in vivo* mouse micronucleus assay of *N*-(2-hydroxy-2-phenylethyl)-2-isopropyl-5,5-dimethylcyclohexane-1-carboxamide showed no significant increases of micronucleated bone marrow cells in male Crl:CD1(ICR) mice (Aoyama, 2017). Based on he overall weight of evidence based on the lack of mutagenicity in the Ames assay and the negative in vivo micronucleus induction assay, the Panel did not identify specific concerns for the genotoxic potential of *N*-(2-hydroxy-2-phenylethyl)-2-isopropyl-5,5-dimethylcyclohexane-1-carboxamide. In a 90-day toxicity study in male and female Crl:CD(SD) rats, oral administration of the structurally related substance, *N*-(ethoxycarbonyl)methyl)-*p*-menthane-3-carboxamide (FEMA 4309), resulted in a NOAEL of 225 mg/kg bw/day (Kirkpatrick, 2011), which is 225,000 times the anticipated daily *per capita* intake of N-(2-hydroxy-2-phenylethyl)-2-isopropyl-5,5-dimethylcyclohexane-1-carboxamide from use as a flavor ingredient. A 28-day toxicity study of structurally related substance, *N*-ethyl-2-isopropyl-5-methylcyclohexane carboxamide (FEMA 3455), in male and female Crj: CD (SD) rats resulted in a NOAEL of 8 mg/kg bw/day (Miyata, 1995). This NOAEL is 8,000 times the anticipated daily *per capita* intake of *N*-(2-hydroxy-2-phenylethyl)-2-isopropyl-5,5-

dimethylcyclohexane-1-carboxamide from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding allulose (CAS 551-68-8) and concluded that the substance is GRAS (FEMA 4897) (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 FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). This substance was evaluated individually within the context of the chemical group of aliphatic poly-hydroxy compounds and derivatives (SLR, B1F). The Panel calculated the anticipated *per capita* intake ("eaters only") of allulose from use as a flavor ingredient to be 34,000 µg/person/day, which is above the threshold of toxicological concern for structural class 1 (1800 µg/person/day) (Munro et al., 1996). This substance occurs naturally in figs, raisins, tomato ketchup, brown sugar, and caramel sauce (Oshima et al., 2006). The consumption ratio was calculated to be 0.1 based on the available quantitative data. 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). Approcimately 98% of ^{14}C-allulose administered to rats was rapidly excreted within the first 6 hours (Whistler et al., 1974). The panel also considered a 14C radio label experiment in which eight humans were administered allulose which was then eliminated through urine. Similar rapid excretion was observed when human volunteers orally consumed allulose with the majority eliminated in the urine within 24 hours of consumption. No mutagenic potential was observed in the presence and absence of S9 metabolic activation in an Ames assay for this substance conducted in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as in *E. coli* strain WP2 *uvr*A (pKM101) at doses up to 5,000 µg/plate (Huntington Lab, 2011 as cited in GRN 400). A micronucleus study of this substance in CD1 mice yielded no significant increases in micronucleated polychromatic erythrocytes at concentrations up to 2,000 mg/kg/day relative to the control group (Huntington Lab, 2011). An *in vivo* chromosomal aberration assay of allulose (synonym D-psicose) yielded negative results at doses up to 1,800 µg/mL (Huntington Lab, 2011). 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 allulose. In a 90-day comparative dietary feeding study in which male Wistar rats were administered 3% allulose and 3% sucrose, or 1.67 g/kg bw/day of allulose and sucrose, histopathology assessments of major organs shown no significant toxicologic effects (Matsuo et al., 2011). A 12-18 month study of allulose and sucrose administered to male Wistar rats at the same doses found significantly higher mean value of pathological lesions in the liver for the allulose group than the sucrose group at the conclusion of the study (Yagi and Matsuo, 2009). The Panel determined the Lowest Observed Adverse Effect Level (LOAEL) to be 1.67 g/kg bw/day (Matsuo et al., 2011; Yagi and Matsuo, 2009), which is greater than 2,900 times the anticipated daily *per capita* intake of allulose from use as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding *trans*-5-octenal (CAS 41547-29-9) and concluded that the substance is GRAS (FEMA 4898) (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 substance was evaluated individually within the context of the chemical group of linear and branch-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids, and related esters (JECFA, 1999, 2012; SLR, M1). The Panel calculated the anticipated *per capita* intake ("eaters only") of *trans*-5-octenal from use as a flavor ingredient to be 7 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). This substance occurs naturally in trace amounts in lemon peels (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. It is presumed that *trans*-5-octenal will undergo oxidation to the corresponding unsaturated carboxylic acid. Because the double bond is at an odd-numbered carbon, the resulting *D*-3 enoyl-CoA from acetyl-CoA fragmentation must be isomerized by enoyl-CoA isomerase to the *trans-delta*-2 enoyl-CoA before it can re-enter the fatty acid cycle for complete metabolism to CO_2 and water (Smith et al., 2018). Negative results were observed in an Ames assay incubating *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 with the geometric isomer *cis*-5-octenal (FEMA 3749) in the presence and absence of S9 metabolic activation (Asquith, 1990a). In another Ames assay conducted in *S. typhimurium* strains TA98 and TA100 for the constitutional isomer *trans*-6-octenal (FEMA 4787), no mutagenicity was observed up to 50 µg/plate in the presence and absence of S9 (Kawaguchi and Komai, 2012). 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 *trans*-5-octenal. A 98-day toxicity study of structural relative *cis*-3-hexen-1-ol (FEMA 2563) administered to male and female SPF-derived CFE weanling rats via drinking water resulted in a No Observed Effect Level (NOEL) of 120 mg/kg bw/day (Gaunt et al., 1969). This is 1,000,000 times the anticipated daily *per capita* intake of *trans*-5-octenal from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)-2,6-dimethylisonicotinamide (CAS 1622458-34-7; 2079034-28-7) and concluded that the substance is GRAS (FEMA 4899) (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 substance was evaluated individually within the context of the chemical group of miscellaneous nitrogen compounds (JECFA, 2006, 2009, 2012, 2015, 2019; SLR, D19). The Panel calculated the anticipated *per capita* intake ("eaters only") of *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)-2,6-dimethylisonicotinamide from use as a flavor ingredient to be 285 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). It is presumed that *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)-2,6-dimethylisonicotinamide is minimally metabolized and, although poorly orally bioavailable, the small percentage of this substance that is metabolized undergoes hydroxylation. Additionally, *O*-dealkylation followed by carbonyl reduction is expected to occur to a minor extent. The parent compound and its metabolites are expected to be excreted in the feces (Shen, 2008, 2009). Negative results were observed for this substance in Ames assays conducted in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as in *E. coli* strain WP2 *uvr*A in the presence and absence of S9 metabolic activation (Bruce, 2017; Wagner, 2016). An *in vitro* micronucleus assay in human peripheral blood lymphocytes produced negative results for the genotoxicity of this substance both in the presence and absence of S9 (Roy, 2016). 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 *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)-2,6-dimethylisonicotinamide. A developmental toxicity study for this substance in female CD® [Crl:CD® (SD)] rats resulted in maternal and fetal NOAELs of the highest tested dose of 1,000 mg/kg bw/day (McElroy, 2017a, b). A 28-day toxicity study in male and female CD® [Crl:CD® (SD)] rats for *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)-2,6-dimethylisonicotinamide resulted in a NOAEL equivalent to the highest tested dose of 100 mg/kg bw/day (Daly, 2016). A 90-day toxicity study for *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)-2,6-dimethylisonicotinamide in male and female CD® [Crl:CD® (SD)] rats resulted in a NOAEL equivalent to the highest tested dose of 140 mg/kg bw/day (Daly, 2017), which is greater than 28,000 times the anticipated daily *per capita* intake of *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)-2,6-dimethylisonicotinamide from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding hexyl propyl disulfide (CAS 64580-54-7) and concluded that the substance is GRAS (FEMA 4900) (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 substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic sulfides and thiols (JECFA, 2000, 2004, 2008, 2011; SLR, B4). The Panel calculated the anticipated *per capita* intake ("eaters only") of hexyl propyl disulfide 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 hexyl propyl disulfide will be metabolized to its corresponding monothiols, hexyl sulfide and propyl sulfide, followed by enzymatic oxidation to produce sulfenic acids, sulfinic acids, and ultimately, sulfonic acids. The sulfinic and sulfonic acid products are easily excreted. The thiol products could also react with glutathione to form mixed disulfide products that undergo reduction and oxidative desulfuration or undergo oxidation to sulfonic acid through their corresponding thiosulfinate and sulfinic acid intermediates (Dutton and Illing, 1972; Maiorino et al., 1988; McBain and Menn, 1969; Richardson et al., 1991). An Ames assay in *S. typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 yielded negative results in the presence and absence of S9 at doses of up to 333 µg/plate for the structural relative allyl propyl disulfide (FEMA 4073) (Zeiger et al., 1988). Positive results were observed in sister chromatid exchange and chromosomal aberration assays conducted in CHO cells for a second structural relative, allyl disulfide (FEMA 2028). An increase in chromosomal aberrations was observed in CHO cells treated with allyl disulfide (FEMA 2028) in the presence of S9 and a decrease in the occurrence of sister chromatid exchanges was noted for allyl disulfide (FEMA 2028) in the presence of S9 (Musk et al., 1997). No increases in micronucleated polychromatic erythrocytes in ICR mouse bone marrow cells were observed, when groups of male ICR mice were gavage administered a 50 or 100 mg/kg bw corn oil mixture of allyl disulfide (FEMA 2028), allyl sulfide (FEMA 2042), and diallyl trisulfide (FEMA 3265) (Marks et al., 1992). Based on weight of evidence, 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 hexyl propyl disulfide. A 90-day toxicity study of structural relative propyl disulfide (FEMA 3228) in male and female Charles River CD rats resulted in NOAELs of 7.29 and 8.17 mg/kg bw/day respectively (Posternak et al., 1969). The dose of 7.29 mg/kg bw/day is greater than 1,400,000 times the anticipated daily *per capita* intake of hexyl propyl disulfide from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *O*-ethyl *S*-(3-methylbut-2-en-1-yl) thiocarbonate (CAS 2097608-89-2) and concluded that the substance is GRAS (FEMA 4901) (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 substance was evaluated individually within the context of the chemical group of aliphatic thiols, subgroup of acyclic sulfides with oxidized side-chains (JECFA, 2004, 2012; SLR, A8). The Panel calculated the anticipated *per capita* intake ("eaters only") of *O*-ethyl *S*-(3-methylbut-2-en-1-yl) thiocarbonate from use as a flavor ingredient to be 0.01 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The 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 *O*-ethyl *S*-(3-methylbut-2-en-1-yl) thiocarbonate undergoes rapid hydrolysis by esterases to yield carbonothioic acid, which will be excreted in the urine in its unconjugated or conjugated form (Kurooka et al., 1976). Negative results were observed in an Ames assay for structurally related substance, *O*-ethyl *S*-(2-furylmethyl) thiocarbonate (FEMA 4043), both in the presence or absence of S9 in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as *E. coli* WP2 *uvr*A (Verspeek-Rip, 2000). This same structural relative was tested for its ability to induce chromosomal aberrations in cultured peripheral human lymphocytes under two separate experiments. In the first experiment, *O*-ethyl *S*-(2-furylmethyl) thiocarbonate (FEMA 4043) tested negative at concentrations up to 350 µg/ml in the presence and absence of S9 when incubated for three hours with a 24-hour fixation time. In the second experiment, a dose dependent increase of cells with chromosomal aberrations was observed at 130, 240, and 280 µg/ml under 24-hour exposure followed by 24-hour fixation, and at 100, 130, and 140 µg/ml after 48-hour exposure and 24-hour fixation, in the absence of S9. In the presence of S9,

a dose dependent increase was observed at 325 and 375 µg/ml (Meerts, 2001). The same structural relative tested negative in an oral dose *in vivo* micronucleus assay in SPF mice at up to the highest dose of 500 mg/kg bw/day (Verspeek-Rip, 2001). Based on weight of evidence, 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 *O*-ethyl *S*-(3-methylbut-2-en-1-yl) thiocarbonate. A 28-day toxicity study of *O*-ethyl *S*-(2-furylmethyl) thiocarbonate (FEMA 4043) gavage administered to SPF-bred Wistar rats at 2, 8, and 32 mg/kg bw/day resulted in a NOAEL of 8 mg/kg bw/day (van Otterdijk, 2001), which is greater than 40,000,000 times the anticipated daily *per capita* intake of *O*-ethyl *S*-(3-methylbut-2-en-1-yl) thiocarbonate from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 3-methyl-2(*5H*)-furanone (CAS 22122-36-7) and concluded that the substance is GRAS (FEMA 4902) (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 substance was evaluated individually within the context of the chemical group of aliphatic lactones(Adams et al., 1998; JECFA, 1999, 2004, 2011; SLR, B1C). The Panel calculated the anticipated *per capita* intake ("eaters only") of 3-methyl-2(*5H*)-furanone from use as a flavor ingredient to be 0.3 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This material is known to occur naturally in dried bonito, parmesan cheese, and shoyu but no consumption ratio could be calculated as only qualitative data was available (Njissen, 2019). 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 3-methyl-2(*5H*)-furanone will hydrolyze to its corresponding ring opened *alpha,beta*-unsaturated hydroxycarboxylic acid. Upon hydrolysis, condensation with acetyl CoA yields a *delta*2-enoyl product, a substrate in the fatty acid pathway. Hydration of the *cis* double bond in this lactone yields (*R*)-3-hydroxyacyl CoA which is isomerized to (*S*)-3-hydroxyacyl CoA by 3-hydroxyacyl CoA epimerase before undergoing fatty acid metabolism. Alternatively, the *alpha,beta*-unsaturated lactone could conjugate with glutathione and be excreted as its cysteine or mercapturic acid derivative (Nelson and Cox, 2008). In an Ames assay for 3-methyl-2(5*H*)-furanone in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as in *E. coli* strain WP2 *uvr*A, no mutagenicity was observed in the presence and absence of S9 at concentrations up to 5000 µg/plate (Ogura, 2014). An *in vivo* micronucleus assay recorded no increase in the frequency of micronucleated polychromatic erythrocytes at concentrations up to 750 mg/kg bw 3-methyl-2(*5H*)-furanone in male Crl:CD1(ICR) mice but showed significant increases in micronucleated cells at a mid-dose level of 500 mg/kg bw in female Crl:CD1(ICR) mice. However, because an increase in micronucleated cells was not observed at the low and high doses of 250 and 1000 mg/kg bw in the female mice, this positive result was not considered significant. (Ogura, 2017). An Ames assay conducted for structural relative furan-2(5H)-one (FEMA 4138) in *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 yielded negative results up to 5000 µg/plate with and without S9 using the plate incorporation and pre-incubation methodologies (Bowen, 2011). An *in vitro* micronucleus assay in human peripheral blood lymphocytes incubated with furan-2(5H)-one (FEMA 4138) for 3 hours followed by a 21-hour recovery period in the presence of S9 resulted in an increase of the frequency of micronuclei but no such increase was observed when the lymphocytes were incubated with the test substance for 3 hours followed by a 21-hour recovery period in the absence of S9 or when incubated with the test substance for 24 hours with no recovery period in the absence of S9 (Whitwell, 2012). As a follow-up to these results, a combined *in vivo* mouse micronucleus and liver comet assay for furan-2(5H)-one (FEMA 4138) was conducted in outbred male Han Wistar rats. In this assay, no increase in micronucleated polychromatic erythrocytes was observed compared to concurrent and historical controls. A small increase in group mean % tail intensity was observed at the highest tested dose of 250 mg/kg bw, but not at the mid- and low-dose treatments in the comet assay. Coincident with the increase in group mean% tail intensity, decreased glycogen vacuolation and duodenum villous tip necrosis were observed for the 250 mg/kg bw group. These results were within the historical control range of the testing facility, and therefore were not attributed to the treatment with furan-2(5*H*)-one. The liver comet assay for furan-2-(5*H*)-one yielded negative results for DNA damage in the liver (Beevers, 2014). 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 3-methyl-2(*5H*)-furanone. A 13-week toxicity study of structural relative 4-hydroxybutyric acid (FEMA 3291) in male and female F344/N rats resulted in a NOAEL of 450 mg/kg bw/day (NTP, 1992) which is 90,000,000 times the anticipated daily *per capita* intake of 3-methyl-2(*5H*)-furanone from use as a flavor ingredient. A 2-year carcinogenicity study for the same structural relative was administered to B6C3F1 mice and F344/N rats by oral gavage, determined a NOAEL of 225 mg/kg bw/day for F344/N male rats (NTP, 1992). This NOAEL is 45,000,000 times the anticipated daily *per capita* intake of 3-methyl-2(*5H*)-furanone from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding ethyl 3-methyl-2-oxopentanoate (CAS 26516-27-8) and concluded that the substance is GRAS (FEMA 4903) (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 substance was evaluated individually within the context of the chemical group of aliphatic primary alcohols, aldehydes, carboxylic acids, acetals, and esters containing additional oxygenated functional groups (JECFA, 2000, 2011; SLR, B1B). The Panel calculated the anticipated *per capita* intake ("eaters only") of 3-methyl-2-oxopentanoate from use as a flavor ingredient to be 1 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The 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 ethyl 3-methyl-2-oxopentanoate will undergo hydrolysis to its corresponding alcohol and acid. The ethanol product would then be excreted by exhalation or undergo further metabolism in the body. The 2-oxopentanoic acid product is expected to undergo further metabolism by beta-oxidation (Leegwater and van Straten, 1974). In an Ames assay for ethyl 3-methyl-2-oxopentanoate conducted in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as in *E. coli* strain WP2*uvr*A, negative results were observed up to 5,000 µg/plate in the presence and absence of S9 (Verspeek-Rip, 1999). 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 ethyl 3-methyl-2-oxopentanoate. A 28-day dietary study of structurally related substance, ethyl acetoacetate (FEMA 2415), in male and female Sprague-Dawley rats resulted in a NOAEL of greater than a 1000 mg/kg bw/day (Cook et al., 1992). This NOAEL is 50,000,000 times the anticipated daily *per capita* intake of ethyl 3-methyl-2-oxopentanoate from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *trans*-tetradec-4-enal (CAS 115018-39-8) and concluded that the substance is GRAS (FEMA 4904) (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 substance was evaluated individually within the context of the chemical group of linear and branch-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids, and related esters (JECFA, 1999, 2007, 2012; SLR, M1). The Panel calculated the anticipated *per capita* intake ("eaters only") of *trans*-tetradec-4-enal 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*-tetradec-4-enal will undergo oxidation to the corresponding unsaturated carboxylic acid intermediate that will then proceed to a single *beta*-oxidation cycle resulting in the corresponding *delta* 2-enoyl CoA product. This product then undergoes further *beta*-oxidation resulting in an acetyl CoA fragment which would enter the citric acid cycle to ultimately yield CO_2 and water as innocuous products (Feldman and Weiner, 1972; Eckfeldt and Yonetani, 1982; Nakayasu et al., 1978; Beedham, 1988; Nelson and Cox, 2008). An Ames assay for structural relative *cis*-5-octenal (FEMA 3749) conducted in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 yielded negative results up to cytotoxic doses in the presence and absence of S9 (Asquith, 1990). An Ames assay conducted for structural relative 10-undecenal (FEMA 3095) in *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 resulted in negative results for mutengenicity in the presence and absence of S9 (Bhatia et al., 2010; Sokolowski, 2007). An *in vivo* micronucleus assay conducted in male and female NMRI mice gavage-administered structural relative, 10-undecenal (FEMA 3095), resulted in no statistically significant increase in the frequency of micronuclei (Bhatia et al., 2010; Honarvar, 2007). 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 *trans*-tetradec-4-enal. In a 90-day dietary Sprague-Dawley rats were fed an admixture containing, 10-undecenal (FEMA 3095), a structural relative, which resulted in no significant evidence of toxicity. A NOAEL of 14.3 mg/kg bw/day was determined for 10-undecenal (Liwska and Watson, 2012) which is greater than 2,860,000 times the anticipated daily *per capita* intake of *trans*-tetradec-4-enal from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2,6-dimethylhept-5-enyl formate (CAS 2119671-25-7) and concluded that the substance is GRAS (FEMA 4905) (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 substance was evaluated individually within the context of the chemical group of esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids (JECFA, 1999, 2012; SLR, M1). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2,6-dimethylhept-5-enyl formate 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 2,6-dimethylhept-5-enyl formate will undergo ester hydrolysis to yield the corresponding carboxylic acid and alcohol products, formic acid and 2,6-dimethyl heptenol. Formic acid is metabolized to water and CO_2 while 2,6-dimethyl heptenol is expected to oxidize to the corresponding unsaturated carboxylic acid, 2,6-dimethyl heptanoic acid, which would then enter the *beta*-oxidation cycle to undergo complete metabolism to innocuous products, CO_2 and water (Mattia, 1999). In an Ames assay for structural relative 2,6-dimethyl-5-heptenal (FEMA 2389), negative results were observed in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 both in the presence and absence of S9. In an unscheduled DNA synthesis assay for the same substance, negative results were observed at up to 1 mg/ml in rat hepatocytes (Heck et al., 1989). The same substance yielded no increase in incidence of micronuclei formation in an *in vivo* mouse study (Wild et al., 1983). A 90-day toxicity study of structural relative 2,6-dimethyl-5-heptenal (FEMA 2389) in male and female Wistar rats resulted in a NOAEL of 37 mg/kg bw/day (Gaunt et al., 1983) which is 7,400,00 times the anticipated daily *per capita* intake of 2,6-dimethylhept-5-enyl formate from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *L*-carnitine tartrate (CAS 36687-82-8) and concluded that the substance is GRAS (FEMA 4906) (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 substance was evaluated individually within the context of amino acids (JECFA, 2006, 2012; SLR, B3). The Panel calculated the anticipated *per capita* intake ("eaters only") of *L*-carnitine tartrate from use as a flavor ingredient to be 1510 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This substance is naturally occurring in animal protein products and is endogenous to humans (Benvenga et al., 2001). However, since quantitative data was not available, a consumption ratio could not 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). It is presumed that *L*-carnitine tartrate readily dissociates into *L*-carnitine and *L*-tartaric acid in the gastrointestinal tract. Any orally consumed *L*-carnitine that is not absorbed in the gastrointestinal tract passes to the lower intestine to undergo bacterial degradation yielding *gamma*-butyrobetaine which is then eliminated in the feces (EFSA, 2003; Schmidbaur et al., 1998). In an Ames assay for *L*-carnitine tartrate in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, negative results were observed in the presence and absence of S9 up to 5,000 µg/plate (IBR, 1991b). 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 *L*-carnitine tartrate. No toxicity was observed in a 150-day toxicity study in which New Zealand rabbits were provided structural relative sodium tartrate (FEMA 3044) as 7.7% of their diet, otherwise corresponding to an intake of 2,310 mg/kg bw/day (Packman et al., 1963). A 28-day study with a 28-day reversibility phase as well as a 90/93-day study of structural relative betaine (FEMA 4223) provided in the diet to Sprague-Dawley rats resulted in a NOAEL of 2857 mg/kg bw/day (Hayes et al., 2003) which is greater than 114,000 times the anticipated daily *per capita* intake of *L*-carnitine tartrate from use as a flavor ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding *Corynebacterium glutamicum* (*C. glutamicum*) corn syrup fermentation product and concluded that the substance is GRAS (FEMA 4907) (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 FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015).The Panel calculated the anticipated *per capita* intake of *C. glutamicum* corn syrup fermentation product from use as a flavor ingredient to be 2588 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 identity description of the material to be adequate for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Cohen et al., 2018; Smith et al., 2005b). The metabolism of the major marker constituents, glutamic acid, salt, water, and other amino acids are normal components of the human diet and as such are expected to be digested and metabolized in a similar manner to other commonly consumed nutrients (Tafazoli et al., 2017). In an Ames assay for a 2:1 mixture of this substance with FEMA 4908 conducted in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2 *uvr*A, negative results were observed in the presence and absence of S9 (Tafazoli et al., 2017). An HPRT assay for the same test substance conducted in V79 Chinese hamster lung (CHL) cells yielded negative results in the presence and absence of S9 (Tafazoli et al., 2017). Based on these results, as well as the structures of the principal constituents and the identity and arrangement of the functional groups therein, the Panel did not identify specific concerns related to the genotoxicity of *C. glutamicum* corn syrup fermentation product. A 104-week study in Fisher 344 male and female rats dietarily administered monosodium glutamate (FEMA 2756) resulted in a NOAEL of 2,311 mg/kg bw/day, which, based on a lower bound estimate of 38.3% *L*-glutamic acid content in *C. glutamicum* corn syrup fermentation product (Tafazoli et al., 2017) is greater than 140,000 times the anticipated daily *per capita* intake of *C. glutamicum* corn syrup fermentation product from use as a flavor ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding *Corynebacterium stationis* (*C. stationis*) corn syrup fermentation product and concluded that the substance is GRAS (FEMA 4908) (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). (Smith et al., 2005a). The Panel calculated the anticipated *per capita* intake of *C. stationis* corn syrup fermentation product from use as a flavor ingredient to be 2588 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 identity description of the material to be adequate for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Cohen et al., 2018; Smith et al., 2005b). The metabolism of the major marker constituents, inosine 5'-monophosphate as well as other nucleotides, amino acids, minerals, water, sugars, and organic acids, are normal components of the human diet and as such are expected to be digested and metabolized in a similar manner to other commonly consumed nutrients (Tafazoli et al., 2017). In an Ames assay for a 2:1 mixture of FEMA 4107 and this substance conducted in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2 *uvr*A, negative results were observed in the presence and absence of S9 (Tafazoli et al., 2017). An HPRT assay for the same tst substance conducted in V79 Chinese hamster lung (CHL) cells yielded negative results in the presence and absence of S9 (Tafazoli et al., 2017). Based on these results, as well as the structures of the principal constituents and the identity and arrangement of the functional groups therein, the Panel did not identify specific concerns related to the genotoxicity of *C. stationis* corn syrup fermentation product. In a 90-day toxicity study in male and female Wistar rats dietarily administered a 2:1 mixture of *C. glutamicum* corn syrup fermentation product and *C. stationis* corn syrup fermentation product resulted in a NOAEL of 1666 mg/kg bw/day for *C. stationis* corn syrup fermentation product (Tafazoli et al., 2017) which is greater than 38,000 times the anticipated daily *per capita* intake of *C. stationis* corn syrup fermentation product from use as a flavoring ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding glucosyl steviol glycosides, 70-80% (CAS 57817-89-7) and concluded that the material is GRAS (FEMA 4909) 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 (Cohen et al., 2018; Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of glucosyl steviol glycosides 70-80% from use as a flavor ingredient to be 1926 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This substance is reported to occur in *Stevia rebaudiana* leaves (Wood et al., 1955). The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Metabolic 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., 2003a; Geuns et al., 2003b; Koyama et al., 2003a; Koyama et al., 2003b; Nikiforov et al., 2013; Purkayastha et al., 2015; Purkayastha et al.,

2016; Purkayastha et al., 2014; Renwick and Tarka, 2008). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in in vitro mutagenicity assays, in vivo studies do not provide evidence of genotoxic effects (Nakajima, 2000; Pezzuto et al., 1985, 1986;(Rumelhard 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 glucosyl steviol glycosides 70-80%. 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 2,700 times the anticipated daily per capita intake of the. anticipated daily *per capita* intake of glucosyl steviol glycosides 70-80% from use as a flavoring ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding glucosylated steviol glycosides, 40% (CAS 57817-89-7) and concluded that the substance is GRAS (FEMA 4910) (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 substance was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of glucosylated steviol glycosides, 40% from use as a flavor ingredient to be 1294 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 identity description of the material to be adequate for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Metabolic 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., 2003a; Geuns et al., 2003b; Koyama et al., 2003a; Koyama et al., 2003b; Nikiforov et al., 2013; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha et al., 2014; Renwick and Tarka, 2008). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in in vitro mutagenicity assays, in vivo studies do not provide evidence of genotoxic effects (Nakajima, 2000; Pezzuto et al., 1985, 1986;(Rumelhard 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 glucosyl steviol glycosides 40%. 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 4,100 times the anticipated daily per capita intake of the. anticipated daily *per capita* intake of glucosyl steviol glycosides 40% from use as a flavoring ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding stevia extract stevioside, 70% (CAS 91722-21-3) and concluded that the substance is GRAS (FEMA 4911) (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 substance was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of stevia extract stevioside, 70% from use as a flavor ingredient to be 1427 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 identity description of the material to be adequate for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Metabolic 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., 2003a; Geuns et al., 2003b; Koyama et al., 2003a; Koyama et al., 2003b; Nikiforov et al., 2013; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha et al., 2014; Renwick and Tarka, 2008). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in in vitro mutagenicity assays, in vivo studies do not provide evidence of genotoxic effects (Nakajima, 2000; Pezzuto et al., 1985, 1986;(Rumelhard 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 stevia extract stevioside, 70%. 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 3,700 times the anticipated daily per capita intake of the. anticipated daily *per capita* intake of stevia extract stevioside, 70% from use as a flavoring ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding hibiscus blossom extract (*Hibiscus sabdariffa* L.) (CAS 4775-96-2) and concluded that the substance is GRAS (FEMA 4912) (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 substance was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of hibiscus blossom extract from use as a flavor ingredient to be 150 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 identity description of the material to be adequate for FEMA GRAS evaluation. Based on metabolic data for a representative member of the principal congeneric group, it is presumed that the group would be metabolized by well-established pathways to yield innocuous products. An Ames assay conducted with hibiscus blossom extract in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as in *E. coli* strain WP2 *uvr*A (pKM1010) was negative up to cytotoxic concentrations in the presence and absence of S9 using the plate incorporation and preincubation techniques (Leuschner, 2017). Based on these assays and the composition of the material therein, the Panel did not identify specific concerns related to the genotoxicity of hibiscus blossom extract. A 270-day study in which male and female Sprague-Dawley rats received hibiscus blossom extract by water resulted in a NOAEL of 200 mg/kg bw/day (Api et al., 2004; Lambert and Hopkins, 1996) which is 80,000 times the anticipated daily *per capita* intake of hibiscus blossom extract from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 3,7-dimethyl-2-methyleneoct-6-en-1-ol (CAS 18478-46-1) and concluded that it is GRAS (FEMA 4913) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This 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 (JECFA, 1999, 2006, 2012; SLR, M1). The Panel calculated the anticipated *per capita* intake ("eaters only") of 3,7-dimethyl-2-methyleneoct-6-en-1-ol from use as a flavor ingredient to be 14 µg/person/day, which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). This substance is known to naturally occur in lemon eucalyptus (*Eucalyptus citridora*) (Luis et al., 2017). However, because only qualitative data was available, a consumption ratio could not be calculated. In its evaluation the Panel noted that the major markers of identity are ≥93%, 3,7-dimethyl-2-methyleneoct-6-en-1-ol and ≥3% 2,3,7-trimethyloct-6-en-1-ol (mixture of isomers) and considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is anticipated that 3,7-dimethyl-2-methyleneoct-6-en-1-ol shares similar metabolic fates as other structurally related aliphatic branched chain primary alcohols. These branched-chain terpene alcohols have been shown to undergo alcohol oxidation, omega-oxidation, hydration and selective hydrogenation to yield polar metabolites forming glucuronide or sulfate conjugates that are rapidly eliminated in the urine (Chadha and Madyastha, 1982; Diliberto et al., 1990). The structural relative 3,7-dimethyl-2-methyleneoct-6-en-1-al (CAS 22418-66-2) was negative for genotoxicity in an Ames assay in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as E. coli strain WP2 uvrA in either the presence or absence of S9 metabolic activation (Thompson, 2002). Based on these results, as well as the structure and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for genotoxic potential of 3,7-dimethyl-2-methyleneoct-6-en-1-ol when used as a flavoring ingredient. A 28-day study in which male and female Sprague-Dawley rats, gavage administration of the structural relative 2,6-dimethylhept-5-en-1-al (FEMA 2389) resulted in clinical signs of toxicity at the highest dose tested (3000 mg/kg bw/day). Male rats at the high and middle dose (1500 mg/kg bw/day) showed evidence of $\alpha_{2\mu}$-globulin nephropathy. No such findings were found at the lowest dose of 300 mg/kg bw/day (Terrill, 1990). In a 90-day study in male and female Wistar rats, the same structural relative was provided in the diet at concentrations of 9, 37, and 150 mg/kg bw/day resulted in a NOAEL of 37 mg/kg bw/day (Gaunt et al., 1983), which is 185,000 times versus the anticipated daily *per capita* intake of 3,7-dimethyl-2-methyleneoct-6-en-1-ol from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding *bis*-(3-methyl-2-butenyl)disulfide (CAS 24963-39-1) and concluded that it is GRAS (FEMA 4914) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This substance was evaluated individually within the context of the chemical groups of simple aliphatic and aromatic sulfides and thiols (JECFA, 2000, 2004, 2008, 2011; SLR, B4). The Panel calculated the anticipated *per capita* intake ("eaters only") of *bis*-(3-methyl-2-butenyl)disulfide from use as a flavor ingredient to be 0.1 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The 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 predicted that *bis*-(3-methyl-2-butenyl)disulfide will be reduced either enzymatically by GSH reductase (Waring, 1996) or thioltransferases (Wells et al., 1993), or chemically by exchange with GSH, thioredoxin, cysteine or other endogenous thiols to yield 3-methyl-2-butenyl thiol. This simple thiol is expected to undergo enzymatic oxidation to yield the corresponding sulfenic acid, sulfinic acid and ultimately, sulfonic acid. The sulfinic and sulfonic acids are water soluble and easily excreted. Alternatively, the thiol that is formed may react with glutathione and cysteine to form mixed disulfides that can then undergo reduction and oxidative desulfuration, or oxidation to sulfonic acid via the intermediate thiosulfinate and sulfinic acid (Dutton and Illing, 1972; Maiorino et al., 1989; McBain and Menn, 1969; Richardson et al., 1991). There are also several possible thiol-disulfide exchange reactions that may occur (Cotgreave et al., 1989). *bis*-(3-Methyl-2-butenyl)disulfide did not increase the frequency of revertant colonies in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as in *E. coli* strain WP2*uvr*A either in the presence or absence of S9 metabolic activation by the pre-incubation method (Komai, 2017a). In a mouse micronucleus assay, gavage administration of a 68:20:12 mixture containing the structurally related flavor ingredients, allyl disulfide (FEMA 2028), allyl sulfide (FEMA 2042), and diallyl trisulfide (FEMA 3265), did not increase the frequency of micronucleated polychromatic erythrocytes in bone marrow cells. This test mixture provided estimated doses of the structurally related substance, allyl disulfide (FEMA 2028), of 48 and 98 mg/kg bw/day (Marks et al., 1992). The structurally related substance, allyl propyl disulfide (FEMA 4073), did not increase the frequency of revertant colonies when tested up to 333 µg/plate in *S. typhimurium* strains TA97, TA98, TA100, TA102, TA1535, and TA1537 either in the presence or absence of S9 metabolic activation (Zeiger et al., 1988). In a separate experiment, both structural relatives, allyl propyl disulfide (FEMA 4073) and allyl disulfide (FEMA 2028) did not increase the frequency of revertant

colonies in *S. typhimurium* strain TA100 at doses ranging from 0.0015-0.15 µg/mL either in the presence or absence of S9 metabolic activation (Eder et al., 1982; Eder et al., 1980). Based on the results for the substance and structural relatives, as well as on the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for genotoxic potential of *bis*-(3-methyl-2-butenyl) disulfide when used as a flavoring ingredient. In a 6-day study in female Sprague-Dawley rats, gavage administration of the structural relative allyl disulfide (FEMA 2028) resulted in a NOAEL of 36 mg/kg bw/day (Munday and Manns, 1994). This is greater than 21,600,000 times versus the anticipated daily *per capita* intake of *bis*-(3-methyl-2-butenyl) disulfide from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding (5*Z*)-3,4-dimethyl-5-propylidene-2(5*H*)-furanone (CAS 2142634-65-7) and concluded that it is GRAS (FEMA 4915) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This substance was evaluated individually within the context of the chemical groups) of furanones and related substances (JECFA, 2006, 2017; SLR, D9). The Panel calculated the anticipated *per capita* intake (“eaters only”) of (5*Z*)-3,4-dimethyl-5-propylidene-2(5*H*)-furanone from use as a flavor ingredient to be 0.1 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This substance is reported to occur in kombu dashi (brown algae stock) (Tomita, 2017). 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. (5*Z*)-3,4-Dimethyl-5-propylidene-2(5*H*)-furanone is predicted to be metabolized in a manner similar to other five-membered lactone rings. α,β-Unsaturated lactones, such as (5*Z*)-3,4-dimethyl-5-propylidene-2(5*H*)-furanone, are predicted to hydrolyze to the corresponding ring-opened α,β-unsaturated hydroxycarboxylic acids (Köppel and Tenczer, 1991). Following hydrolysis, condensation with acetyl CoA yields a delta-2-enoyl CoA product that is a substrate in the fatty acid pathway (Nelson and Cox, 2008). Since the stereochemistry of the double bond in a lactone is cis, hydration yields (*R*)-3-hydroxyacyl CoA, which is then isomerized to (*S*)-3-hydroxyacyl CoA by 3-hydroxyacyl CoA epimerase prior to entering into fatty acid metabolism. Alternately, the α,β-unsaturated lactone may conjugate with glutathione and be excreted as the cysteine or mercapturic acid derivative (Boyland and Chasseaud, 1970; Chasseaud, 1979; Fry et al., 1993). In an Ames assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2uvrA, (5Z)-3,4-dimethyl-5-propylidene-2(5H)-furanone did not increase the frequency of revertant colonies in the absence and presence of S9 metabolic activation at concentrations up to 5000 µg/plate (Komai, 2017b).. In an *in vitro* micronucleus induction assay in human peripheral blood lymphocytes, 3,4-dimethylpentylidenefuran-2(5*H*)-one did induce a statistically significant effect on micronuclei frequency in the presence of S9 metabolic activation (Lloyd, 2014), but in a combined comet/micronucleus assay in rats, the substance did not increase micronucleated cells in the bone marrow or induce DNA damage in the liver, as analyzed by the comet assay, when tested up to the maximum tolerated dose of 500 mg/kg bw/day (Beevers, 2014). In an Ames assay in *S. typhimurium* strains TA98 and TA100, the structural relative 4-(4-methyl-3-penten-1-yl)-2(5*H*)-furanone (FEMA 4868) did not increase the frequency of revertant colonies in the absence and presence of S9 metabolic activation at concentrations up to 500 µg/plate(Kawaguchi, 2016). Based on the results for the substance and structural relatives, as well as on the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for genotoxic potential of (5*Z*)-3,4-dimethyl-5-propylidene-2(5*H*)-furanone when used as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2-methyl-3-butene-2-thiol (CAS 124831-34-1) and concluded that it is GRAS (FEMA 4916) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic sulfides and thiols (JECFA, 2000, 2004, 2008, 2011; SLR, A8). The Panel calculated the anticipated *per capita* intake (“eaters only”) of 2-methyl-3-butene-2-thiol from use as a flavor ingredient to be 0.07 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 predicted that 2-methyl-3-butene-2-thiol will undergo oxidation of the thiol group resulting in the corresponding sulfenic acid, sulfinic acid, and sulfonic acid. Sulfenic acids are unstable and readily undergo further oxidation to sulfinic and sulfonic acids or combine with nucleophiles. The sulfinic and sulfonic acids are water soluble and easily excreted (Dutton and Illing, 1972; Klancnik et al., 1992; Maiorino et al., 1989; McBain and Menn, 1969; Renwick, 1996; Richardson et al., 1991). Alternatively, the thiol may react with glutathione and cysteine to form mixed disulfides that can then undergo reduction and oxidative desulfuration, or oxidation to sulfonic acid via the intermediate thiosulfinate and sulfinic acids. 2-Methyl-3-butene-2-thiol is also anticipated to undergo *S*-methylation in mammals to produce the corresponding methyl thioether that can be successively oxidized to the corresponding sulfoxide and sulfone (Shaw and Blagbrough, 1989; Tateishi et al., 1978; Tateishi and Tomisawa, 1989). In an Ames assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2*uvr*A, 2-methyl-3-butene-2-thiol did not increase the frequency of revertant colonies in the absence and presence of S9 metabolic activation (Sato, 2017). Based on these results, as well as on the structure and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for genotoxic potential of 2-methyl-3-butene-2-thiol when used as a flavoring ingredient. In a 14-day dietary administration study in male and female rats with the structural relative prenylthiol (FEMA 3896), an average daily intake of 12.8 mg/kg bw/day for both sexes resulted in a significant reduction in food consumption for males, but this is presumed to be related to palatability of the test diet since the change in food consumption was not accompanied by a significant difference in body weight gain between test and control groups. Gross necropsy and histopathological examination of kidney and liver tissues revealed effects related to the test article. Relative kidney and liver weights showed no significant differences between test and control groups (Wnorowski, 1997). In a 90-day study in albino weanling rats, dietary addition of the structural relative

2,3-butanedithiol (FEMA 3477) at a dose of 0.703 mg/kg bw/day resulted in no hematological, biochemical and urinary deviations from normal ranges of tested parameter or any unusual microscopic pathological observations (Morgareidge, 1974). In an OECD 408 compliant 90-day in male and female Sprague-Dawley rats, gavage administration of the structural relative 4-mercapto-4-methyl-2-pentanone (FEMA 3997) at doses of 13, 20, and 26 mg/kg/day resulted in a NOAEL of 26 mg/kg bw/day (Bauter, 2017). This is 22,000,000 times the anticipated daily *per capita* intake of 2-methyl-3-butene-2-thiol from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding (*Z*)-9-dodecenoic acid (CAS 22032-47-9) and concluded that it is GRAS (FEMA 4917) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This 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 (JECFA, 1999, 2006, 2012; SLR, M1). The Panel calculated the anticipated *per capita* intake ("eaters only") of (*Z*)-9-dodecenoic acid from use as a flavor ingredient to be 0.1 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). It is anticipated that (*Z*)-9-dodecenoic acid will form micelle aggregates, esterify with glycerol in chylomicrons and low-density lipoproteins, and then be transported via the lymphatic system for absorption (Borgström, 1974). Alternatively, (*Z*)-9-dodecenoic acid could undergo β-oxidative cleavage and complete metabolism to carbon dioxide in the fatty acid pathway and the citric acid cycle (Gibson et al., 1982; Masoro, 1977; Schulz, 1983). In an Ames assay conducted in *S. typhimurium* strains TA98 and TA100, (*Z*)-9-dodecenoic acid did not increase the frequency of revertant colonies in the absence and presence of S9 metabolic activation. In an Ames assay in *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537, the structural relative 10-undecenal (FEMA 3095) did not increase the frequency of revertant colonies in the absence and presence of S9 metabolic activation using both the plate incorporation and pre-incubation methodologies (Bhatia et al., 2010; Sokolowski, 2007). In an *in vivo* micronucleus assay in male and female NMRI mice, gavage administration at doses up to 2000 mg/kg bw/day of the structural relative 10-undecenal (FEMA 3095) produced no statistically significant increases in the frequency of micronuclei (Bhatia et al., 2010; Honarvar, 2007). Based on these results, the very low intake of the substance and the structure and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for genotoxic potential of 1-ethyl-(*Z*)-9-dodecenoic acid when used as a flavoring ingredient. A 90-day dietary administration study for the structurally related substance, 10-undecenal (FEMA 3095), was conducted in male and female Sprague-Dawley rats resulted in a NOAEL of 14.3 mg/kg bw/day due to no toxicologically significant clinical observations or macroscopic abnormalities (Liwska, 2012; Tsang, 2018). This is greater than 8,500,000 times the anticipated daily *per capita* intake of (*Z*)-9-dodecenoic acid from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding tridec-5-enal (CAS 68820-38-2) and concluded that it is GRAS (FEMA 4918) (Smith et al., 2005) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This 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 (JECFA, 1999, 2006, 2012; SLR, M1).The Panel calculated the anticipated *per capita* intake ("eaters only") of tridec-5-enal from use as a flavor ingredient was calculated 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). In its evaluation of tridec-5-enal, the Panel noted that the major markers of identity are >90% *cis*-tridec-5-enal and >5% *trans*-tridec-5-enal and considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. It is predicted that tridec-5-enal will be oxidized to the corresponding unsaturated carboxylic acid before proceeding into the β-oxidation cycle (Feldman & Weiner, 1972; Eckfeldt & Yonetani, 1982; Nakayasu et al., 1978; Beedham, 1988). The cis-carboxylic acid intermediate will undergo a single β-oxidation cycle and the corresponding cis Δ-3 double bond of the C11 intermediate will then be converted to the corresponding trans Δ-2 double bond (via enoyl CoA isomerase). It then proceeds into the next β-oxidation cycle. Acetyl CoA units will continue to be cleaved off in β-oxidation until the final cleavage, which yields acetyl CoA and propionyl CoA. Acetyl CoA enters the citric acid cycle directly, while propionyl CoA is transformed into succinyl CoA that then enters the citric acid cycle. Based on this, it is therefore predicted that 5-tridecenal will undergo complete metabolism to innocuous products (CO_2 and water) (Nelson and Cox, 2008). In an Ames assay in *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537, the structurally related substance, 10-undecenal (FEMA 3095), did not increase the frequency of revertant colonies in the absence and presence of S9 metabolic activation (Bhatia et al., 2010; Sokolowski, 2007). In an *in vivo* micronucleus assay in male and female NMRI mice, gavage administration at doses up to 2000 mg/kg bw/day of the structurally related substance, 10-undecenal (FEMA 3095), produced no statistically significant increases in the frequency of micronuclei (Bhatia et al., 2010; Honorvar, 2007). Based on these results, as well as the structure of the substance and the identity and arrangement of the functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of tridec-5-enal. A 90-day dietary administration study for the structurally related substance, 10-undecenal (FEMA 3095), was conducted in male and female Sprague-Dawley rats resulted in a NOAEL of 14.3 mg/kg bw/day, reporting no toxicologically significant clinical observations or macroscopic abnormalities (Liwska, 2012; Tsang, 2018). This is 2,860,000 times the anticipated daily per capita intake of 5-tridecenal from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding refined soybean oil extract (CAS 8001-22-7) and concluded that it is GRAS (FEMA 4919) (Smith et al., 2005a) for use as a flavor 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 (Cohen et al., 2018; Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of refined soybean oil extract from use as a flavor ingredient was calculated to be 0.3 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 assay and supporting spectral data provided for FEMA GRAS evaluation. It is expected that phytosterols, the predominant constituents of refined soybean oil extract, will be poorly absorbed (<5% of dietary concentrations) in the gastrointestinal tract. Excess dietary phytosterols are excreted unchanged in the feces (Maki et al., 2001; Miettinen et al., 1990; Ostlund, 2002; Rozner and Garti, 2006; Salen et al., 1985; Sanders et al., 2000). In an Ames assay in *S. typhimurium* strains TA1535, TA1537, TA98, TA100 a phytosterol mixture (*β*-sitosterol, 45.5-51.0%; campesterol, 26.7-28.1%; and stigmasterol, 17.7-18.7%) did not increase the frequency of revertant colonies in the absence and presence of S9 metabolic activation (Wolfreys and Hepburn, 2002). In an Ames assay in *S. typhimurium* strains TA1535, TA1537, TA98, TA100 and *E. coli* strain WP2*uvr*A the phytosterol mixture was esterified with fatty acids from sunflower oil, and the resulting phytosterol ester mixture did not increase the frequency of revertant colonies in the absence and presence of S9 metabolic activation (Wolfreys and Hepburn, 2002). Neither the phytosterol mixture nor the phytosterol ester mixture induced chromosomal aberrations in vitro in human peripheral blood lymphocytes in either the presence or absence of S9 metabolic activation (Evans and O'Riordan, 1975 as cited in Wolfreys and Hepburn, 2002). The phytosterol ester mixture was negative in a mouse lymphoma forward mutation assay in L5178Y tk +/- mouse lymphoma cells in the absence and presence of S9 metabolic activation (Wolfreys and Hepburn, 2002). No clastogenic potential was observed in the bone marrow of male Crl:HanWist (Glx:BRL) rats when the phytosterol ester mixture was administered via oral gavage at doses up to 2000 mg/kg bw (Wolfreys and Hepburn, 2002). The Panel concluded that despite the different composition of the test materials relative to the composition of refined soybean oil extract, these results provided sufficient evidence to conclude that there was a lack of genotoxic potential for refined soybean oil extract. The phytosterol ester (PE) mixture, 49.4% sitosterol, 27.9% campesterol, 18.5% stigmasterol, and others was evaluated in a two-generation daily dietary administration reproductive study in rats. Administration of up to 8.1% w/w phytosterol esters, equivalent to a dose of 2.5-9.1 g PE/kg bw/day dependent on the period of the study, in the diet over two generations was found to have no effects on reproduction of parental F0 and F1 generation Wistar rats nor the development of the F1 and F2 pups or in the sexual maturation of the F1 weanlings. Therefore, 8.15% w/w phytosterol esters, equivalent to 2.5 g PE/kg bw/day at the most conservative period of the study, the NOAEL following daily administration for PE for two successive generations (Waalkens-Berendsen et al., 1999). A 13-week oral gavage administration study in male and female Sprague-Dawley rats with a mixture of plant sterol esters, isolated from soybean and esterified with oleic acid to increase solubility, was conducted at doses of 1000, 3000 and 9000 mg/kg bw/day. The composition of the test material was 49.4% sitosterol, 27.9% campesterol, 18.5% stigmasterol, and other minor components. Suppressed body weight gains in both sexes and cardiomyopathy with mononuclear cell infiltration were observed in high dose males. No other adverse effects were noted and a NOAEL of 3000 mg/kg bw/day was determined for both sexes (Kim et al., 2002). This is 600,000,000 times the daily per capita intake of refined soybean oil extract from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 1-ethyl-2-(1-pyrrolylmethyl)pyrrole (CAS 2204262-51-9) and concluded that it is GRAS (FEMA 4920) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This substance was evaluated individually within the context of the chemical group of pyridine, pyrrole and quinoline derivatives (JECFA, 2006, 2012; SLR, D3). The Panel calculated the anticipated *per capita* intake ("eaters only") of 1-ethyl-2-(1-pyrrolylmethyl)pyrrole from use as a flavor ingredient to be 0.0001 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. 1-Ethyl-2-(1-pyrrolylmethyl)pyrrole is predicted to be rapidly absorbed from the gastrointestinal tract and oxidized to polar metabolites that would be eliminated primarily in the urine. 1-Ethyl-2-(1-pyrrolylmethyl)pyrrole may also undergo cytochrome P450 (CYP450)-induced side chain oxidation to yield the corresponding alcohol that is expected to be excreted as either the glucuronic acid or sulfate conjugate (Gillam et al., 2000; Ruangyuttikarn et al., 1992; Thornton-Manning et al., 1993). 1-Ethyl-2-(1-pyrrolylmethyl)pyrrole did not increase reverse mutations in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2*uvr*A up to 500 µg/plate either in the presence or absence of S9 metabolic activation (Komai, 2017c). The structural relative 1*H*-pyrrole-2-carboxaldehyde did not increase reverse mutations in *S. typhimurium* strains TA98 or TA100 either in the presence or absence of S9 metabolic activation when tested up to 9510 µg/plate (Lee et al., 1994). Based on these results and also based on the structure and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for genotoxic potential of 1-ethyl-2-(1-pyrrolylmethyl)pyrrole when used as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding rebaudioside D 95% (CAS 63279-13-0) and concluded that it is GRAS (FEMA 4921) (Smith et al., 2005a) for use as a flavor 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 (Cohen et al., 2018; Smith et al., 2005b). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015).The Panel calculated the anticipated *per capita* intake ("eaters only") of rebaudioside D 95% from use as a flavor ingredient to be 111 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This substance is reported to occur in *Stevia rebaudiana* leaves (Chaturvedula et al., 2011; Wood et al., 1955). The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Metabolic 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., 2003a; Geuns et al., 2003b; Koyama et al., 2003a; Koyama et al., 2003b; Nikiforov et al., 2013; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha et al., 2014; Renwick and Tarka, 2008). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in in vitro mutagenicity assays, in vivo studies do not provide evidence of genotoxic effects (Nakajima, 2000b; Pezzuto et al., 1985; Pezzuto et al., 1986; Rumelhard 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 stevia extract stevioside, 70%. 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), This is greater than 48,000 times the anticipated daily *per capita* intake of rebaudioside D 95% from use as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding rebaudioside M 95% (CAS 1220616-44-3) and concluded that it is GRAS (FEMA 4922) (Smith et al., 2005a) for use as a flavor 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 (Cohen et al., 2018; Smith et al., 2005b). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Panel calculated the anticipated *per capita* intake ("eaters only") of Rebaudioside M 95% from use as a flavor ingredient to be 111 µg/person/day, which is above the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). This substance is reported to occur in *Stevia rebaudiana* leaves (Ohta et al., 2010). The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Metabolic 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., 2003a; Geuns et al., 2003b; Koyama et al., 2003a; Koyama et al., 2003b; Nikiforov et al., 2013; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha et al., 2014; Renwick and Tarka, 2008). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in in vitro mutagenicity assays, in vivo studies do not provide evidence of genotoxic effects (Nakajima, 2000b; Pezzuto et al., 1985; Pezzuto et al., 1986; Rumelhard 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 stevia extract stevioside, 70%. 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), This is greater than 48,000 times the anticipated daily *per capita* intake of rebaudioside M 95% from use as a flavoring ingredient.

The Panel reviewed the natural flavor complex GRAS applications and supporting information regarding Buchu leaves extract (*Barosma betulina* Bartl. et Wendl., *B. crenulata* (L.) Hook, *B. serratifolia* Willd.), Peppermint oil terpeneless (*Mentha piperita* L.) and Spearmint oil terpeneless (*Mentha spicata* L.) and concluded that they are GRAS for use as flavoring ingredients in the food categories and at the use levels specified in the GRAS applications (FEMA 4923-4925, 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., 2018). These natural flavor complexes are derived from commonly consumed herbs. The Panel considered the identity descriptions of each material to be adequate for FEMA GRAS evaluation. These natural flavor complexes 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 (Cohen et al., 2020).

The Panel reviewed the GRAS application and supporting information regarding (*Z*)-8-pentadecenal (CAS 65398-36-9) and concluded that it is GRAS (FEMA 4926) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This 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 (JECFA, 1999, 2006, 2012; SLR, M1). The Panel calculated the anticipated *per capita* intake ("eaters only") of (*Z*)-8-pentadecenal from use as a flavor ingredient to be 0.001 µg/person/day, which is above 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. (*Z*)-8-Pentadecenal is anticipated to be efficiently oxidized to the corresponding unsaturated carboxylic acid before proceeding into the beta-oxidation cycle for complete metabolism to innocuous products (Beedham, 1988; Eckfeldt and Yonetani, 1982; Feldman and Weiner, 1972; Nakayasu et al., 1978; Nelson and Cox, 2008). (*Z*)-8-Pentadecenal was negative for mutagenicity in an Ames assay in *S. typhimurium* strains TA100, TA1535, TA98, TA1537 and *E. coli* strain WP2*uvr*A in either the presence or absence of S9 metabolic activation by the pre-incubation method up to 5000 µg/plate (Komai, 2018a).Based on the results for the substance, as well as on

the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify any specific concerns related to the genotoxic potential of (*Z*)-8-pentadecenal. In a 98-day study in male and female SPF-derived CFE weanling rats, the structurally related substance, *cis*-3-hexen-1-ol (FEMA 2563), was provided at 310, 1250 and 5000 ppm in drinking water. Test article-related changes that were observed were increased relative kidney and adrenal weights in males administered 5000 ppm. A NOAEL of 1250 ppm, or approximately 120-150 mg/kg bw/day, was assigned (Gaunt et al., 1969). In a 90-day dietary administration study in male and female Sprague-Dawley rats, the structurally related substance, 10-undecenal (FEMA 3095), was administered at 14.3, 138.6, 382.3, and 1136 mg/kg bw/day. No toxicologically significant clinical observations or macroscopic abnormalities were detected. Histopathology analysis showed possible stomach irritation associated with the route of administration. Minimal centrilobular hepatocellular hypertrophy was observed in males at 138.6, 382.3, and 1136 mg/kg bw/day, but this was not accompanied by degenerative or inflammatory changes. The NOAEL was identified to be 14.3 mg/kg bw/day (Liwska and Watson, 2012; Tsang et al., 2018). This NOAEL is 858,000,000 times the anticipated daily *per capita* intake of (*Z*)-8-pentadecenal from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 4,7-decadienal (CAS 934534-30-2) and concluded that it is GRAS (FEMA 4927) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This 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 (JECFA, 1999, 2006, 2012; SLR, M1). The Panel calculated the anticipated *per capita* intake ("eaters only") of 4,7-decadienal from use as a flavor ingredient to be 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 has been reported to naturally occur in *Acorus calamus L.* oil (Calamus oil) (Njissen, 2019). 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. 4,7-Decadienal is anticipated to be efficiently oxidized to the corresponding unsaturated carboxylic acid before proceeding into the beta-oxidation cycle for complete metabolism to innocuous products (Feldman and Weiner, 1972; Eckfeldt and Yonetani, 1982; Nakayasu et al., 1978; Beedham, 1988; Nelson and Cox, 2008). An Ames assay was conducted for 4,7-decadienal in *S. typhimurium* strains TA1535, TA1537, TA98, TA100 and TA102, both with and without S9 metabolic activation using both the plate incorporation and pre-incubation methodologies. No substantial increase in revertant colony numbers of any of the five tested strains was observed at any dose level either in the presence or absence of S9 metabolic activation (Sokolowski, 2009).). Based on the results for the substance, as well as on the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify any specific concerns related to the genotoxic potential of 4,7-decadienal. In a 98-day study in male and female SPF-derived CFE weanling rats, the structurally related substance, *cis*-3-hexen-1-ol (FEMA 2563), was administered at doses of 310, 1250 and 5000 ppm via drinking water. The only non-transitory test article-related changes that were observed were increased relative kidney and adrenal weights in males administered 5000 ppm. A NOAEL of 1250 ppm, or approximately 120-150 mg/kg bw/day, was assigned (Gaunt et al., 1969). In a 90-day dietary administration study in male and female Sprague-Dawley rats, the structurally related substance, 10-undecenal (FEMA 3095), was administered at 14.3, 138.6, 382.3, and 1136 mg/kg bw/day. No toxicologically significant clinical observations were detected. No macroscopic abnormalities were detected. Histopathology examination showed possible stomach irritation associated with the route of administration. Minimal centrilobular hepatocellular hypertrophy was observed in males at 138.6, 382.3, and 1136 mg/kg bw/day, but this was not accompanied by degenerative or inflammatory changes. The NOAEL was concluded to be 14.3 mg/kg bw/day (Liwska and Watson, 2012; Tsang et al., 2018). This is greater than 214,000 times the anticipated daily *per capita* intake of 4,7-decadienal from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 2-methylthiophene (CAS 554-14-3) and concluded that it is GRAS (FEMA 4928) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This substance was evaluated individually within the context of the chemical group of sulfur-containing heterocyclic compounds (Cohen et al., 2017b; JECFA, 2003, 2007, 2012, 2015; SLR, D15). The Panel calculated the anticipated *per capita* intake ("eaters only") of 2-methylthiophene from use as a flavor ingredient to be 0.01 µg/person/day, which is below the threshold of toxicological concern for structural class II (540 µg/person/day) (Munro et al., 1996). The material is known to occur in nature in beef (0.0072-0.23 ppm), clams, coffee, egg, papaya (0.05-0.1 ppm), pork, and shrimp. Based on the quantitative concentration data that are available, a consumption ratio of 23,000 could be calculated (Njissen et al., 2019; Stofberg and Grunschober, 1987). 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-Methylthiophene is predicted to undergo ring epoxidation and *S*-oxidation. The subsequent intermediates are expected to conjugate with glutathione and then be eliminated in the urine as the mercapturic acid derivatives (Cohen et al., 2017a). In an Ames assay using *S. typhimurium* strains TA98 and TA100, 2-methylthiophene did not increase the frequency of revertant colonies in either the absence or presence of S9 metabolic activation (Komai, 2018b). Two additional Ames assays in *S. typhimurium* strains TA98, TA100 and TA102 did not show signs of mutagenic activity either in the absence or presence of S9 metabolic activation, but only limited study details were provided (Aeschbacher et al., 1989; Lee et al., 1994). Based on these results 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-methylthiophene. In an OECD 408 compliant 90-day dietary administration study in male and female Sprague-Dawley rats, pentylthiophene (FEMA 4387) a structurally related substance, was administered at mean achieved dosages of either 1.4, 7, or 33 mg/kg bw/day in males and 1.5, 8 or 39 mg/kg bw/day in females. No significant differences were found in mortality, body weight, food consumption or food efficiency. The clinical and ophthalmological examinations did not reveal any effects, nor did histopathological evaluation. Statistically significant changes were observed in hematology, coagulation, and urinalysis at the two highest dose levels, but these were mostly within the historical control ranges, and did not have accompanying histological findings. Therefore, these

changes were not considered to be biologically relevant. Additionally, some high dose females were observed to have increased relative kidney weight, but the change was not considered to be biologically relevant since no accompanying histological effects were identified. The NOAEL of 33 and 39 mg/kg bw/day were identified for male and female rats, respectively (Bauter, 2013). The NOAEL of 33 mg/kg bw/day was greater than 198,000,000 times the anticipated daily *per capita* intake of 2-methylthiophene from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 4-methylidene-2-(2-methylprop-1-enyl)oxane (CAS 60857-05-8) and concluded that it is GRAS (FEMA 4929) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This substance was evaluated individually within the context of the chemical group of aliphatic and aromatic ethers (JECFA, 2004, 2012; SLR, C22, D12). The Panel calculated the anticipated *per capita* intake ("eaters only") of 4-methylidene-2-(2-methylprop-1-enyl)oxane 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 Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. 4-Methylidene-2-(2-methylprop-1-enyl)oxane is predicted to be hydroxylated on the methyl groups of the isopropenyl moiety. The corresponding metabolite will be excreted either unchanged or after conjugation (Smith et al., 2018). In an Ames assay in *S. typhimurium* strains TA1535, TA1537, TA98, TA100, and *E. coli* WP2 uvrA, 4-methylidene-2-(2-methylprop-1-enyl)oxane did not increase the frequency of revertant colonies either in the absence or presence of S9 metabolic activation (Komai, 2018c). In an Ames assay in *S. typhimurium* strains TA1535, TA1537, TA98, TA100 and TA102 the structurally related substance, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran (FEMA 3236), did not increase the frequency of revertant mutations in the absence or presence of S9 metabolic activation (Verspeek-Rip, 2002). In two separate additional Ames assays in *S. typhimurium* strains TA1535, TA97a, TA98, TA100 and TA102 the same structural relative did not increase the frequency of revertant colonies in the absence or presence of S9 metabolic activation (Scheerbaum, 2001). In *in vitro* micronucleus tests in Chinese hamster V79 cells the same structural relative did not induce statistically significant increases in the frequency of micronuclei in either the absence or presence of S9 metabolic activation in any treatment arm or treatment concentration tested (Wollny, 2012). In two OECD 474 compliant *in vivo* micronucleus assays, structurally related substance, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran (FEMA 3236), was administered by gavage to male and female Crl:NMRI mice at concentrations of 250, 500 or 1000 mg/kg bw. In the first experiment, high variability in micronucleated polychromatic erythrocyte incidence was noted, yielding a weak, dose-related increase in the number of polychromatic erythrocytes containing micronuclei. These increases slightly exceeded the historical control range in the mid and high-dose groups but were not statistically significant when compared to the controls. The authors considered the increase not to be biologically relevant. In the second experiment, a weak, dose-related increase in micronucleated polychromatic erythrocyte incidence was observed. The number of micronucleated polychromatic erythrocytes in the high dose group slightly exceeded the vehicle and negative control values but was considered not to be biologically relevant by the authors as they were not statistically significant (Schulz, 2012). Based on the results for the substance and the structurally related substance, and also 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 4-methylidene-2-(2-methylprop-1-enyl)oxane.

The Panel reviewed the GRAS application and supporting information regarding 4-isopropoxycinnamaldehyde (CAS 159017-89-7) and concluded that it is GRAS (FEMA 4930) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This substance was evaluated individually within the context of the chemical group of cinnamyl alcohol and related substances (JECFA, 2000, 2017; SLR, C11; SLR, C16). The Panel calculated the anticipated *per capita* intake ("eaters only") of 4-isopropoxycinnamaldehyde from use as a flavor ingredient to be 15 µg/person/day, which is below the threshold of toxicological concern for structural class I (1800 µg/person/day) (Munro et al., 1996). The Panel considered the specification of the material to be adequately characterized by the purity assay and supporting spectral data provided for FEMA GRAS evaluation. 4-Isopropoxycinnamaldehyde is anticipated to be metabolized by oxidation to 4-isopropoxycinnamic acid. This would then be converted to the corresponding coenzyme A derivative, which would then undergo glycine conjugation or beta-oxidation, possibly leading to the formation of the 4-isopropoxybenzoyl coenzyme A derivative. This is then either conjugated with glycine, yielding 4-isopropoxyhippuric acid, or hydrolyzed to yield free 4-isopropoxybenzoic acid which is then excreted (Nutley et al., 1994; Samuelsen et al., 1986; Snapper et al., 1940; Solheim and Scheline, 1973, 1976). In an Ames assay in *S. typhimurium* strains TA98 and TA100, 4-isopropoxycinnamaldehyde did not increase the frequency of revertant colonies in either the absence or presence of S9 metabolic activation (Kawaguchi and Komai, 2016). In an OECD 471 compliant Ames assay in *S. typhimurium* strains TA1535, TA1537, TA100, TA98, and *E. coli* strain WP2*uvr*A, 4-isopropoxycinnamaldehyde did not increase the frequency of revertant colonies in either the absence or presence of S9 metabolic activation (Yamaguchi, 2017). In an OECD 487 compliant *in vitro* micronucleus induction assay in TK6 cells, 4-isopropoxycinnamaldehyde did not induce statistically significant increases in the frequency of micronuclei in the presence of S9 metabolic activation in a short-term treatment condition. A dose-dependent increase was observed without metabolic activation in the short-term treatment condition, and a significant, dose-dependent increase was observed in the continuous treatment condition in the absence of S9 metabolic activation (Fukuda, 2017). In an OECD 474 compliant rat bone marrow micronucleus study in Crl:CD(SD) rats, 4-isopropoxycinnamaldehyde was administered by gavage at doses of 250, 500, or 1000 mg/kg twice at 24-hour intervals. The test substance did not increase the frequency of micronuclei relative to controls. Clinical observations in the dose range finder at 2000 mg/kg included decreased spontaneous movement and bradypnea, providing evidence that the substance could achieve systemic exposure (Ishii, 2017). On the basis of a weight-of-evidence approach, including the negative results observed in the Ames assays

conducted on the test substance and that the positive results observed in the *in vitro* micronucleus assay were not confirmed in the *in vivo* study, the Panel concluded that it did not identify a specific concern for the genotoxic potential of 4-isopropoxycinnamaldehyde. In a 90-day dietary study in rats, the structurally related substance, *o*-methoxycinnamaldehyde (FEMA 3181), was administered at average doses of 47.1 mg/kg bw/day and 52.2 mg/kg bw/day for males and females, respectively. There were no biologically relevant findings in the study (Posternak et al., 1969). In a 90-day dietary toxicity study, structural relative, *o*-methoxycinnamaldehyde (FEMA 3181) was administered at concentrations of 47.1 and 52.2 mg/kg bw/day in the feed. There were no significant differences in growth, body weights, food intake, hematology or clinical chemistry measurements. Organ weights or pathology observations between test and control groups There were no differences between the exposure groups and controls The NOAEL of 47.1 mg/kg bw/day is greater than 188,000 time the anticipated daily *per capita* intake of 4-isopropoxycinnamaldehyde from use as a flavor ingredient.

The Panel reviewed the natural flavor complex GRAS application and supporting information regarding glucosylated steviol glycosides, 90% (CAS 57817-89-7) and concluded that the substance is GRAS (FEMA 4931) (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 substance was evaluated within the context of the procedure for the safety evaluation of natural flavor complexes (Cohen et al., 2018; Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of glucosylated steviol glycosides, 90% from use as a flavor ingredient to be 713 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 identity description of the material to be adequate for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Metabolic 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., 2003a; Geuns et al., 2003b; Koyama et al., 2003a; Koyama et al., 2003b; Nikiforov et al., 2013; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha et al., 2014; Renwick and Tarka, 2008). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in in vitro mutagenicity assays, in vivo studies do not provide evidence of genotoxic effects (Nakajima, 2000b; Pezzuto et al., 1985; Pezzuto et al., 1986; Rumelhard 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 stevia extract stevioside, 70%. 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 7,500 times the anticipated daily *per capita* intake of glucosylated steviol glycosides, 90% from use as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding *Chaenomeles speciosa* leaf extract (CAS 2263901-84-2) and concluded that it is GRAS (FEMA 4932) (Smith et al., 2005a) for use as a flavor 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 (Cohen et al., 2018; Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of *Chaenomeles speciosa* leaf extract from use as a flavor ingredient was calculated to be 71 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Cramer et al., 1984; Munro et al., 1996). The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Panel concluded that the principal components of *Chaenomeles speciosa* leaf extract were carbohydrate in nature, and that these were either endogenous or would be readily metabolized in the body to yield innocuous products that would be excreted or incorporated into the biosynthesis of other biomolecules. The Panel found the metabolism data adequate for the FEMA GRAS evaluation. In an Ames assay in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2 *uvr*A, *Chaenomeles speciosa* leaf extract did not increase the frequency of revertant colonies in the presence or absence of S9 in an OECD guideline 471 compliant Ames assay using both the plate incorporation and pre-incubation methodologies (Roy, 2019). In an OECD guideline 487 compliant *in vitro* micronucleus assay, no significant increase in micronuclei induction was observed when *Chaenomeles speciosa* leaf extract was incubated with human lymphocytes at 156.25-5,000 µg/ml for 4 hours in the presence and absence of S9 as well as for 24 hours win the absence of S9 (Vashi, 2019). Based on these results, the Panel did not identify a specific concern for the genotoxic potential of *Chaenomeles speciosa* leaf extract.

The Panel reviewed the GRAS application and supporting information regarding *Eriobotrya japonica* leaves extract (CAS 91770-19-3) and concluded that it is GRAS (FEMA 4933) (Smith et al., 2005a) for use as a flavor 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 (Cohen et al., 2018; Smith et al., 2005b). The Panel calculated the anticipated *per capita* intake ("eaters only") of *Eriobotrya japonica leaves extract* from use as a flavor ingredient was calculated to be 14 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day)(Munro et al., 1996). The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Panel concluded that the principal components of *Eriobotrya japonica* leaves extract would be readily metabolized in the body to yield innocuous products that would be excreted or incorporated into the biosynthesis of other biomolecules. The Panel found the metabolism data adequate for the FEMA GRAS evaluation. No increases in reverse mutations were observed when 5 concentrations of *Eriobotrya japonica* leaves

extract ranging from 15.9 to 5000 ug/plate were tested in *S. typhimurium* strains TA98, TA100, TA97a and TA1535 and *E. coli* WP2*uvr*A pKM101 in the absence and presence of S9 (Swartz, 2018). In an *in vivo* micronucleus assay in male and female Balb/c mice, gavage administration of doses up to 10,000 mg/kg bw/day of an ethanolic *Eriobotrya japonica* leaves extract produced no statistically significant increases in the frequency of micronuclei (Jin and Dong, 2017). Based on these results, the Panel did not identify a specific concern for the genotoxic potential of *Eriobotrya japonica* leaves extract. In a 28-day toxicity study in male and female ICR mice were administered an *Eriobotrya japonica* leaves extract analogous to the test material at doses of 150, 300, or 600 mg/kg bw/day via gavage administration. The highest dose resulted in a statistically significant reduction in body weight in the high dose males. High dose males and females showed statistically significant changes in several clinical biochemistry parameters, but without corresponding histopathology. The author of the study determined that the changes in clinical biochemistry parameters were not considered biologically relevant. Based on weight reductions and biochemical changes at the highest dose, the Panel determined a NOAEL of 300 mg/kg bw/day. This is greater than 1,280,000 times the daily per capita intake of *Eriobotrya japonica* leaves extract from use as a flavor ingredient (Li et al., 2017).

The Panel reviewed the GRAS application and supporting information regarding sodium gluconate (CAS 527-07-1) and concluded that it is GRAS (FEMA 4934) (Smith et al., 2005a) for use as a flavor 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). This substance was evaluated individually within the context of the chemical group of aliphatic poly-hydroxy compounds and derivatives (JECFA, 2001; SLR, B1F). The Panel calculated the anticipated *per capita* intake ("eaters only") of sodium gluconate from use as a flavor ingredient to be 1070 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 honey (Ramachandran et al., 2006). 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). Sodium gluconate is predicted to be excreted unchanged in the urine and any sodium gluconate absorbed in the gastrointestinal tract is expected to be metabolized to innocuous products. *d*-Gluconic acid is an endogenously occurring metabolite of glycolysis (Smith et al., 2018). In an Ames assay in *S. typhimurium strains* TA1535, TA1537, and TA1538 and *Saccharomyces cerevisiae* (strain D4), sodium gluconate did not increase the frequency of revertant colonies either in the absence or presence of S9 metabolic activation (Brusick, 1975). Sodium gluconate tested negative for genotoxicity in both single dose and repeated oral administration (4 days) chromosomal aberration assays in mouse bone marrow cells (Yamashita, 1974). In an Ames assay in *S. typhimurium* strains TA97, TA98, TA100, and TA104 the structurally related substance, malic acid (FEMA 2655), did not increase the frequency of revertant colonies in either the absence or presence of S9 metabolic activation. Based on the results for the substance and the structurally related substance, and also 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 sodium gluconate. A 28-day gavage study of sodium gluconate provided in the feed of male and female beagle dogs (4/sex/group) resulted in a NOAEL of 500 mg/kg bw/day (Okamoto, 1995). In a 28-day dietary study, Crj:CD(SD) Sprague-Dawley SPF rats were administered concentrations equal to 0, 1.25, 2.5, or 5% w/w sodium gluconate, or 0, 1000, 2000, and 4100 mg/kg bw/day (Mochizuki, 1997). The authors concluded that the NOEL was 4100 mg/kg bw per day. In a repeat dose 28-day toxicity study, male and female Crj:CD (SD) rats (12/sex/group) were administered sodium gluconate by gavage at doses of 500, 1000 and 2000 mg/kg bw/day (Mochizuki, 1995). No toxicologically significant changes were observed at any dose level. Subsequent histopathological examinations revealed a thickening of the stomach lining in male rats at the highest dose level. The Panel agreed with the author's conclusion that this was not of toxicological concern to humans. The NOAEL was concluded by the Panel to be the top dose of 4100 mg/kg bw/day for both male and female rats, which is greater than 229,000 times the daily per capita intake of sodium gluconate from use as a flavor ingredient.

The Panel reviewed the GRAS application and supporting information regarding 3-methylbutane-1,3-dithiol (CAS 98139-71-0) and concluded that it is GRAS (FEMA 4935) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic sulfides and thiols (JECFA, 2000, 2004, 2008, 2011; SLR, D1). The Panel calculated the anticipated *per capita* intake ("eaters only") of 3-methylbutane-1,3-dithiol from use as a flavor ingredient to be 0.01 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. 3-Methylbutane-1,3-dithiol is expected to be methylated and undergo enzymatic oxidation to yield the corresponding sulfoxide or sulfone, followed by excretion. Alternatively, the thiols may react with glutathione to form mixed disulfides that can then undergo reduction and oxidative desulfuration, or oxidation to sulfonic acid via the thiosulfinate and sulfinic acid intermediates (Smith et al., 2018). Negative results were obtained in Ames assays for 3-methylbutane-1,3-dithiol in *S. typhimurium* TA98 and TA100 with and without metabolic activation (Komai, 2018d). In an Ames assay of structurally related substance, 1,2-ethanedithiol (FEMA 3484), conducted in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537, no increase in the frequency of revertant colonies was observed in the presence and absence of S9 metabolic activation at up to 5000 µg/plate using the plate incorporation method (PhillipsPetroleumCompany, 1990). In the mouse lymphoma forward mutation assay conducted in L5178Y TK +/- mouse lymphoma cells, the same structurally related substance was concluded by the study author to be mutagenic due to an increase in the induction of forward mutations in the absence of S9. No increase in forward mutations was observed in the

presence of S9 metabolic activation (Pence, 1982). The Panel concluded that though the study was valid, the rates of forward mutation reported in the absence of S9 metabolic activation were within the global historical controls and therefore 1,2-ethanedithiol (FEMA 3484) is of no genotoxic concern (Moore et al., 2003; Moore et al., 2006). The same structurally related substance was considered by the study author to be mutagenic in a sister chromatid exchange assay conducted in Chinese hamster ovary cells due to a positive response observed at the two highest concentrations of 16 and 50 μg/ml without metabolic activation and at concentrations greater than 1.6 μg/ml with metabolic activation (Pence et al., 1983). However, the Panel noted that this study is of questionable relevance since the OECD withdrew its guideline for this assay (OECD, 2014). Based on the negative Ames tests, and on the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a concern for the genotoxic potential of 3-methylbutane-1,3-dithiol. No hematological, biochemical and urinary adverse effects were observed when a mean daily intake of 0.703 mg/kg bw/day of the structurally related substance, 2,3-butanedithiol (FEMA 3477), was provided in the diet to male and female Sprague-Dawley rats for 90 days (Cox et al., 1974a). The NOAEL of 0.703 mg/kg bw/day established for the structurally related substance (Cox et al., 1974a) is 4,200,000 times the anticipated daily *per capita* intake of 3-methylbutane-1,3-dithiol from use as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding rebaudioside E ≥85% (CAS 63279-14-1) and concluded that it is GRAS (FEMA 4936) (Smith et al., 2005a) for use as a flavor 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 (Cohen et al., 2018; Smith et al., 2005b). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Panel calculated the anticipated *per capita* intake ("eaters only") of rebaudioside E ≥85% from use as a flavor ingredient to be 83 μg/person/day, which is below the threshold of toxicological concern for structural class III (90 μg/person/day) (Munro et al., 1996). This substance is reported to occur in *Stevia rebaudiana* leaves (Ibrahim et al., 2014). The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013). Metabolic 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., 2003a; Geuns et al., 2003b; Koyama et al., 2003a; Koyama et al., 2003b; Nikiforov et al., 2013; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha et al., 2014; Renwick and Tarka, 2008). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in in vitro mutagenicity assays, in vivo studies do not provide evidence of genotoxic effects (Nakajima, 2000b; Pezzuto et al., 1985; Pezzuto et al., 1986; Rumelhard 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 stevia extract stevioside, 70%. 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). This is greater than 64,000 times the anticipated daily *per capita* intake of rebaudioside E ≥85% from use as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding rebaudioside I 95% (CAS 1220616-34-1) and concluded that it is GRAS (FEMA 4937) (Smith et al., 2005a) for use as a flavor 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 (Cohen et al., 2018; Smith et al., 2005b). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Panel calculated the anticipated *per capita* intake ("eaters only") of rebaudioside I 95% from use as a flavor ingredient to be 83 μg/person/day, which is below the threshold of toxicological concern for structural class III (90 μg/person/day) (Munro et al., 1996). This substance is reported to occur in *Stevia rebaudiana* leaves (Prakash et al., 2014). The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. The Panel evaluated sensory data included within the application and found it satisfactory with regard to intended conditions of use for the flavoring ingredient (Harman and Hallagan, 2013).Metabolic 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., 2003a; Geuns et al., 2003b; Koyama et al., 2003a; Koyama et al., 2003b; Nikiforov et al., 2013; Purkayastha et al., 2015; Purkayastha et al., 2016; Purkayastha et al., 2014; Renwick and Tarka, 2008). The genotoxicity of the major marker constituents (steviol glycosides) has been thoroughly examined in a wide range of studies. While some positive results are reported in in vitro mutagenicity assays, in vivo studies do not provide evidence of genotoxic effects (Nakajima, 2000b; Pezzuto et al., 1985; Pezzuto et al., 1986; Rumelhard 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 stevia extract stevioside, 70%. 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). This is greater than 64,000 times the anticipated daily *per capita* intake of rebaudioside E ≥85% from use as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding *S*-methyl 5-(1-ethoxyethoxy) tetradecanethioate (CAS 2180135-08-2) and concluded that it is GRAS (FEMA 4938) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). This substance was evaluated individually within the context of the chemical group of simple aliphatic and aromatic sulfides and thiols (JECFA, 2000, 2004, 2008, 2011; SLR, D1). The Panel calculated the anticipated *per capita* intake ("eaters only") of *S*-methyl 5-(1-ethoxyethoxy)tetradecanethioate from use as a flavor ingredient to be 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. *S*-methyl 5-(1-ethoxyethoxy)tetradecanethioate is expected to undergo hydrolysis of the acetal or thioester to yield ethanol, acetaldehyde, an aliphatic 5-hydroxycarboxylic acid and methanethiol. Hydrolysis of the acetal group may result in ethanol, acetaldehyde and 5-hydroxy methyl thioester and hydrolysis of the thioester group may result in acetal carboxylic acid and methanethiol. Hydroxycarboxylic acid and their ester and acetal derivatives are readily hydrolyzed, absorbed and fully metabolized through the fatty acid β-oxidation pathway followed by excretion. Methanethiol is expected to undergo methylation and enzymatic oxidation to yield the corresponding sulfoxide by sulfone, followed by excretion. Methanethiol may also react with glutathione to form mixed disulfides that can undergo reduction and oxidative desulfuration, or oxidation to sulfonic acid via thiosulfinate and sulfinic acid intermediates. Additionally, methanethiol may be enzymatically oxidized to yield the corresponding sulfenic acid, sulfinic acid and ultimately, sulfonic acid. Sulfinic and sulfonic acids are water soluble and readily excreted (Bosron and Ting-Kai, 1980; Morgareidge, 1962; Williams, 1959). *S*-Methyl 5-(1-ethoxyethoxy)tetradecanethioate tested negative for mutagenicity in an Ames assay conducted in *S. typhimurium* TA98 and TA100 in the presence and absence of S9 metabolic activation at concentrations up to 5000 μg/plate using the pre-incubation method (Komai, 2018e). Based on these results as well as on the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a concern for the genotoxic potential of *S*-methyl 5-(1-ethoxyethoxy)tetradecanethioate.

The Panel reviewed the GRAS application and supporting information regarding *S*-methyl 5-(1-ethoxyethoxy)decanethioate (CAS 2180135-09-3) and concluded that it is GRAS (FEMA 4939) (Smith et al., 2005a) for use as a flavor in the food categories and at the use levels specified in the GRAS application (see Table 2). The Panel calculated the anticipated *per capita* intake ("eaters only") of *S*-methyl 5-(1-ethoxyethoxy)decanethioate 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. *S*-methyl 5-(1-ethoxyethoxy) decanethioate is expected to undergo hydrolysis of the acetal or thioester groups to yield ethanol, acetaldehyde, an aliphatic 5-hydroxycarboxylic acid and methanethiol. Hydrolysis of the acetal group may result in ethanol, acetaldehyde and 5-hydroxy methyl thioester and hydrolysis of the thioester group may result in acetal carboxylic acid and methanethiol. Hydroxycarboxylic acid and their ester and acetal derivatives are readily hydrolyzed, absorbed and fully metabolized through the fatty acid β-oxidation pathway followed by excretion. Methanethiol is expected to undergo methylation and enzymatic oxidation to yield the corresponding sulfoxide by sulfone, followed by excretion. Methanethiol may also react with glutathione to form mixed disulfides that can undergo reduction and oxidative desulfuration, or oxidation to sulfonic acid via thiosulfinate and sulfinic acid intermediates. Additionally, methanethiol may be enzymatically oxidized to yield the corresponding sulfenic acid, sulfinic acid and ultimately, sulfonic acid. Sulfinic and sulfonic acids are water soluble and readily excreted (Bosron and Ting-Kai, 1980; Morgareidge, 1962; Williams, 1959). *S*-Methyl 5-(1-ethoxyethoxy) decanethioate tested negative for mutagenicity in an Ames assay conducted in *S. typhimurium* TA98 and TA100 in the presence and absence of S9 metabolic activation at concentrations up to 5000 μg/plate using the pre-incubation method (Komai, 2018e). Based on these results as well as on the structure of the substance and the identity and arrangement of functional groups therein, the Panel did not identify a concern for the genotoxic potential of *S*-methyl 5-(1-ethoxyethoxy)decanethioate.

The Panel reviewed the GRAS application and supporting information regarding β-bisabolene ≥88% (CAS 495-61-4) and concluded that it is GRAS (FEMA 4940) (Smith et al., 2005a) for use as a flavor 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 (Cohen et al., 2018; Smith et al., 2005). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Panel calculated the anticipated *per capita* intake ("eaters only") of β-bisabolene ≥88% from use as a flavor ingredient to be 277 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 identity description of the material to be adequate for FEMA GRAS evaluation. The major marker constituent, β-bisabolene, is expected to undergo oxidative metabolism in a manner similar to limonene, either by side chain oxidation or epoxidation of the alkene groups. Alternatively, alkene groups could undergo epoxidation followed by hydrolysis and formation of glucuronic acid or sulfate conjugates, leading to rapid elimination in the urine (Smith et al., 2018). The structurally-related substance, *d*-limonene (FEMA 2633), gave no evidence of mutagenicity in an Ames assay in *S. typhimurium* strains TA98, TA100, TA102, TA1535, TA1537, TA1538, UTH8413, and UTH8414 either in the presence or absence of S9 metabolic activation (Connor et al., 1985; Florin et al., 1980b; Haworth et al., 1983; Heck et al., 1989; Müller et al., 1993). *d*-Limonene was also negative in a chromosomal aberration study in Chinese hamster ovary

(CHO) cells at up to 500 µg/ml and a mouse lymphoma forward mutation assay in L5178Y cells up to a maximum concentration of 100 µg/ml, either in the presence or absence of S9 metabolic activation (Anderson et al., 1990; Heck et al., 1989; Myhr et al., 1990). In an OECD 471 compliant Ames assay using *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537, the structurally related substance, bisabolene (a mixture of isomers) (FEMA 3331), did not increase the frequency of revertant colonies in either the absence or presence of S9 metabolic activation using both the plate incorporation and pre-incubation methodology (OECD, 1997; Poth, 2002). Based on these results as well as 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 β-bisabolene ≥88%. A 90-day gavage study of *d*-limonene (FEMA 2633) in male and female F344/N rats (10/sex/dose) resulted in a NOAEL of 215 mg/kg bw/day for female rats (NTP, 1990) which is 46,000, times the anticipated daily *per capita* intake of β-bisabolene ≥88% from use as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding nootkatone complex (CAS 4674-50-4) and concluded that it is GRAS (FEMA 4941) (Smith et al., 2005a) for use as a flavor 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 (Cohen et al., 2018; Smith et al., 2005b). This material was evaluated within the context of the procedure for the FEMA GRAS evaluation of flavor ingredients produced through biotechnology processes (Cohen et al., 2015). The Panel calculated the anticipated *per capita* intake (“eaters only”) of nootkatone complex from use as a flavor ingredient to be 69 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). A consumption ratio of 11 could be calculated from the quantitative data, indicating that the intake of nootkatone is predominantly from natural occurrence in foodstuffs (Njissen, 2019). The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. Nootkatone complex is expected to undergo metabolism in a manner similar to other lipophilic ketones or those with sterically hindered functional groups, through oxidation at a ring position followed by conjugation and excretion in the urine. Alternatively, reduction of the functional ketone group could occur followed by conjugation and excretion in the urine (Smith et al., 2018). In an Ames assay for major marker constituent, nootkatone (FEMA 3166), conducted in *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537, no increase in the frequency of revertant colonies was observed in either the presence or absence of S9 (Marzin, 1998). An *in vitro* micronucleus assay for the same major marker substance resulted in no statistically significant effects on micronuclei frequency in the presence and absence of S9 (Stone, 2011). In a liquid microplate Ames assay, up to 160 µg/ml of nootkatone complex did not increase the frequency of revertant colonies when tested in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* combined strains WP2(pKMN101) and WP2uvrA (Ziemianska, 2017). In an in vivo micronucleus assay, nootkatone complex did not increase the frequency of micronucleated bone marrow cells at up to 1000 mg/kg bw/day when interperitoneally injected in male NMRI mice (Donath, 2017). Based on these results as well as on the composition 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 nootkatone complex. A 28-day gavage study of major marker substance, nootkatone (FEMA 3166), in male and female Sprague-Dawley Crl:CD (SD) IGS BR rats resulted in observations of *α*2u-globulin nephropathy, an effect determined to be specific to male rats and therefore not relevant to human exposure.A NOAEL of 10 mg/kg bw/day was determined (Jones et al., 2004). This is greater than 8600 times the anticipated daily *per capita* intake of nootkatone complex from use as a flavoring ingredient.

The Panel reviewed the GRAS application and supporting information regarding modified guaiac wood extract (CAS 2247239-04-7) and concluded that it is GRAS (FEMA 4942) (Smith et al., 2005a) for use as a flavor 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 (Cohen et al., 2018; Smith et al., 2005). The Panel calculated the anticipated *per capita* intake (“eaters only”) of modified guaiac wood extract from use as a flavor ingredient to be 1 µg/person/day, which is below the threshold of toxicological concern for structural class III (90 µg/person/day) (Munro et al., 1996). The Panel considered the identity description of the material to be adequate for FEMA GRAS evaluation. Metabolic data of representative members of the principal congeneric groups, as well as anticipated levels of intake of this substance, indicate that constituents in these congeneric groups would be metabolized to innocuous products based on well-established metabolic pathways (Smith et al., 2018). In an OECD 471 compliant Ames assay of modified guaiac wood extract conducted in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as *E. coli* strain WP2*uvr*A, no evidence of mutagenicity was observed in the presence and absence of S9 metabolic activation at doses up to 3160 µg/plate using both the plate incorporation and pre-incubation methodologies (Spruth, 2017). No induction of micronuclei relative to controls was observed in an *in vitro* micronucleus study for modified guaiac wood extract when incubated in human lymphocytes for 4 hours in the presence and absence of S9 at doses up to 156 µg/ml or for 24 hours in the absence of S9 at doses up to 114 µg/ml (Naumann, 2018). An Ames assay for triethyl citrate (FEMA 3083), a major marker constituent of modified guaiac wood extract, yielded negative results in the presence and absence of S9 at doses up to 5000 µg/plate (Bhalli, 2015a). No genotoxicity was observed in an *in vitro* micronucleus assay for triethyl citrate (FEMA 3083) incubated in human peripheral blood lymphocytes (Bhalli, 2015b). Based on these results as well as on the identity of the major marker constituents and the identity and arrangement of functional groups therein, the Panel did not identify a specific concern for the genotoxic potential of modified guaiac wood extract.

References

Adams, T.B., Greer, D.B., 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., 1998. The FEMA GRAS Assessment of Lactones Used as Flavour Ingredients. Food and Chemical Toxicology 36, 249-278.

Adams, T.B., McGowen, M.M., Williams, M.C., Cohen, S.M., Feron, V.J., Goodman, J.I., Marnett, L.J., Munro, I.C., Portoghese, P.S., Smith, R.L., Waddell, W.J., 2007. The FEMA GRAS assessment of aromatic substituted secondary alcohols, ketones, and related esters used as flavor ingredients. Food and Chemical Toxicology 45, 171-201.

Aeschbacher, H.U., Wolleb, U., Löliger, J., Spadone, J.C., Liardon, R., 1989. Contribution of Coffee Aroma Constituents to the Mutagenicity of Coffee. Food and Chemical Toxicology 27, 227-232.

Amano, H., Kazamori, D., Itoh, K., Kodera, Y., 2015. Metabolism, excretion, and pharmacokinetics of S-allyl-L-cysteine in rats and dogs. Drug Metab Dispos 43, 749-755.

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.

Aoyama, N., 2017. Micronucleus test of CA-047 ITO in mice, UBE Scientific Analysis Laboratory, Inc., Yamaguchi Prefecture, Japan. Unpublished report provided to the FEMA Expert Panel.

Api, A., Smith, R.L., Pipino, S., Marczylo, T., de Matteis, F., 2004. Evaluation of the oral subchronic toxicity of AHTN (7-Acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene) in the rat. Food and Chemical Toxicology 42, 791-801.

Api, A.M., Ritacco, G., Sipes, I.G., 2013. Disposition and excretion of 14C-AHTN (7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene) and 14c-hhcb (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta-gamma-2-benzopyran) after intravenous administration to Sprague-Dawley rats and domestic pigs. International journal of toxicology 32, 288-295.

Api, A.M., San, R.H.C., 1999. Genotoxicity tests with 6-acetyl-1,1,2,4,4,7-hexamethyltetraline and 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-y-2-benzopyran. Mutation research 446, 67-81.

Asquith, J.C., 1990a. Bacterial reverse mutation assay ST 14C 89, Toxicol Laboratories Limited, Herefordshire, England. Unpublished report provided to the FEMA Expert Panel.

Asquith, J.C., 1990b. Bacterial reverse mutation assay ST 13C 89. Toxicol Laboratories Limited, Herefordshire, England. Unpublished report provided to the FEMA Expert Panel.

Bauter, M., 2017. 2-Methyl-4-oxopentane-2-thiol: A 90-day oral gavage study in rats. Product Safety Labs, Dayton, New Jersey. Unpublished report provided to the FEMA Expert Panel by the International Organization of the Flavor Industry.

Bauter, M.R., 2013. 2-Pentylthiophene: a 90-day dietary study in rats, Product Safety Labs, Dayton, NJ, USA. Unpublished report provided to the FEMA Expert Panel by the International Organization of the Flavor Industry.

Beedham, C., 1988. Molybdenum Hydroxylases, Enzyme Systems that Metabolize Drugs and Other Xenobiotics. John Wiley & Sons, Ltd, pp. 147-187.

Beevers, C., 2014. 3,4-Dimethyl-5-pentylidenefuran-2(5H)-one: Combined Comet assay in the liver and a bone marrow micronucleus test in treated rats.Covance Laboratories Ltd., North Yorkshire, England. Unpublished report provided to the FEMA Expert Panel by the International Organization of the Flavor Industry.

Benvenga, S., Ruggeri, R.M., Russo, A., Lapa, D., Campenni, A., Trimarchi, F., 2001. Usefulness of L-carnitine, a naturally occurring peripheral antagonist of thyroid hormone action, in iatrogenic hyperthyroidism: a randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab 86, 3579-3594.

Bhalli, J., 2014a. cis-3-hexenol (CAS # 928-96-1): Bacterial reverse mutation assay: plate incorporation method with a confirmatory assay, Covance Laboratories Inc., Greenfield, IN, USA. Unpublished report to the FEMA Expert Panel. Provided by the Research Institute for Fragrance Materials.

Bhalli, J., 2014b. cis-3-hexenol (CAS # 928-96-1): In vitro micronucleus assay in human peripheral blood lymphocytes, Covance Laboratories Inc., Greenfield, IN, USA. Unpublished report to the FEMA Expert Panel. Provided by the Research Institute for Fragrance Materials.

Bhalli, J., 2015a. Triethyl citrate (CAS # 77-93-0): Bacterial Reverse Mutation Assay: Plate Incorporation Method with a Confirmatory Assay. Covance Laboratories, Greenfield, Indiana, USA., Unpublished report to the FEMA Expert Panel. Provided by the Research Institute for Fragrance Materials.

Bhalli, J., 2015b. Triethyl citrate (CAS # 77-93-0): In Vitro Micronucleus Assay in Human Peripheral Blood Lymphocytes. Covance Laboratories, Greenfield, Indiana, USA., Unpublished report to the FEMA Expert Panel. Provided by the Research Institute for Fragrance Materials.

Bhatia, S., Politani, V.T., Api, A., 2010. Genotoxicity Tests Conducted on a Group of Structurally Related Aldehydes, Unpublished report to the FEMA Expert Panel. Provided by the Research Institute for Fragrance Materials.

Borgström, B., 1974. Fat Digestion and Absorption, Intestinal Absorption. Springer Science + Business Media, pp. 555-620.

Bosron, W.F., Ting-Kai, L., 1980. Alcohol dehydrogenase. , in: W.B. Jacoby (Ed.), Ezymatic Basis of Detoxification. Academic Press, New York, pp. 231-248.

Bowen, R., 2011. Reverse mutation in five histidine-requiring strains of Salmonella typhimurium: 3,4-Dimethyl-5-pentylidenefuran-2(5H)-one, Study no. 8233097 ed. Unpublished report provided to the FEMA Expert Panel, Covance Laboratories Ltd., North Yorkshire, England.

Boyland, E., Chasseaud, L.F., 1970. The Effect of Some Carbonyl Compounds on Rat Liver Glutathione Levels. Biochemical Pharmacology 19, 1526-1528.

Bruce, S., 2017. Bacterial Reverse Mutation Assay of Synthetic Intermediate of FEMA 4899. BioReliance

Corporation, Rockville, MD, USA. Unpublished report provided to the FEMA Expert Panel.

Brusick, D., 1975. Mutagenic evaluation of compound FDA 75-5 000527-07-1 sodium gluconate, FCC, fine granular. Unpublished report provided to the FEMA Expert Panel, Litton Bionetics, Inc., Kensington, Maryland.

Butterworth, K.R., Carpanini, F.M.B., Gaunt, I.F., Kiss, I.S., Gangolli, S.D., 1975. Short-term toxicity of dimethyl sulphide in the rat. Food and Cosmetics Toxicology 13, 15-22.

Cannon, R.J., Kazimierski, A., Curto, N.L., Li, J., Trinnaman, L., Janczuk, 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.

Chadha, A., Madyastha, M., 1982. Omega-hydroxylation of acyclic monoterpene alcohols by rat lung microsomes. Biochemical and Biophysical Research Communications 108, 6.

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.

Chaturvedula, V.S., Upreti, M., Prakash, I., 2011. Diterpene glycosides from Stevia rebaudiana. Molecules 16, 3552-3562.

Cheung, Y.-L., 2016a. CA-016: Stability in simulated gastric and intestinal fluids, Envigo CRS Limited, Cambridgeshire, UK.

Cheung, Y.-L., 2016b. CA-016: Human hepatocyte metabolism, Envigo CRS Limited, Cambridgeshire, UK.

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

Cohen, S.M., Eisenbrand, G., Fukushima, S., Gooderham, N.J., Guengerich, F.P., Hecht, S.S., Rietjens, I., Davidsen, J.M., Harman, C.L., Taylor, S.V., 2018. Updated procedure for the safety evaluation of natural flavor complexes used as ingredients in food. Food Chem Toxicol 113, 171-178.

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., 2017a. Safety evaluation of substituted thiophenes used as flavoring ingredients. Food and Chemical Toxicology, 40-59.

Cohen, S.M., Fukushima, S., Gooderham, N.J., Guengerich, F.P., Hecht, S.S., Rietjens, I.M.C.M., Smith, R.L., Bastaki, M., Harman, C.L., McGowen, M.M., Taylor, S.V., 2016. FEMA expert panel review of p-mentha-1,8-dien-7-al genotoxicity testing results. Food and Chemical Toxicology 98, Part B, 201-209.

Cohen, S.M., Fukushima, S., Gooderham, N.J., Guengerich, F.P., Hecht, S.S., Rietjens, I.M.C.M., Smith, R.L., Bastaki, M., Harman, C.L., McGowen, M.M., Valerio, L.G., Taylor, S.V., 2017b. Safety evaluation of substituted thiophenes used as flavoring ingredients. Food and Chemical Toxicology 99, 40-59.

Cohen, S.M., Eisenbrand, G., Fukushima, S., Gooderham, N.J., Guengerich, F.P., Hecht, S.S., Rietjens, I., Bastaki, M., Davidsen, J.M., Harman, C.L., McGowen, M.M., Taylor, S.V., 2020. FEMA GRAS assessment of natural flavor complexes: Mint, buchu, dill and caraway derived flavoring ingredients. Food and Chemical Toxicology https://doi.org/10.1016/j.fct.2019.110870.

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.

Cook, W.M., Purchase, R., Ford, G.P., Creasy, D.M., Brantom, P.G., Gangolli, S.D., 1992. A 28-day feeding study with ethyl acetoacetate in rats. Food and Chemical Toxicology 30, 567-573.

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

Cox, G.E., Bailey, D.E., Morganreidge, K., 1974a. 90-day feeding study in rats with compound 14865 (2,3-butanedithiol). Food and Drug Research Laboratories, Inc. , Unpublished report provided to the FEMA Expert Panel.
.
Cox, G.E., Bailey, D.E., Morganreidge, K., 1974b. 90-Day Feeding Study in Rats with Compound 14935. Food and Drug Laboratories Inc. Unpublished report provided to the FEMA Expert Panel.

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.

Curry, P.T., 1995. *In vitro* mammalian cytogenetic test with 6-Acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN), Study No. G94AP80.337005 ed. Microbiological Associantes Inc, Rockville, Maryland, USA. Unpublished report to the FEMA Expert Panel provided by the Research Institute for Fragrance Materials.

Daly, J., 2016. FEMA 4899: A 28-day dietary administration toxicity study in rats. MPI Research, Mattawan, Michigan, USA. Unpublished report to the FEMA Expert Panel

Daly, J., 2017. FEMA 4899: A 13-week dietary administration toxicity study in rats. Unpublished report provided to the FEMA Expert Panel., MPI Research, Mattawan, Michigan, USA.

Damani, L.A., 1987. Metabolism of sulphur-containing drugs, in: D.J. Benford, J.W. Bridges, G.G. Gibson (Eds.), Drug metabolism -- from molecules to man. Taylor & Francis, London, New York, Philadelphia, pp. 581-603.

De Flora, S., Bennicelli, C., Rovida, A., Scatolini, L., Camoirano, A., 1994. Inhibition of the "spontaneous" mutagenicity in Salmonella typhimurium TA102 and TA104. Mutation research 307, 157-167.

Dhinsa, N.K., 2006. FEMA 4928 Twenty-eight day repeated dose oral (gavage) toxicity study in the rat. Unpublished report provided to the FEMA Expert Panel, Safepharm Laboratories Limited, Derbyshire, UK. Unpublished report to the FEMA Expert Panel.

Diaz, D., Scott, A., Carmichael, P., Shi, W., Costales, C., 2007. Evaluation of an automated in vitro micronucleus assay in CHO-K1 cells. Mutation research 630, 1-13.

Diliberto, J.J., Srinivas, P., Overstreet, D., Usha, G., Burka, L.T., Birnbaum, L.S., 1990. Metabolism of citral, an alpha-beta-unsaturated aldehyde, in male F344 rats. American Society for Pharmacology and Experimental Therapeutics 18, 866-875.

Dirscherl, W., Wirtzfeld, A., 1964. Vanillinsaure im menschlichen Urin Ihre Isolierung, Bestimmung und Herkunft Acta endocr., Copenh 47.

Donath, C., 2017. Mammalian micronucleus test in murine peripheral blood cells with nootkatone 70 natural. I, Eurofins BioPharma, Planegg, Germany. Unpublished report to the FEMA Expert Panel.

Dutton, G.J., Illing, H.P.A., 1972. Mechanism of biosynthesis of thio-β-d-glucuronides and thio-β-d-glucosides. Biochem. J. 129, 539-550.

Eapen, A., 2007. A 90-day oral (dietary) toxicity study of GR-72-0180 in rats with a 28-day recovery period, WIL Research Laboratories, LLC, Ashland, Ohio, United States. Unpublished report to the FEMA Expert Panel.

Eckfeldt, J.H., Yonetani, T., 1982. [79] Isozymes of aldehyde dehydrogenase from horse liver, Methods in Enzymology. Elsevier BV, pp. 474-479.

Eder, E., Henschler, D., Neudecker, T., 1982. Mutagenic properties of allylic and α,β-unsaturated compounds: Consideration of alkylating mechanisms. Xenobiotica 12, 831-848.

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

EFSA, 2003. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to L-carnitine-L-tartrate for use in foods for particular nutritional uses.

Feldman, R.I., Weiner, H., 1972. Horse liver aldehyde dehydrogenase. I. Purification and characterization. J Biol Chem 247, 260-266.

FEMA 1975. SLR A7. Scientific literature review of aliphatic amines. PB85141075/LL. National Technical Information Service.

FEMA 1975. SLR A8. Scientific literature review of aliphatic thiols. PB85141075/LL. National Technical Information Service.

FEMA 1976. SLR B4. Scientific literature review of aliphatic mono-, di- and trisulfides. . PB85141133/LL. National Technical Information Service.

FEMA 1976. SLR, B5B. Scientific literature review of selected oxygenated derivatives of mercaptans and sulfides. PB85141158/LL. National Technical Information Service.

FEMA 1978. SLR C11. Scientific literature review of cinnamyl alcohol and related substances. PB284-961/AS. National Technical Information Service.

FEMA 1978. SLR C14. Scientific literature review of aryl substituted secondary alcohols, ketones and derivatives. PB284-963/AS. National Technical Information Service. , 1978.

FEMA 1978. SLR C16. Scientific literature review of alpha-alkylcinnamaldehydes and related substances. PB283-505/AS. National Technical Information Service.

FEMA 1978. SLR C21. Scientific literature review of capsaicin and related compounds. PB284-868/AS. National Technical Information Service.

FEMA 1978. SLR C22. Scientific literature review of aromatic ethers. PB284-867/AS. National Technical Information Service.

FEMA 1978. SLR D1. Scientific literature review of dithiols and related substances. PB291-113/AS. National Technical Information Service.

FEMA 1978. SLR D12. Scientific literature review of aliphatic ethers. PB141166/AS. National Technical Information Service.

FEMA 1978. SLR D15. Scientific literature review of thiophene derivatives. PB291-102/AS. National Technical Information Service. 1978.

FEMA 1979. SLR D3. Scientific literature review of pyrrole and related substances. . PB296-007/AS. National Technical Information Service.

FEMA 1979. SLR D9. Scientific literature review of furanones and related substances. PB85141240/AS. National Technical Information Service. 1978, 1979.

FEMA 1979. SLR D19. Scientific literature review of miscellaneous substances. PB85141299/LL. National Technical Information Service. 1979, 1983.

FEMA 1979. SLR B1F. Scientific literature review of aliphatic poly-hydroxy compounds and derivatives. PB85-141117/LL. National Technical Information Service. 1976, 1979.

FEMA 1984. SLR B1B. Scientific literature review of aliphatic keto- and hydroxy-acids with oxygen functions and related compounds. PB85141091/LL. National Technical Information Service. 1976, 1979, 1984. .

FEMA 1984. SLR B1C. Scientific literature review of aliphatic lactones. PB86-155850/LL. National Technical Information Service. 1979, 1984.

FEMA 1984 SLR B3. Scientific literature review of amino acids. PB85141125/LL. National Technical Information Service.

FEMA 1984. SLR C9. Scientific literature review of Benzyl alcohol, benzaldehyde, benzoic acid and related compounds. . PB85141216/LL. National Technical Information Service. 1978, 1984.

FEMA 1984. SLR C12. Scientific literature review of phenols. PB86-155868/AS. National Technical Information Service. 1979, 1984.

FEMA,1984.SLR A1. Scientific literature review of aliphatic ketones, secondary alcohols and related esters. PB85141059/LL. National Technical Information Service.

FEMA 1985. SLR A5. Scientific literature review of alicyclic compounds of carbon, hydrogen and oxygen. PB86-155835/LL. National Technical Information Service. 1976, 1978, 1985.

FEMA 1985. SLR M1. Scientific literature review of aliphatic primary alcohols, aldehydes, esters and acids. PB86-155926. National Technical Information Service. 1974, 1978, 1979, 1984, 1985.

Flanders, L., 2017. Micronucleus Test in the Mouse., Envigo Research Limited, Derbyshire, England. Unpublished report provided to the FEMA Expert Panel.

Florin, I., Rutberg, L., Curvall, M., Enzell, C.R., 1980a. Screening of tobacco smoke constituents for mutagenicity using Ame's test. Toxciology 18, 219-232.

Florin, I., Rutberg, L., Curvall, M., Enzell, C.R., 1980b. 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.

Fukuda, T., 2017. An *in vitro* micronucleus test in TK6 human lymphoblastoid cells treated with (E)-3-(4-isopropyloxyphenyl)prop-2-enal. BoZo Research Center Inc., Tokyo, Japan. Unpublished report to the FEMA Expert Panel.

Furukuma, S., 2017. In vitro mammalian cell micronucleus test of CA-047 ITO, UBE Scientific Analysis Laboratory, Inc., Yamaguchi Prefecture, Japan. Unpublished report provided to the FEMA Expert

Gardana, C., Simonetti, P., Canzi, E., Zanchi, R., Pietta, P., 2003. Metabolism of stevioside and rebaudioside A from Stevia rebaudiana extracts by human microflora. Journal of agricultural and food chemistry 51, 6618-6622.

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.

Gaunt, I.F., Wright, M.G., Cottrell, R., Gangolli, S.D., 1983. Short-Term Toxicity of 2,6-Dimethylhept-5-en-1-al in Rats. Chem. Toxic. 21, 543-549.

Geuns, J.M., Augustijns, P., Mols, R., Buyse, J.G., Driessen, B., 2003a. Metabolism of stevioside in pigs and intestinal absorption characteristics of stevioside, rebaudioside A and steviol. Food Chem Toxicol 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.

Geuns, J.M.C., Malheiros, R.D., Moraes, V.M.B., Decuypere, E.M.P., Compernolle, F., Buyse, J.G., 2003b. Metabolism of Stevioside by Chickens. Journal of agricultural and food chemistry 51, 1095-1101.

Gibson, G.G., Orton, T.C., Tamburini, P.P., 1982. Cytochrome P -450 induction by clofibrate. Purification and properties of a hepatic cytochrome P -450 relatively specific for the 12- and 11-hydroxylation of dodecanoic acid (lauric acid). Biochem. J. 203, 161-168.

Gillam, E.M., Notley, L.M., Cai, H., De Voss, J.J., Guengerich, F.P., 2000. Oxidation of indole by cytochrome P450 enzymes. Biochemistry 39, 13817-13824.

Girkin, R., 1998. Metabolite profiles in rat and pig urine. Huntington Life Sciences Ltd. Cambridgeshire, England. Unpublished report to the FEMA Expert Panel.

Gomes-Carneiro, M.R., Felzenszwalb, I., Paumgartten, F.J.R., 1998. Mutagenicity testing (+/-)-camphor, 1,8-cineole, citral, citronellal, (-)-menthol and terpineol with the Salmonella/microsome assay. Mutation research 416, 129-136.

GRAS Applicant, 2015. Metabolism Study Summary Report: Allulose. Unpublished report provided to the FEMA Expert

Gudi, R., Ritter, P., 1997. Micronucleus cytogenetic assay in mice, Study No. G96BV66.122 Microbiological Associates, Inc. Rockville, Maryland, USA. Unpublished report to the FEMA Expert Panel.

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. Fd Cosmet. Toxicol. 5, 141-157.

Hall, R.L., 1979. Citronellol. Joint FAO/WHO Expert Committee on Food Additives, Geneva.

Hall, R.L., Oser, B.L., 1965. Recent Progress in the Consideration of Flavoring Ingredients Under the Food Additives Amendment III. GRAS Substances. Food Technology.

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.

Hashimoto, J., 2015. Bacterial reverse mutation test of CA-016-ITO, UBE Scientific Analysis Laboratory, Inc., Yamaguchi Prefecture, Japan. Unpublished report provided to the FEMA Expert Panel.

Hashimoto, J., 2016. Bacterial reverse mutation test of CA-047-ITO, UBE Scientific Analysis Laboratory, Inc., Yamaguchi Prefecture, Japan. Unpublished report provided to the FEMA Expert Panel.

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., Zeiger, E., 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. mutagen 5, 3-49.

Hayes, K.C., Pronczuk, A., Cook, M.W., Robbins, M.C., 2003. Betaine in sub-acute and sub-chronic rat studies. Food and Chemical Toxicology 41, 1685-1700.

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.

Hobbs, C.A., Taylor, S.V., Beevers, C., Lloyd, M., Bowen, R., Lillford, L., Maronpot, R., Hayashi, S.-m., 2016. Genotoxicity assessment of the flavouring agent, perillaldehyde. Food and Chemical Toxicology 97, 232-242.

Honarvar, N., 2007. Micronucleus assay in bone marrow cells of the mouse with 10-undecenal. RCC Cytotest Cell Research GmbH, Rossdorf, Germany. Unpublished report to the FEMA Expert Panel.

Hooks, W.N., Kirk, S.J., Smith, H.L., Crook, D., Gibson, W.A., Gregson, R.L., Gopinath, D., Anderson, A., Dawe, S.I., 1992. Ethyl vanillin toxicity to rats by repeated dietary administration. Unpublished report to the FEMA Expert Panel. Provided by the Research Institute for Fragrance Materials.

Hooth, M.J., Sills, R.C., Burka, L.T., Haseman, J.K., Witt, K.L., Orzech, D.P., Fuciarelli, A.F., Graves, S.W., Johnson, J.D., Bucher, J.R., 2004. Toxicology and carcinogenesis studies of microencapsulated trans-cinnamaldehyde in rats and mice. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 42, 1757-1768.

Horrigan, M., 2016. Metabolite Characterization of the Subject Compound in Rat and Human Hepatocytes, Study No. XT160033., XenoTech, LLC, Kansas City, Kansas, USA. Unpublished report to the FEMA Expert Panel.

Huntington Lab, 2011. Safety of D-psicose report prepared for CJ CheilJedang. Food and Drug Administration (FDA), https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=400&sort=GRN_No&order=DESC&startrow=1&type=basic&search=400.

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.

IBR, 1991b. Acute Oral Toxicity Test of “5497” in Rats. Final Report dated 15.3.91. Sponsored by Lonza AG, Basel, Switzerland (cited in EFSA, 2003; Norwegian, 2015). IBR Forschungs GmbH, Walsrode, Germany.

Ibrahim, M.A., Rodenburg, D.L., Alves, K., Fronczek, F.R., McChesney, J.D., Wu, C., Nettles, B.J., Venkataraman, S.K., Jaksch, F., 2014. Minor Diterpene Glycosides from the Leaves of Stevia rebaudiana. Journal of Natural Products 77, 1231-1235.

Inouye, T., Sasaki, Y.F., Imanishi, H., Watanebe, M., Ohta, T., Shirasu, Y., 1988. Suppression of mitomycin C-induced micronuclei in mouse bone marrow cells by post-treatment with vanillin. Mutation research 202, 93-95.

Ishida, T., Toyota, M., Asakawa, Y., 1989. Terpenoid biotransformation in mammals. V. Metabolism of (+)-citronellal, (±)-7-hydroxycitronellal, citral, (−)-perillaldehyde, (−)-myrtenal, cuminaldehyde, thujone, and (±)-carvone in rabbits. Xenobiotica 19, 843-855.

Ishidate, M., Sofuni, T., Yoshikawa, D., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A., 1984. Primary mutagenicity screening of food additives currently used in Japan. Fd Chem. Toxic. 22, 623-636.

Ishii, T., 2017. (E)-3-(4-isopropyloxyphenyl) prop-2-enal: Micronucleus test with rat bone marrow cells. BoZo Research Center Inc., Shizuoka, Japan. Unpublished report to the FEMA Expert Panel.

James, 1974. Animal studies - Summaries of results, Huntingdon Research Center, UK. Unpublished report provided to the FEMA Expert Panel.

Jansson, T. Curvall, M., Hedin, A., Enzell, C.R. 1986. In vitro studies of biological effects of cigarette smoke condensate. II. Induction of sister-chromatid exchanges in human lymphocytes by weakly acidic, semi volatile constituents. Mutation Research. 169(3), 129-139.

Jansson, T, Zech, L., 1987. Effects of vanillin on sister-chromatid exchanges and chromosome aberrations in human lymphocytes. Mutation Research. 190, 221-224.

JECFA, 1999. Safety Evaluation of Certain Food Additives (Fifty-first Meeting of Joint FAO/WHO Expert Committee on Food Additives). Food Additives Series No. 42.

JECFA, 2000. Safety evaluation of certain food additives and contaminants. WHO Food Additive Series 44.

JECFA, 2001. Safety evaluation of certain food additives and contaminants. WHO Food Additive Series 48.

JECFA, 2003. Toxicological evaluation of certain veterinary drug residues in food (Sixtieth Meeting of Joint FAO/WHO Expert Committee on Food Additives). Food Additives Series No. 51.

JECFA, 2004. Safety evaluation of certain food additives and contaminants prepared by the fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives WHO Food Additive Series No. 52.

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

JECFA, 2007. Safety evaluation of certain food additives and contaminants. WHO Food Additive Series 58.

JECFA, 2008. Safety evaluation of certain food additives and contaminants (prepared by the sixty-eighth meeting of JECFA). WHO Food Additive Series No. 59, 175-236.

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

JECFA, 2011. Safety evaluation of certain food additives and contaminants (seventy-third meeting of Committee on Food Additives). WHO Food Additive Series No. 64.

JECFA, 2012. Safety evaluation of certain food additives and contaminants (seventy-sixth meeting of Committee on Food Additives). WHO Food Additive Series No. 67.

JECFA, 2014. Safety evaluation of certain food additives and contaminants. WHO Food Additive Series 68.

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

JECFA, 2017. Safety evaluation of certain food additives. WHO Food Additive Series No. 73.

JECFA, 2019. Safety evaluation of certain food additives (eighty-sixth report of Committee on Food Additives). WHO Food Additive Series No. 86.

Jin, X., Dong, H., 2010. Acute toxicity and mutagenicity of extract from *Eriobotrta japonica*, 4th International Conference on Bioinformatics and Biomedical Engineering. Unpublished report provided to the FEMA Expert Panel

Jin, X., Dong, H., 2017. Acute toxicity and mutagenicity of extract from *Eriobotrta japonica* Huainan Union University, Huainan, China. Unpublished report provided to the FEMA Expert Panel

Jones, E., 1986. Ames metabolic activation test to assess the potential mutagenic effect of Vanillin, USP. Huntingdon Research Center Ltd. England, Unpublished report (EuroVanillin KS, Norway). As cited in the OECD SIDS.

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 to the FEMA Expert Panel.

Kamil, I.A., Smith, J.N., Williams, R.T., 1953. Studies in detoxication. 46. The metabolism of aliphatic alcohols. The glucuronic acid conjugation of acyclic aliphatic alcohols. Biochem. J. 53, 129-136.

Karanewsky, D.S., Arthur, A.J., Liu, H., Chi, B., Markison, S., 2015. Toxicological evaluation of a novel cooling compound: 2-(4-methylphenoxy)-N-(1H-pyrazol-3-yl)-N-(2-thienylmethyl)acetamide. Toxicology Reports 2, 1291-1309.

Kasamaki, A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T., Urasawa, S., 1982. Genotoxicity of flavoring agents. Mutation research 105, 387-392.

Kaspers, U., 2002. 6-Methylhept-5-en-2-one (Methylheptenon) – Subchronic toxicity study in wistar rats administration by gavage for 3 months, Experimental Toxicology and Ecology, Ludwigshafen, Germany. Unpublished report provided to the FEMA Expert Panel.

Kawaguchi, R., 2016. 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., Komai, T., 2012. Reverse mutation assay "Ames Test" using Salmonella typhimurium: (E)-6-octenal. Unpublished report provided to the FEMA Expert Panel.

Kawaguchi, R., Komai, T., 2016. Reverse mutation assay "Ames Test" using Salmonella Typhimurium: 3-(4-Isopropoxyphenyl)prop-(2E)-enal. Unpublished report provided to the FEMA Expert Panel.

Kim, J.C., Kang, B.H., Shin, C.C., Kim, Y.B., Lee, H.S., Kim, C.Y., Han, J., Kim, K.S., Chung, D.W., Chung, M.K., 2002. Subchronic toxicity of plant sterol esters administered by gavage to Sprague-Dawley rats. . Food and Chemical Toxicology 40, 1569-1580.

Kirkpatrick, J.B., 2011. WS-5: A 90-day oral gavage toxicity study with a 14-day recovery period in Sprague-Dawley rats (OECD 408), WIL Research Laboratories, LLC, Ashland, Ohio, USA. Biotechnics, LLC, Hillsborough, North Carolina, USA. Unpublished report provided to the FEMA Expert Panel.

Klancnik, J.M., Cuenod, M., Gahwiler, B.H., Jiang, Z.P., Do, K.Q., 1992. Release of endogenous amino acids, including homocysteic acid and cysteine sulphinic acid, from rat hippocampal slices evoked by electrical stimulation of Schaffer collateral-commissural fibres. Neuroscience 49, 557-570.

Kodera, Y., Suzuki, S., Imada, O., Kasuga, S., Sumioka, I., Kanezawa, A., Taru, N., Fujikawa, M., Nagae, S., Masamoto, K., Maeshige, K., Ono, K., 2002. Physical, Chemical, and Biological Properties of S-Allylcysteine, an Amino Acid Derived from Garlic. Journal of agricultural and food chemistry 50, 622-632.

Komai, T., 2016a. Reverse mutation assay "Ames Test" using Salmonella Enterica: 3-p-Menthen-7-al, Kawasaki-shi, Japan. Unpublished report provided to the FEMA Expert Panel.

Komai, T., 2016b. Reverse mutation assay "Ames Test" using Salmonella Typhimurium: (E)-3-Methyl-4-dodecenoic acid, Kawasaki-shi, Japan. Unpublished report provided to the FEMA Expert Panel.

Komai, T., 2016c. Reverse mutation assay "Ames Test" using Salmonella Typhimurium: cis-Cascarillic acid. Unpublished report provided to the FEMA Expert Panel, Kawasaki-shi, Japan.

Komai, T., 2017a. Reverse mutation assay "Ames Test": bis(3-methyl-2-butenyl) disulfide. Unpublished report provided to the FEMA Expert Panel.

Komai, T., 2017b. Reverse mutation assay "Ames Test": 3,4-Dimethyl-5-propylidenefuran-2(5H)-one. Unpublished report provided to the FEMA Expert Panel.

Komai, T., 2017c. Reverse mutation assay "Ames Test": 1-Ethyl-2-(1-pyrrolylmethyl)pyrrole. Unpublished report provided to the FEMA Expert Panel..

Komai, T., 2018a. Reverse mutation assay "Ames Test": (Z)-8-Pentadecenal. Unpublished report provided to the FEMA Expert Panel.

Komai, T., 2018b. Reverse mutation assay "Ames Test": 2-Methylthiophene. Unpublished report provided to the FEMA Expert Panel.

Komai, T., 2018c. Reverse mutation assay "Ames Test": Dehydrorose oxide. Unpublished report provided to the FEMA Expert Panel.

Komai, T., 2018d. Reverse Mutation Assay "Ames Test" 3-Methylbutane-1,3-dithiol. Unpublished report provided to the FEMA Expert Panel.

Komai, T., 2018e. Reverse Mutation Assay "Ames Test" Test Material S-methyl 5-(1-ethoxyethoxy) decanethioate. Unpublished report to the FEMA Expert Panel.

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 Chem Toxicol 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 Chem Toxicol 41, 875-883.

Kroes, R., Renwick, A.G., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schlatter, J., van Schothorst, F., Vos, J.G., Wurtzen, G., 2004. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food and Chemical Toxicology 42, 65-83.

Kuroda, K., Tanaka, S., Yu, Y., Ishibashi, T., 1984. Rec-assay of food additives. Nippon Kosyu Eisei Zasshi 31, 277-281.

Kurooka, S., Hashimoto, M., Tomita, M., Maki, A., Yoshimura, Y., 1976. Relationship between the structures of S-acyl thiol compounds and their rates of hydrolysis by pancreatic lipase and hepatic carboxylic esterase. Journal of biochemistry 79, 533-541.

Lawlor, T.E., 1991. Mutagenicity test on Vanillin in the Salmonella/mammalian-microsome reverse mutation assay (Ames test). Report no. 12389-0-401. ed. Hazleton Laboratories America, Inc., Unpublished report to the FEMA Expert Panel.provided by the Research Institute for Fragrance Materials.

Lawrence, B.M., 1977. Essential Oils 1976-1978. Reprint: Progress in Essential Oils. Perfumer & Flavorist 2, 3. Wheaton, IL: Allured Publishing Corporation, pp. 21.

Lee, H., Shuh Shyuan, B., Yi Ling, C., 1994. Genotoxicity of 1,3-dithiane and 1,4-dithiane in the CHO/SCE assay and the Salmonella/microsomal test. Mutation Research/Genetic Toxicology 321, 213-218.

Leegwater, D.C., van Straten, S., 1974. In vitro study on the hydrolysis of twenty-six organic esters by pancreatin. Centraal Instituut Voor Voedingsonderzoek, Zeist, The Netherlands. Unpublished report provided to the FEMA Expert Panel.

Leuschner, J., 2017. Mutagenicity study of hibiscus blossom extract in the Salmonella typhimurium and Escherichia coli reverse mutation assay (in vitro), Laboratory of Pharmacology and Toxicology GmbH & Co., Hamburg, Germany. Unpublished report provided to the FEMA Expert Panel.

Li, F., Li, Y., Li, Q., Shi, X., Guo, Y., 2017. Acute and Subacute Oral Toxicity Evaluation of Eriobotrya japonica Leaf Triterpene Acids in ICR Mice. Evid Based Complement Alternat Med 2017, 4837839.

Liwska, K., 2012. 10-Undecenal ninety day repeated dose oral (dietary) toxicity study in the rat.., Harlan Laboratories Ltd., Derbyshire, UK. Unpublished report to the FEMA Expert Panel.provided by the Research Institute for Fragrance Materials.

Lloyd, M., 2014. Induction of micronuclei in cultured human peripheral blood lymphocytes: 4-Acetyl-2,5-dimethylfuran-3(2H)-one. Covance Laboratories, Harrogate, England. Unpublished report provided to the FEMA Expert Panel by the International Organization of the Flavor Industry.

Luis, A., Duarte, A.P., Pereira, L., Domingues, F., 2017. Chemical Profiling and Evaluation of Antioxidant and Anti-Microbial Properties of Selected Commercial Essential Oils: A Comparative Study. Medicines (Basel) 4.

Maiorino, R.M., Bruce, D.C., Aposhian, H.V., 1989. Determination and metabolism of dithiol chelating agents. Toxicology and Applied Pharmacology 97, 338-349.

Maki, K.C., Davidson, M.H., Umporowicz, D.M., Schaefer, E.J., Dicklin, M.R., Ingram, K.A., Chen, S., McNamara, J.R., Gebhart, B.W., Ribaya-Mercado, J.D., Perrone, G., Robins, S.J., Franke, W.C., 2001. Lipid responses to plant-sterol-enriched reduced-fat spreads incorporated into a National Cholesterol Education Program Step I diet. The American Journal of Clinical Nutrition 74, 33-43.

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.

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.

Marr, A., 2007. FEMA 4928 Limited twenty-eight day repeated dose oral (gavage) toxicity study in the rat. Safepharm Laboratories Limited, Derbyshire, UK. Unpublished report provided to the FEMA Expert Panel.

Marzin, D., 1979a. Rhône-Poulenc unpublished / DREBS (Department Recherche et Essais Biologiques Stallergènes) study R-905017. Citation: Euclid Data Sheet for Vanillin by Rhône-Poulenc Chimie, created 26.01.95, updated 01.06.95). As cited in the OECD SIDS.

Marzin, D., 1979b. Recherche d'une action mutagène par le test du micronucleus chez la souris du produit: Vanilline., Report no. 906010 ed. DREBS (Department Recherche et Essais Biologiques Stallergènes). Unpublished report (Rhône-Poulenc, France). As cited in the OECD SIDS.

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.

Masoro, E.J., 1977. Lipids and Lipid Metabolism. Annual Review of Physiology 39, 301-321.

Matsuo, T., Ishii, R., Shirai, Y., 2011. The effects of 90-day feeding of D-psicose syrup in male wistar rats. Open Journal of Preventive Medicine 1, 6.

McBain, J.B., Menn, J.J., 1969. S-methylation, oxidation, hydroxylation and conjugation of thiophenol in the rat. Biochemical Pharmacology 18, 2282-2285.

McElroy, 2017a. An Oral (Gavage) Developmental Toxicity Study of FEMA 4899 (Salt) in Sprague-Dawley Rats. Charles River Laboratories. Unpublished report provided to the FEMA Expert Panel.

McElroy, 2017b. An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of FEMA 4899 (Salt) in Sprague-Dawley Rats. Charles River Laboratories. Unpublished report provided to the FEMA Expert Panel.

Meerts, I., 2001. Evaluation of the ability of coffee precursor to induce chromosome aberrations in cultured peripheral human lymphocytes. NOTOX B.V.,Hertogenbosch, the Netherlands. Unpublished report provided to the FEMA Expert Panel,

Miettinen, T.A., Tilvis, R.S., Kesaniemi, Y.A., 1990. Serum plant sterols and cholesterol precursors reflect cholesterol absorption and synthesis in volunteers of a randomly selected male population. American Journal of Epidemiology 131, 20-31.

Miyata, K., 1995. Twenty-eight day repeated dose oral toxicity study of WS 3 in rats, Hita Research Laboratories, Oita, Japan. Unpublished report provided to the FEMA Expert Panel.

Mochizuki, M., 1995. A 4-week oral toxicity study of sodium gluconate (FR2531) in rats. BoZo Research Center Inc., Tokyo, Japan. Unpublished report provided to the FEMA Expert Panel.

Mochizuki, M., 1997. A 28-day toxicity study in rats fed diet containing sodium gluconate (FR2531). BoZo Research Center Inc., Tokyo, Japan. Unpublished report provided to the FEMA Expert Panel.

Moore, M.M., Honma, M., Clements, J., Blocsfoldi, G., Cifone, M., Delongchamp, R., Fellows, M., Gollapudi, B., Jenkinson, P., Kirby, P., Kirchner, S., Muster, W., Myhr, B., O'Donovan, M., Oliver, J., Omori, T., Ouldelhkim, M.C., Pant, K., Preston, R., Riach, C., San, R., Stankowski, L.F., Thakur, A., Wakuri, S., Yoshimura, I., 2003. Mouse Lymphoma Thymidine Kinase Gene Mutation Assay: International Workshop on Genotoxicity Tests Workgroup Report—Plymouth, UK 2002. Mutation research 540, 127-140.

Moore, M.M., Honma, M., Clements, J., Bolcsfoldi, G., Burlinson, B., Cifone, M., Clarke, J., Delongchamp, R., Durward, R., Fellows, M., Gollapudi, B., Hou, S., Jenkinson, P., Lloyd, M., Majeska, J., Myhr, B., O'Donovan, M., Omori, T., Riach, C., San, R., Stankowski, L.F., Thakur, A., van Goethem, F., Wakuri, S., Yoshimura, I., 2006. Mouse Lymphoma Thymidine Kinase Gene Mutation Assay: Follow-up Meeting of the International Workshop on Genotoxicity Testing--Aberdeen, Scotland, 2003--Assay Acceptance Criteria, Positive Controls, and Data Evaluation. Environmental and Molecular Mutagenesis 47, 1-5.

Morgareidge, K., 1962. In vitro digestion of four acetals. Food and Drug Research Laboratories. Unpublished report provided to the FEMA Expert Panel.

Morgareidge, K., 1974. 90-Day feeding studies in rats with compound 14935, Unpublished report provided to the FEMA Expert Panel.

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., Zeigher, E., 1986. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environmental Mutagenesis 8, 1-119.

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.

Munday, R., Manns, E., 1994. Comparative Toxicity of Prop(en)yl Disulfides Derived from Alliaceae: Possible Involvement of 1-Propenyl Disulfides in Onion-Induced Hemolytic Anemia. J. Agric. Food Chem. 42, 959-962.

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., 1997. 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.

Nagabhushan, M., Bhide, S.V., 1985. Mutagenicity of chili extract and capsaicin in short-term tests. Environmental Mutagenesis 7, 881-888.

Nakajima, M., 2000a. Chromosome aberration assay of rebaudioside A in cultured mammalian cells. Test number 5001 (079-085). Biosafety Research Center, Japan. Unpublished report provided to the FEMA Expert Panel.

Nakajima, M., 2000b. 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.

Nakayasu, H., Mihara, K., Sato, R., 1978. Purification and properties of a membrane-bound aldehyde dehydrogenase from rat liver microsomes. Biochemical and Biophysical Research Communications 83, 697-703.

National Toxicology Program (NTP), 1990. Carcinogenicity and toxicology studies of d-limonene in F344/N Rats and B6C3F1. US Department of Health and Human Services.

National Toxicology Program (NTP), 2003. Toxicology and carcinogenesis studies of citral (microencapsulated) in F344/N rats and B6C3F$_1$ mice. U.S. Department of Health and Human Servies, National Institutes of Heath.

National Toxicology Program (NTP), 2004. Studies of trans-Cinnamaldehyde (microencapsulated) in F344/and B6C3F mice. National Toxicology Program Technical Report Series 514, 1-284.

National Toxicology Program (NTP), 1992. Toxicology and Carcinogenesis Studies of y-butyrolactone (CAS no. 96-48-0) in F344/N Rats and B6C3F_1 Mice (Gavage Studies). National Toxicology Program Technical Report Series.

Naumann, S., 2018. Modified guaiac wood extract (Guaiacum spp.): Micronucleus Test in Human Lymphocytes In vitro. Envigo CRS GmbH, Rossdorf, Germany, Unpublished report to the Expert Panel of the Flavor and Extract Manufacturers Association.

NCI, 1996. Clinical development plan: l-Perillyl alcohol. Journal of Cellular Biochemistry 26S, 137-148.

Nelson, D.L., Cox, M.M., 2008. Lehninger Principles of Biochemistry, 5th ed. W.H. Freeman, New York.

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.

Njissen, L.M.I.-V., C.A. van; Donders, J.J.H. [eds]. 2019. VCF Volatile Compounds in Food: Database Version 16.6.1 – Zeist (The Netherlands): Triskelion B.V., 1963-2018

Nohmi, T., 2018. Thresholds of Genotoxic and Non-Genotoxic Carcinogens. Toxicol. Res. 34, 281-290.

Nutley, B.P., Farmer, P., Caldwell, J., 1994. Metabolism of trans-cinnamic acid in the rat and the mouse and its variation with dose. Food and Chemical Toxicology 32, 877-886.

Oda, Y., Hamono, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1979. Mutagenicity of food flavours in bacteria. . Shokuhin Eisei Hen 9, 177-181.

OECD, 1997. Test No. 471: Bacterial Reverse Mutation Test. OECD Publishing.

OECD SIDS, 2004. Gluconic acid and derivatives. Paris, France. , SIDS Initial Assessment Report for SIAM 18.

Ogura, 2014. Mutagencity Test of OG-5 Using Microorganisms, Study No. K01-5742 ed. Unpublished report provided to the FEMA Expert Panel.

Ohta, M., Sasa, S., Inoue, A., Tamai, T., Fujita, I., Morita, K., Matsuura, F., 2010. Characterization of Novel Steviol Glycosides from Leaves of Stevia rebaudiana Morita. Journal of Applied Glycoscience 57, 199-209.

Okamoto, M., 1995. Four-weeks oral dose toxicity study of sodium gluconate in dog. Unpublished report provided to the FEMA Expert Panel.

Oshima, H., Kimura, I., Izumori, K., 2006. Psicose Contents in Various Food Products and its Origin. Food Science and Technology Research 12, 137-143.

Ostlund, R.E., 2002. Phytosterols in Human Nutrition. Annual Review of Nutrition 22, 533-549.

Packman, E.W., Abbott, D.D., Harrisson, J.W.E., 1963. Comparative subacute toxicity for rabbits of citric, fumaric, and tartaric acids. Toxicology and Applied Pharmacology 5, 163-167.

Pence, D.H., 1982. Mouse Lymphoma Forward Mutation Assay 1,2-Ethanedithiol and in Vitro Sister Chromatid Exchange in Chinese Hamster Ovary Cells 1,2-Ethandithiol. Hazelton Laboratories America, Inc. Vienna, Virginia, USA. Unpublished report provided to the FEMA Expert Panel.

Pence, D.H., Farrow, M.G., Cortina, T.A., 1983. In vitro Sister Chromatid Exchange in Chinese Hamster Ovary Cells 1,2-Ethanedithiol. Hazelton Laboratories America, Inc. , Unpublished report provided to the FEMA Expert Panel .

Pezzuto, J.M., Compadre, C.M., Swanson, S.M., Nanayakkara, D., Kinghorn, A.D., 1985. Metabolically activated steviol, the aglycone of stevioside, is mutagenic. Proceedings of the National Academy of Sciences of the United States of America 82, 2478-2482.

Pezzuto, J.M., Nanayakkara, N.P., Compadre, C.M., Swanson, S.M., Kinghorn, A.D., Guenthner, 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.

PhillipsPetroleumCompany, 1990. Toxicity Study Summary: 1,2-Ethanedithiol. TOX071. Unpublished report submitted to the FEMA Expert Panel.

Pienta, R.J., 1980. Evaluation and relevance of the syrian hamster embryo cell system. In: The predictive value of short-term screening tests in carcinogenicity evaluation. Williams G.M., Kroes R., Waaijers H.W., and Poll K.W. van de (Eds.) Elsevier. North-Holland Biomedical Press 149-169.

Pool, B.L., Lin, P.Z., 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., Linder, A., Vodoz, C.A., 1969. Summaries of toxicological data. Food and Cosmetics Toxicology 7, 405-407.

Poth, A., 2002. Salmonella typhimurium reverse mutation assay with bisabolene., RCC Cytotest Cell Research GmbH, Rossdorf, Germany. Unpublished report provided to the FEMA Expert Panel

Prakash, I., Markosyan, A., Bunders, C., 2014. Development of Next Generation Stevia Sweetener: Rebaudioside M. Foods (Basel, Switzerland) 3, 162-175.

Pritchard, L., 2006. GR-72-0180 Mouse micronucleus test, Huntingdon Life Sciences Limited, Cambridgeshire, England. Unpublished report provided to the FEMA Expert Panel by the International Organization of the Flavor Industry.

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 : RTP 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 : RTP 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 : RTP 68, 259-268.

Ramachandran, S., Fontanille, P., Pandey, A., Larroche, C., 2006. Gluconic Acid: Properties, Applications and Microbial Production.

Rapson, W.H., Nazar, M.A., Butsky, V.V., 1980. Mutagenicity produced by aqueous chlorination of organic compounds. Bull. Environm. Contam. Toxicol. 24, 590-596.

Renwick, A.G., 1996. Sulfur-Oxygen Compounds, in: S.C. Mitchell (Ed.), Biological Interactions of Sulfur Compounds. Taylor & Fancis, London, pp. 44-75.

Renwick, A.G., Tarka, S.M., 2008. Microbial hydrolysis of steviol glycosides. Food and Chemical Toxicology 46, S70-S74.

Richardson, K.A., Edwards, V.T., Jones, B.C., Hutson, D.H., 1991. Metabolism in the rat of a model xenobiotic plant metabolite S -benzyl- N -malonyl-L-cysteine. Xenobiotica 21, 371-382.

Rivedal, E., Mikalsen, S.O., Sanner, T., 2000. Morphological transformation and effect on gap junction intercellular communication in Syrian hamster embryo cells as screening tests for carcinogens devoid of mutagenic activity. Toxicology in Vitro 14, 185-192.

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.

Rockwell, P., Raw, I., 1979. A Mutagenic Screening of Various Herbs, Spices, and Food Additives. Nutrition and Cancer 1, 10-15.

Roy, S., 2015. 2-Methyl-2-hepten-6-ol (CAS No. 1569-60-4): In vitro mammalian cell micronucleus assay in human peripheral blood lymphocytes (HPBL), BioReliance Corporation, Rockville, MD, USA. Unpublished report provided to the FEMA Expert Panel.

Roy, S., 2016. FEMA 4899: In vitro mammalian cell micronucleus assay in human peripheral blood lymphocytes (HPBL). BioReliance Corporation, Rockville, MD, USA. Unpublished report provided to the FEMA Expert Panel.

Rozner, S., Garti, N., 2006. The activity and absorption relationship of cholesterol and phytosterols. Colloids and Surfaces A: Physiochemical and Engineering Aspects 282-283, 435-456.

Ruangyuttikarn, W., Skiles, G.L., Yost, G.S., 1992. Identification of a cysteinyl adduct of oxidized 3-methylindole from goat lung and human liver microsomal proteins. Chemical research in toxicology 5, 713-719.

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 Chem Toxicol 89, 73-84.

Salen, G., Kwiterovich, P.O., Shefer, S., Tint, G.S., Horak, I., Shore, V., Dayal, B., Horak, E., 1985. Increased plasma cholestanol and 5 alpha-saturated plant sterol derivatives in subjects with sitosterolemia and xanthomatosis. Journal of Lipid Research 26, 203-209.

Sammons, H.G., Williams, R.T., 1941. The metabolism of vanillin and vanillic acid in the rabbit. The identification of glucurovanillin and the structure of glucurovanillic acid. Studies in Detoxification. Biochemistry Journal 35(10-11), 1175-1189.

Samuelsen, O.B., Brenna, J., Solheim, E., Scheline, R.R., 1986. Metabolism of the cinnamon constituent o -methoxycinnamaldehyde in the rat. Xenobiotica 16, 845-852.

Sanders, D.J., Minter, H.J., Howes, D., Hepburn, P.A., 2000. The Safety Evaluation of Phytoseterol Esters. Part 6. The Comparative Absorption and Tissue Distribution of Phytosterols in the Rat. Food and Chemical Toxicology 38, 485-491.

Sanyal, R., Darroudi, F., Parzefall, W., Nagao, M., Knasmüller, S., 1997. Inhibition of the genotoxic effects of heterocyclic amines in human derived hepatoma cells by dietary bioantimutagens. Mutagenesis, 12(4), 297-303.

Sasaki, Y.F., Imanishi, H., Ohta, T., Shirasu, Y., 1987. Effects of antimutagenic flavourings on SCEs induced by chemical mutagens in cultured Chinese hamster cells. Mutation Research. 189(3), 313-318.

Sasaki, Y.F., Ohta, T., Imanishi, H., Watanabe, M., Matsumoto, K., Kato, T., Shirasu, Y., 1990.
Suppressing effects of vanillin, cinnamaldehyde and anisaldehyde on chromosome aberrations induces by X-rays in mice. Mutation Research, 243, 299-302.

Sato, R., 2017. A bacterial reverse mutation test of 2-methyl-3-butene-2-thiol. Unpublished report provided to the FEMA Expert Panel.

Scheerbaum, D., 2001. Reverse mutation assay (Amestest) with *Salmonella typhimurium*. Dr. U. Noack Laboratorium, Sarstedt, Germany. Unpublished report provided to the FEMA Expert Panel

Schmidbaur, H., Schier, A., Bayler, A., 1998. The solution and solid state structure of L-carnitine-L-tartrate. Zeitschrift für Naturforschung 53, 788-791.

Schulz, H., 1983. Metabolism of 4-pentenoic acid and inhibition of thiolase by metabolites of 4-pentenoic acid. Biochemistry 22, 1827-1832.

Schulz, M., 2012. Micronucleus test in bone marrow cells of the mouse. Rose oxide 90. Ludwigshafen, Germany. Unpublished report to the FEMA Expert Panel.provided by the Research Institute for Fragrance Materials.

Shaw, P.N., Blagbrough, I.S., 1989. Cysteine conjugate beta-lyase, II: isolation, properties and structure-activity relationships. Wiley-Blackwell, New York.

Shen, H., 2008. Metabolic Stability Test of FEMA 4701 in Rat and Human Liver Microsomes. QPS, LLC, Newark, DE, USA. Unpublished report provided to the FEMA Expert Panel

Shen, H., 2009. In Vitro Biotransformation of FEMA 4701 in Sprague-Dawley Rat and Human Liver Microsomes. QPS, LLC, Newark, DE, USA. Unpublished report provided to the FEMA Expert Panel

Shimizu, H., Suzuki, Y., Takemura, N., Goto, S., Matsushita, H., 1985. The results of microbial mutation test for forty-three industrial chemicals. Sangyo Igaku 27, 400-419.

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., 2005. Criteria for the safety evaluation of flavoring substances. Food and Chemical Toxicology 43, 1141-1177.

Smith, R.L., Cohen, S.M., Fukushima, S., Gooderham, N.J., Hecht, S.S., Guengerich, F.P., Rietjens, I.M.C.M., Bastaki, M., Harman, C.L., McGowen, M.M., Taylor, S.V., 2018. The safety evaluation of food flavouring substances: the role of metabolic studies. Toxicology Research 7, 618-646.

Snapper, I., Yu, T.F., Chiang, Y.T., 1940. Cinnamic Acid Metabolism in Man. Experimental Biology and Medicine 44, 30-34.

Sokolowski, A., 2007. Salmonella typhimurium reverse mutation assay with 10-undecenal. RCC Cytotest Cell Research, Rossdorf, Germany. Unpublished report to the FEMA Expert Panel.provided by the Research Institute for Fragrance Materials.

Solheim, E., Scheline, R.R., 1973. Metabolism of Alkenebenzene Derivatives in the Rat I. p - Methoxyallylbenzene (Estragole) and p - Methoxypropenylbenzene (Anethole). Xenobiotica 3, 493-510.

Solheim, E., Scheline, R.R., 1976. Metabolism of Alkenebenzene Derivatives in the Rat. II. Eugenol and Isoeugenol Methyl Ethers. Xenobiotica 6, 137-150.

Soltesova, A., 2015. The subject compound: Bacterial reverse mutation test. HLS study number TDG0002. Unpublished report provided to the FEMA Expert Panel.

Spruth, B., 2017. Mutagenicity Study of Modifed Guaiac Wood Extract (Guaiacum spp) 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 to the FEMA Expert Panel.

Stofberg, J., Grundschober, F., 1987. Consumption ratio and food predominance of flavoring materials. Perfumer and Flavorist 12, 27.

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.

Sutou, S., Mitsui, Y., Mochizuki, M., Takada, M., Wong, L.Q., 1999. Antimutagenicity testing of glucopuranosylvanillin and vanillin examined in a mouse peripheral blood micronucleus test system. Journal of Kankyo Hen'igen Kenkyu, Unpublished report provided to the FEMA Expert Panel provided by the Research Institute for Fragrance Materials. .

Suttajit, M., Vinitketkaumnuen, U., Meevatee, U., Buddhasukh, D., 1993. Mutagenicity and human chromosomal effect of stevioside, a sweetener from Stevia rebaudiana Bertoni. Environmental health perspectives 101 Suppl 3, 53-56.

Swartz, C., 2018. Mutagenicity assessment of Loquat Leaf Extract as determined by a bacterial reverse mutation assay, Study No. 50064.013. Integrated Laboratory Systems, Inc. Morrisville, NC, USA. Unpublished report provided to the FEMA Expert Panel,

Tafazoli, S., Vo, T.D., Petersen, A., Constable, A., Coulet, M., Phothirath, P., Lang, J., Baldwin, N., 2017. Genotoxicity, acute and subchronic toxicity evaluation of savory food ingredients. Regulatory Toxicology and Pharmacology 87, 71-87.

Tateishi, M., Suzuki, S., Shimizu, H., 1978. Cysteine conjugate beta-lyase in rat liver. A novel enzyme catalyzing formation of thiol-containing metabolites of drugs. The Journal of biological chemistry 253, 8854-8859.

Tateishi, M., Tomisawa, H., 1989. Cysteine conjugate beta-lyase, I: toxic thiol production. Ellis Horwood Limited, England.

Terai, T., Ren, H., Mori, G., Yamaguchi, Y., Hayashi, T., 2002. Mutagenicity of steviol and its oxidative derivatives in Salmonella typhimurium TM677. Chemical & pharmaceutical bulletin 50, 1007-1010.

Terrill, J.B., 1990. 28-Day oral toxicity study in rats. , Study No. 642-482 ed., Hazleton Laboratories America, Inc. Rockville, Maryland, USA. Unpublished report provided to the FEMA Expert Panel.

Thompson, P.W., 2002. Reverse mutation assay "Ames Test" using Salmonella typhimurium and Escherichia coli, Study No. 1543/004. Safepharm Laboratories Limited, Derby, UK. Unpublished report provided to the FEMA Expert Panel.

Thornton-Manning, J.R., Nichols, W.K., Manning, B.W., Skiles, G.L., Yost, G.S., 1993. Metabolism and bioactivation of 3-methylindole by Clara cells, alveolar macrophages, and subcellular fractions from rabbit lungs. Toxicol Appl Pharmacol 122, 182-190.

Tislow, R., Margolin, S., Foley, E.J., Lee, S.W., 1950. Toxicity of undecylenic acid. The Journal of Pharmacology and Experimental Therapeutics 98, 31-32.

Tomita, N.A., T.; Masuda, Y.; Haraguchi, K.; Inenaga, S., 2017. Aroma-Active Compounds in Kombu Dashi. 61st Symposium on the Chemistry of Terpenes, Essential Oils and Aromatics Kanazawa Institute of Technology.

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.

Tsang, S.P., A.; Api, A., 2018. An OECD 408 dietary 90-day toxicity study on 10-undecenal. Society of Toxicology 57th Annual Meeting and ToxExpo Abstract No. 1630. Poster No. P870. Unpublished report to the FEMA Expert Panel.provided by the Research Institute for Fragrance Materials.

van Otterdijk, F.M., 2001. Subacute 28-day oral toxicity with coffee precursor by daily gavage in the rat. NOTOX B.V., 's

Hertogenbosch, The Netherlands. Unpublished report provided to the FEMA Expert Panel,

Vashi, K.D., 2019. *In vitro* mammalian cell micronucleus test of *Chaenomeles speciosa* leaf extract, RD102311-003 in human peripheral blood lymphocytes, Study No. 497-1-06-22481. Jai Research Foundation, Gujarat, India. Unpublished report provided for the FEMA Expert Panel.

Verspeek-Rip, C.M., 1999. Evaluation of the mutagenic activity of ST 06 C 98 in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (with independent repeat). NOTOX B.V., 's-Hertogenbosch, The Netherlands. Unpublished report provided to the FEMA Expert Panel.

Verspeek-Rip, C.M., 2000. Evaluation of the mutagenic activity of coffee precursor in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (with independent repeat). NOTOX B.V., 's-Hertogenbosch, The Netherlands. Unpublished report provided to the FEMA Expert Panel.

Verspeek-Rip, C.M., 2001. Micronucleus test in bone marrow cells of the mouse with coffee precursor. NOTOX B.V., 's-Hertogenbosch, The Netherlands. Unpublished report provided to the FEMA Expert Panel.

Verspeek-Rip, C.M., 2002. Evaluation of the mutagenic activity of rose oxide co in the *Salmonella typhimurium* reverse mutation assay. NOTOX B.V., 's-Hertogenbosch, The Netherlands. Unpublished report provided to the FEMA Expert Panel

Vollmuth, T.A., Bennett, M.B., Hoberman, A.M., Christian, M.S., 1990. An evaluation of food flavoring ingredients using an in vivo reproductive and developmental toxicity screening test. Teratology 41(5), 597-598.

Waalkens-Berendsen, D.H., Wolterbeek, A.P.M., Wijnands, M.V.W., Richold, M., Hepburn, P.A., 1999. Safety evaluation of phytosterol esters. Part 3. Two-generation reproduction study in rats with phytosterol esters--a novel functional food. . Food and Chemical Toxicology 37, 683-696.

Wagner, V.O., 2016. Bacterial Reverse Mutation Assay FEMA 4899. BioReliance Corporation, Rockville, MD, USA. 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.

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 Chem Toxicol 46 Suppl 7, S54-60.

Whistler, R.L., Singh, P.P., Lake, W.C., 1974. D-Psicose metabolism in the rat. Carbohydrate research 34, 200-202.

Whitwell, J., 2012. Induction of micronuclei in cultured human peripheral blood lymphocytes. Furan-2(5H)-one. Study Number: 8233100. Covance Laboratories Ltd., North Yorkshire, England. Unpublished report provided to the FEMA Expert Panel by the International Organization of the Flavor Industry.

Wild, D., King, M.T., Gocke, E., Eckhardt, K., 1983. Study of artificial flavouring substances for mutagenicity in the Salmonella/microsome, Basc and micronucleus tests. Fd Chem. Toxic. 21, 707-719.

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

Williams, R.T., 1959. Detoxication mechanisms. The metabolism and detoxication of drugs, toxic substances, and other organic compounds, 2nd ed.

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 A[1]. Birkhauser Verlag 37, 519-520.

Wisher, M., 2016. Subject compound: reverse mutation assay 'Ames Test' using *Salmonella typhimurium* and *Escherichia coli*, Study No. HM52MF. Envigo Research Limited, Derbyshire, UK. Unpublished report provided to the FEMA Expert Panel.

Wnorowski, G., 1997. 14-Day dietary toxicity study: Rats. Prenylthiol. Product Safety Labs, East Brunswick, New Jersey. Unpublished report provided to the FEMA Expert Panel.

Wolfreys, A.M., Hepburn, P.A., 2002. Safety evaluation of phytosterol esters. Part 7. Assessment of mutagenic activity of phytosterols, phytosterol esters and the cholesterol derivative, 4-cholesten-3-one. Food and Chemical Toxicology 40, 461-470.

Wollny, H.-E., 2012. Gene mutation assay in chinese hamster V79 cells in vitro (V79/HPRT) with rosenoxid 90. Harlan Cytotest Cell Research GmbH, Rossdorf, Germany. Unpublished report to the FEMA Expert Panel.provided by the Research Institute for Fragrance Materials.

Wong, K.P., Sourkes, T.L., 1966. Metabolism of Vanillin and Related Substances in the Rat. Canadian Journal of Biochemistry 44, 635-644.

Wood, H.B., Allerton, R., Diehl, H.W., Fletcher, H.G., 1955. Stevioside. I. The structure of the glucose moieties. The Journal of Organic Chemistry 20, 875-883.

Yagi, K., Matsuo, T., 2009. The study on long-term toxicity of d-psicose in rats. Journal of clinical biochemistry and nutrition 45, 271-277.

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.

Yamaguchi, N., 2017. A bacterial reverse mutation test of (E)-3-(4-isopropyloxyphenyl)prop-2-enal. Unpublished report provided to the FEMA Expert Panel.

Yamashita, T., 1974. *In vivo* chromosomal aberration test of glucono-delta-lactone and sodium gluconate with mouse bone marrow cells. Unpublished report provided to the FEMA Expert Panel.

Yang, Y., Zhang, Y., Zhang, J., Shao, B., 2015. Identification of metabolites of AHTN in rat urine and feces by liquid chromatography/electrospray ionization quadrupole time-of-flight tandem mass spectrometry. Analytical Methods 7, 4443-4449.

Yoo, Y.S., 1986. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. . J Osaka City Med Center, pp. 267-288.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., 1988. Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals. Environmental and Molecular Mutagenesis 11, 1-18.

Zhao, Y., 2016. ADME Tox Study of One Compound, Study No. 100029840 ed. Eurofins Panlabs, St. Charles, MO, USA. Unpublished report provided to the FEMA Expert Panel.

Ziegler, S.J., Sticher, O., 1988. HPLC of *S*-Alk(en)yl-L-cysteine Derivatives in Garlic including Quantitative Determination of (+)-*S*-Allyl-L-cysteine Sulfoxide (Alliin), Planta Medica 55, pp. 372-378.

Ziemianska, S., 2017. Determination of genotoxicity of natural nootkatone on reverse mutation AMES MPF™ Penta I test. Selvita S.A. Krakow, Poland. Unpublished report provided to the FEMA Expert Panel.