Scientific opinion of flavouring group evaluation 503 (FGE.503): grill flavour 'Grillin' CB-200SF'

Vittorio Silano, Claudia Bolognesi, Laurence Castle, Kevin Chipman, Jean Pierre J. P. Cravedi, Karl-heinz Engel, Paul Fowler, Roland Franz, Konrad Grob, Rainer Gürtler, et al.

SCIENTIFIC OPINION

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Scientific opinion of Flavouring Group Evaluation 503 (FGE.503): grill flavour 'Grillin' CB-200SF'

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), Vittorio Silano, Claudia Bolognesi, Laurence Castle, Kevin Chipman, Jean-Pierre Cravedi, Karl-Heinz Engel, Paul Fowler, Roland Franz, Konrad Grob, Rainer Gürtler, Trine Husøy, Sirpa Kärenlampi, Maria Rosaria Milana, Karla Pfaff, Gilles Riviere, Jannavi Srinivasan, Maria de Fátima Tavares Poças, Christina Tlustos, Detlef Wölfle, Holger Zorn, Ulla Beckman Sundh*, Romualdo Benigni, Mona-Lise Binderup, Leon Brimer, Francesca Marcon, Daniel Marzin, Pasquale Mosesso, Gerard Mulder, Agneta Oskarsson, Camilla Svendsen, Maria Carfì, Carla Martino and Wim Mennes

Abstract

The EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel) was requested to deliver a scientific opinion on the implication for human health of the product Grillin' CB-200SF [FL-no: 21.004] in the Flavouring Group Evaluation 503, according to Regulation (EC) No 1331/2008 and Regulation (EC) No 1334/2008 of the European Parliament and of the Council. The product is derived from heat-treated high oleic sunflower oil, and intended to be used as a food flavouring with charbroiled or grilled aroma in a wide variety of food categories either in liquid or powder form. Information on manufacturing and compositional data was considered adequate to show the reproducibility of the production process. However, the Panel noted that a substantial amount of the non-volatile fraction of the product could not be identified. The chronic dietary exposure to the substance estimated using the Added Portions Exposure Technique (APET) was calculated to be 60 mg/person per day for a 60-kg adult and 37.8 mg/person per day for a 15-kg child. The data submitted for evaluating the genotoxic potential of the flavouring was considered insufficient. There are still eight substances in the flavouring for which the evaluation of genotoxic potential is pending. No toxicity studies have been provided on the final product itself. Only information on a number of constituents of the flavouring and data on toxicity of several thermally treated fats and oils were provided by the applicant. However, the Panel considered the time–temperature conditions that were applied in the preparation of the substances tested as not comparable to those applied in the course of the production of the flavouring. The Panel concluded that on the basis of the data provided by the applicant the safety of Grillin' CB-200SF cannot be established.

Keywords: Grillin' CB-200SF, FGE.503, FL-no: 21.004, other flavouring, complex mixture

Requestor: European Commission

Question number: EFSA-Q-2016-00003

Correspondence: fip@efsa.europa.eu

* Member of the Standing Working Group on Flavourings of the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) until 16 June 2017.

Panel members: Claudia Bolognesi, Laurence Castle, Kevin Chipman, Jean-Pierre Cravedi, Karl-Heinz Engel, Paul Fowler, Roland Franz, Konrad Grob, Rainer Gürtler, Trine Husøy, Sirpa Kärenlampi, Wim Mennes, Maria Rosaria Milana, Karla Pfaff, Gilles Riviere, Jannavi Srinivasan, Maria de Fátima Tavares Poças, Vittorio Silano, Christina Tlustos, Detlef Wölfle and Holger Zorn.

Note: The full opinion will be published in accordance with Article 12(3) of Regulation (EC) No 1331/2008 once the decision on confidentiality will be received from the European Commission. The following information has been provided under the confidentiality framework and has been redacted awaiting the decision of the Commission: steps, parameters and flow diagram of the production process.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

1.1.1. Background

The use of flavourings in food is regulated under Regulation (EC) No 1334/2008[1] of the European Parliament and Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods. On the basis of article 9(e) of this Regulation, an evaluation and approval are required for 'other flavourings'.

Regulation (EC) No 1331/2008[2] applies for the evaluation and approval of new 'other flavourings'.

An application for authorisation as a new 'other flavouring' of the product Grillin' CB-200SF, an oil-based grill flavouring product derived from heat-treated sunflower oil has been submitted to the Commission.

In order for the Commission to be able to consider its inclusion in the Union list of flavourings and source materials (Annex I of Regulation (EC) No 1334/2008), the European Food Safety Authority (EFSA) should carry out a safety assessment of this product as a new 'other flavouring'.

1.1.2. Terms of Reference

The European Commission requests EFSA to carry out a safety assessment of the product Grillin' CB-200SF as a new 'other flavouring' in accordance with Regulation (EC) No 1331/2008 establishing a common authorisation procedure for food additives, food enzymes and food flavourings.

1.2. Information on existing authorisation and/or evaluations from other authorities

The Panel is not aware of any official evaluations of Grillin' CB-200SF performed by national or international authorities. According to the applicant, the substance is listed in the US Code of Federal Regulations (CFR), Part 21 Sec 172.515.

2. Data and methodologies

2.1. Data

The applicant has submitted a dossier in support of its application for the authorisation of the flavouring Grillin' CB-200SF for use in a wide range of foods (Red Arrow Products Company LLC, 2015).

2.2. Methodologies

The assessment was conducted in line with the principles described in the EFSA Guidance on transparency in the scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing Guidance from the EFSA Scientific Committee.

The current 'Guidance on the data required for the risk assessment of flavourings to be used in or on foods' (EFSA CEF Panel, 2010) has been followed by the CEF Panel for the evaluation of the application for authorisation of 'Flavourings other than Flavouring Substances – Information to be supplied with an application for the authorisation of Other Flavourings' (PART B. IV) (see Appendix E).

[1] Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. OJ L 354, 31.12.2008, p. 34–50.

[2] Regulation (EC) No 1331/2008 of the European Parliament and of the Council of 16 December 2008 establishing a common authorisation procedure for food additives, food enzymes and food flavourings. OJ L 354, 31.12.2008, p. 1–6.

3. Assessment

3.1. Technical data

3.1.1. Identity

The applicant has provided the following information with respect to the identity of the flavouring Grillin' CB-200SF.

Chemical name:	Not applicable (complex mixture)
FL-no:	21.004
CAS number:	Not available
EINECS number:	Not available
Synonyms:	Not available
Trade name:	Grillin' CB-200SF
Chemical formula:	Not applicable (complex mixture)
Structural formula:	See Appendix A for some of the volatile constituents of Grillin' CB-200SF
Molecular weight:	Not applicable (complex mixture)

3.1.2. Specifications

The specifications for Grillin' CB-200SF as proposed by the applicant are listed in Table 1.

Table 1: Specifications for Grillin' CB-200SF as proposed by the applicant

Product name:	**Grillin' CB-200SF**
Description:	Golden viscous oil with a grill aroma
Solubility:	Soluble in oil; insoluble in water
Aroma:	Strong charbroiled/chargrilled flavour
Source material:	High oleic sunflower oil
Content:	> 96% non-GMO sunflower oil and < 3.5% grill flavour
Specific gravity:	0.894–0.929 g/mL
Microbiological specification:	The material does not support microorganism growth
Formulation:	Grillin' CB-200SF is used in the liquid or powder form

The Panel does not agree with the specification proposed by the applicant for the 'Content'. According to information provided by the applicant, a substantial part of the sunflower oil (~ 27%) used as the source material of the flavouring is converted into unidentified constituents in the course of the production process (see Section 3.1.4).

3.1.3. Manufacturing process

Source material

The flavouring Grillin' CB-200SF is produced starting from high oleic sunflower oil. According to the certificate provided by the supplier, the oil is obtained by expeller pressing from a United States Department of Agriculture (USDA)-approved variety. The edible oil has been refined, bleached, winterised and deodorised. According to information provided in a technical data sheet by the supplier, the oil is routinely monitored for organophosphate and organochlorine pesticide residues; no detectable levels have been reported. Levels of lead, cadmium, chromium, mercury and arsenic are also below the respective limits of detection (0.05 mg/kg). Compositional data regarding the distribution of fatty acids are presented in Table 2.

Table 2: Compositional data of high oleic sunflower oil used as the source for the production of the flavourings Grillin' CB-200SF (Columbus Vegetable Oils, 2014)

Components	Amount %
Total fat (g)[(b)]	100
Saturated fat (g)[(a)]	9.0
Polyunsaturated fatty acids (g)[(a)]	9.5
Monounsaturated fatty acids (g)[(a)]	81.0
Trans-fatty acids (g)[(a)]	0.5
16:0 Palmitic[(b)]	5.0
18:0 Stearic[(b)]	4.0
18:1 Oleic[(b)]	81.0
18:2 Linoleic[(b)]	9.0
18:2 Linoleic (*trans* isomers)[(b)]	0.5
18:3 Linolenic[(b)]	0.5

(a): Calculated.
(b): Based on analytical results.

Genetically Modified Organism

The flavouring neither contains nor is produced from genetically modified organisms (GMOs). The sunflower oil is obtained from non-genetically modified sunflower seeds.

Production Process

Sunflower oil is [redacted]. The [redacted] is then converted to the flavouring Grillin' CB-200SF in a circulating fluid bed thermal processor at a temperature between [redacted] involving air injection. After a reaction time of [redacted], the product is immediately cooled to [redacted] and placed into storage at ambient temperature for further processing. The grill oil [redacted] and finally subjected to a filtration [redacted] (Appendix F) to obtain the liquid form.

In addition to this liquid form, Grillin' CB-200SF is also manufactured as powder. To this end, liquid Grillin' CB-200SF is microencapsulated with a carbohydrate-based polymer. Spray-drying results in a powdered product containing [redacted] of Grillin' CB-200SF.

3.1.4. Compositional data

Volatile constituents

In the original submission, the data provided by the applicant were focused on the volatile constituents of the flavouring.

Three batches of Grillin' CB-200SF were investigated by solid phase microextraction and gas chormatography/mass spectrometry (GC/MS); a total of 120 volatile constituents were reported (Table 3). The concentrations reported were estimated relative to an internal standard. No validation data for the quantification step (e.g. differences between the constituents in the course of the headspace extraction or differences in GC-responses compared to the internal standard) were reported. Therefore, the Panel considered the provided data as semiquantitative.

The volatiles constituents amounted to an average content of 3.4% of Grillin' CB-200SF. The main part (90%) of the volatile fraction is accounted for by a group of 76 aliphatic hydrocarbons (53.7%) and a group of 14 simple linear aliphatic saturated aldehydes and carboxylic acids (36.7%).

The applicant assigned the volatile constituents of Grillin' CB-200SF to six congeneric groups:

1) aliphatic hydrocarbons (53.7% of the volatile fraction or 1.87% of Grillin' CB-200SF);
2) aliphatic linear aldehydes, carboxylic acids, and related esters (36.7% of the volatile fraction or 1.28% of Grillin' CB-200SF);
3) aliphatic linear unsaturated alcohols and aldehydes (7.4% of the volatile fraction or 0.26% of Grillin' CB-200SF);
4) aromatic derivatives (1.1% of the volatile fraction or 0.038% of Grillin' CB-200SF);
5) alkyl furan derivatives (0.8% of the volatile fraction or 0.028% of Grillin' CB-200SF);
6) aliphatic ketones (0.3% of volatile fraction or 0.011% of Grillin' CB-200SF).

Despite the described analytical shortcomings regarding the quantification, the Panel considered the batch-to-batch variability of the volatile constituents reported in Table 3 as acceptable. The data provided indicate that the production process is reproducible.

Table 3: Volatile constituents identified and semi-quantified in Grillin' CB-200SF via Headspace (HS) Solid Phase Microextraction (SPME) – GC/MS

Constituents	CG no.	Concentration mg/kg			Average
		Lot no. 1	Lot no. 2	Lot no. 3	
Aliphatic hydrocarbons	**1**				**18,671**
Octane	1	2.2	2.3	3	2.5
Octene isomer	1	1.7	2	1.9	1.9
Nonane	1	6.8	10	12	9.6
Nonene isomer	1	20	20	17	19
Butyl cyclopentane	1	1.5	1.6	2.3	1.8
Propyl cyclohexane	1	2.3	3.6	2.6	2.8
Nonadiene	1	2.3	2.5	2.7	2.5
Decane	1	7.1	9.5	10	8.9
Decene isomers (2)	1	43	49	50	47.3
Butyl cyclopentene	1	32	35	34	33.7
Propyl cyclohexene	1	12	14	14	13.3
Undecane	1	12	15	17	14.7
Butyl cyclohexene isomers (2)	1	33	33	28	31.3
Undecene isomers (4)	1	1,160	1,500	1,700	1,453
Dodecane	1	10	14	21	15
Pentyl cyclohexene isomers (2)	1	16	16	15	15.7
Hexyl cyclopentene isomers (2)	1	13	13	18	14.7
Dodecene isomers (5)	1	130	150	160	147
Undecadiene isomers (4)	1	870	1,400	930	1,067
Tridecane	1	34	43	51	42.7
Tridecene isomers (3)	1	99	95	114	103
Dodecadiene isomers (4)	1	1,500	2,300	1,600	1,800
Tridecadiene isomers (3)	1	270	320	330	307
Tetradecane	1	25	25	31	27
Tetradecene	1	6.1	9.4	12	9.2
Hexadecene	1	150	170	160	160
Octyl cyclopentene	1	32	35	33	33.3
Tetradecadiene isomers (2)	1	130	130	130	130
Pentadecane	1	82	130	150	121
Cyclotetradecane	1	55	84	110	83
Pentadecene isomers (2)	1	200	260	340	267
Nonyl cyclopentene	1	320	330	320	323
Octyl cyclohexene isomers (2)	1	110	130	130	123
Hexadecane	1	22	26	38	28.7
Nonyl cyclohexane	1	140	210	260	203
Hexadecene isomers (2)	1	430	440	540	470
Nonyl cyclohexene isomers (3)	1	280	320	340	313
Hexadecadiene isomers (2)	1	430	450	480	453
Tetradecadiene	1	1,600	1,800	1,800	1,733
Heptadecane	1	65	84	150	99.7
Heptadecene isomers (2)	1	4,100	5,600	7,100	5,600
Decyl cyclohexene	1	170	210	230	203

Constituents	CG no.	Concentration mg/kg			Average
		Lot no. 1	Lot no. 2	Lot no. 3	
Nonadecene	1	180	190	160	176
Octadecene	1	1,900	3,300	3,500	2,900
Nonadecene isomers(2)	1	44	65	69	59.3
Primary alcohols, aldehydes, acids, esters	**2**				**12,754**
2*H*-Pyran-2-one	2	39	52	61	50.7
Heptanal	2	9	10	11	10
Nonanal	2	150	140	160	150
Acetic acid	2	15	19	19	17.7
Decanal	2	84	93	83	86.7
Hexanoic acid	2	110	150	180	146
Heptanoic acid	2	230	330	430	330
Pentadecanal	2	41	39	36	38.7
Octanoic acid	2	130	200	260	196
Nonanoic acid	2	150	250	330	243
Heptadecanal	2	14	9.3	8.9	10.7
Decanoic acid	2	8,200	12,000	14,000	11,400
Undecanoic acid	2	40	58	64	54
Dodecanoic acid	2	17	19	21	19
Aliphatic linear unsaturated aldehydes and acids	**3**				**2,561**
2-Propenal	3	4.9	5.8	7.3	6
2-Heptenal + 2-hexylfuran	3	17	12	18	15.7
2,4-Hexadienal	3	16	15	19	16.7
2-Octenal	3	8.6	8	8.9	8.5
2-Nonenal	3	22	20	23	21.7
2-Decenal + tetradecadiene	3	580	480	630	563
2-Undecenal	3	800	670	890	786
Pentenoic acid	3	18	19	21	19.3
2,4-Decadienal	3	41	28	47	38.7
2-Dodecenal	3	13	13	17	14.3
Hexenoic acid	3	50	56	60	55.3
Heptenoic acid	3	220	220	260	233
Octenoic acid	3	64	94	110	89.3
Nonenoic acid	3	36	51	54	47
Heptadecenal	3	730	510	360	533
Decenoic acid	3	35	30	46	37
Undecenoic acid isomers (2)	3	57	82	85	74.7
Aromatic derivatives	**4**				**375**
Styrene	4	10	11	13	11.3
Butyl benzene	4	11	12	15	12.7
Pentyl benzene	4	15	10	13	12.7
Benzaldehyde	4	52	78	100	76.7
Naphthalene	4	20	27	28	25
Phenol	4	200	240	270	236
Alkylfuran derivatives	**5**				**276**
2-Methylfuran	5	0.9	0.8	0.9	0.9
Heptylfuran	5	52	51	51	51.3
2-Octylfuran	5	210	210	250	223

Constituents	CG no.	Concentration mg/kg			Average
		Lot no. 1	Lot no. 2	Lot no. 3	
Aliphatic ketones	**6**				**109**
2-Decanone	6	31	32	32	31.7
2-Undecanone	6	36	37	34	35.7
Nonen-3-ol	6	37	45	44	42
Total volatile organic compounds (VOC)					**34,746**

Other constituents

In addition, the applicant provided the following compositional information on the flavouring:

In six batches of Grillin' CB-200SF, the concentrations of cadmium, lead, mercury and arsenic were shown to be below the limits of detection (0.010 mg/kg) of the applied analytical technique (inductively coupled plasma mass spectrometry (ICP-MS)).

Data on the sum of dioxins and polychlorinated biphenyls (PCBs) were determined for six batches of Grillin' CB-200SF and were below the maximum levels for the sum of dioxins and PCBs, as laid down by Regulation (EC) No 1881/2006[3]. However, it is not clear to what extent this legislation is applicable to the flavouring Grillin' CB-200SF.

The content of benzene in Grillin' CB-200SF was below the limit of detection of the applied methodology (0.01 mg/kg).

Data on 21 polycyclic aromatic hydrocarbons (PAHs) have been provided for three batches of Grillin' CB-200SF. The Panel noted that the sum of the four PAHs benzo(a)pyrene, benzo(a)anthracene, benzo(b)fluoranthene and chrysene exceeds the legislative limit of 10 μg/kg for oils and fats used as ingredients in food, as set by Regulation (EC) No 1881/2006. For the three different lots tested, the sum of the four PAHs was found to be 10.1, 14.6 and 18.5 μg/kg. However, it is not clear to what extent this legislation is applicable to the flavouring Grillin' CB-200SF.

The applicant reported a content of 5.01 g *trans*-fatty acids/100 g in Grillin' CB-200SF, which is 10 times higher than in the high oleic sunflower oil used as the source of the flavouring. Considering the use levels proposed by the applicant (Appendix B), the lowest limit set in the EU countries that have limiting legislation on *trans*-fatty acids (i.e. 2 g *trans*-fatty acids/100 g fat; 'Report from the Commission to the European Parliament and the Council regarding trans fats in foods and in the overall diet of the Union population' (SANTE/11129/2015-EN Rev. 4)) can be complied with.

Overall composition

The Panel asked for additional compositional data going beyond the elucidation of the quantitatively minor volatile fraction and providing in particular information on the amount of unidentified non-volatile constituents in the flavouring.

In response to this request, the applicant performed the following combination of analyses and calculations in order to describe the overall composition of Grillin' CB-200SF:

i) Determination of the total, non-oxidised fatty acids (TFA) via hydrolysis and esterification.
TFA: 66.5%
ii) Determination of the free fatty acids (FFA) via titration.
FFA: 12.2%
iii) Calculation of the glycerol-bound fatty acids (TFA – FFA) and extrapolation to triglycerides based on a proportion of 95.6% oleic acid in triglyceride.
TFA – FFA: 66.5 – 12.2% = 54.3% glycerol-bound fatty acids
Triglycerides: 56.8%
iv) Determination of the volatile constituents via HS-SPME.
Volatile constituents: 3.5%
v) Determination of the water content via Karl Fischer.
Water: 0.11%

[3] Regulation (EC) No 1881/2006 of the European Parliament and of the Council of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. OJ L 364, 20.12.2006, p. 5–24.

vi) Calculation of the unidentified non-volatile mass:
100 (%) – triglycerides (%) – free fatty acids (%) – volatiles (%) – water (%) = 27.4%

The resulting overall composition of Grillin' CB-200SF is shown in Figure 1.

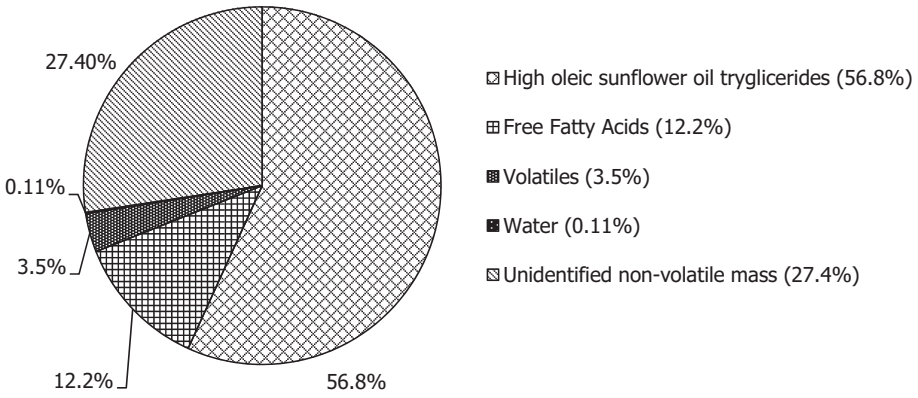

Figure 1: Overall composition of Grillin' CB-200SF

The Panel considered that by this approach the proportion of unidentified constituents (27.4%) is likely to be underestimated. In the absence of water, liberation of free fatty acids is likely to leave behind unsaturated species that have molecular masses in the range of diglycerides. This type of reaction was shown to occur above 300°C (Grob, 1981).

3.1.5. Stability, reaction and fate in food

No information was provided by the applicant.

3.1.6. Particle size[4]

No information was provided by the applicant on the particle size in the powder formulation.

3.2. Structural/metabolic similarity to substances present in existing FGEs

Of the 120 volatile compounds identified in the three batches of Grillin' CB-200SF, 29 are identical to substances included in the Union list of chemically defined flavouring substances,[1] whereas 12 compounds are unidentified isomers of flavouring substances in the Union list (Appendix A). Eighteen of the 29 flavouring substances have been evaluated to be of no safety concern when the intake is estimated based on the Maximised Survey-Derived Daily Intake (MSDI) approach, while three of the 29 flavouring substances are no longer supported by industry. For the remaining eight substances (FL-no: 05.037, 05.060, 05.070, 05.171, 05.076, 05.081, 05.109 and 13.162), additional genotoxicity data are pending to rule out concerns regarding genotoxicity.

The volatile constituents identified in Grillin' CB-200SF, which also listed as flavouring substances in the Union list, are compiled in Appendix A. The FL-no, the name in the Union list and the current status regarding the evaluation by EFSA are presented.

3.3. Information on existing evaluations from EFSA

Grillin' CB-200SF has not been evaluated by EFSA before.

3.4. Exposure assessment

The data for estimating exposure (i.e. normal and maximum occurrence levels for refined subcategories of foods and beverages) are reported in Appendix B.

[4] Commission Recommendation 2011/696/EU of 18 October 2011 on the definition of nano-materials. Official Journal of the European Union L257/38-40 on 20.10.2010 http://ec.europa.eu/environment/chemicals/nanotech/pdf/commission_recommendation.pdf

3.4.1. Chronic dietary exposure

The exposure assessment to be used for the safety evaluation of the flavouring is the chronic added portions exposure technique (APET) estimate (EFSA CEF Panel, 2010). The chronic APET for [FL-no: 21.004] has been calculated for adults and children (see Table 4). Based on use levels provided by the applicant (see Appendix B), the chronic APET calculation is based on the combined normal occurrence level.

Although the flavouring is not intended to be used in food categories specifically intended for infants and toddlers, these could still be exposed through the consumption of foods from the general food categories, which may contain the flavouring. However, at present, there is no generally accepted methodology to estimate chronic dietary exposure in these age groups resulting from consumption of foods from the general categories. Exposure of infants and toddlers is currently under consideration by EFSA.

Table 4: APET – Chronic dietary exposure to Grillin' CB-200SF

Chronic APET[a]	Added[b]		Other dietary sources[c]		Combined[d]	
Use level	**µg/kg bw per day**	**µg/person per day**	**µg/kg bw per day**	**µg/person per day**	**µg/kg bw per day**	**µg/person per day**
Adults[e]	1,000	60,000	0	0	1,000	60,000
Children[f]	2,520	37,800	0	0	2,520	37,800

(a): APET: added portions exposure technique; bw: body weight: the chronic APET calculation is based on the combined **normal** occurrence level.
(b): APET Added is calculated on the basis of the **normal** amount of flavouring added to a specific food category.
(c): APET Other Dietary Sources is calculated based on the natural occurrence of the flavouring in a specified food category.
(d): APET Combined is calculated based on the combined amount of added flavouring and naturally occurring flavouring in a specified food category.
(e): For the adult APET calculation, a 60-kg person is considered representative.
(f): For the child APET calculation, a 3-year-old child with a 15 kg bw is considered representative.

3.4.2. Acute dietary exposure

The acute APET calculation for [FL-no: 21.004] is based on the combined maximum occurrence level and large portion size, i.e. three times standard portion size (see Appendix B).

Although the flavouring is not intended to be used in food categories specifically intended for infants and toddlers, these could still be exposed through consumption of foods from the general food categories. At present, there is no generally accepted methodology to estimate acute dietary exposure in these age groups. Exposure of infants and toddlers is currently under consideration by EFSA.

Data for the chronic APET value for the flavouring are given in Table 5.

Table 5: APET – Acute Dietary Exposure to Grillin' CB-200SF

Acute APET[a]	Added[b]		Other dietary sources[c]		Combined[d]	
Use level	**µg/kg bw per day**	**µg/person per day**	**µg/kg bw per day**	**µg/person per day**	**µg/kg bw per day**	**µg/person per day**
Adults[e]	15,000	900,000	0	0	15,000	900,000
Children[f]	37,800	567,000	0	0	37,800	567,000

(a): APET: added portions exposure technique; bw: body weight: the acute APET calculation is based on the combined **maximum** occurrence level.
(b): APET Added is calculated on the basis of the **maximum** amount of flavouring added to a specific food category.
(c): APET Other Dietary Sources is calculated based on the natural occurrence of the flavouring in a specified food category.
(d): APET Combined is calculated based on the combined amount of added flavouring and naturally occurring flavouring in a specified food category.
(e): For the adult APET calculation, a 60-kg person is considered representative.
(f): For the child APET calculation, a 3-year-old child with a 15 kg bw is considered representative.

3.5. Biological and toxicological data

3.5.1. Genotoxicity

In vitro

Bacterial reverse mutation assay

In order to investigate the potential of Grillin' CB-200 SF and/or its metabolites to induce gene mutations in bacteria, an Ames test was performed according to OECD Test Guideline 471 (OECD, 1997) and following Good Laboratory Practice (GLP) in *Salmonella* Typhimurium (TA98, TA100, TA1535 and TA1537 strains) and *Escherichia coli* (WP2 uvrA strain) in the presence and absence of metabolic activation. Two separate experiments were performed using the plate incorporation method. Appropriate positive control chemicals and acetone (as vehicle control) were evaluated concurrently. All positive control chemicals induced significant increases in revertant colony numbers, confirming the sensitivity of the tests and the efficacy of the S9-mix, while negative controls were within the historical control ranges. The concentrations tested were 1.5, 5.0, 15, 50, 150, 500, 1,500 and 5,000 μg per plate. Precipitate was observed at 500 μg per plate and above. No toxicity was observed. No increase in revertant colony numbers was observed in *S.* Typhimurium and *E. coli* strains at any concentration tested both in the presence and absence of metabolic activation. The Panel noted that the potential mutagenic activity of some chemicals resulting from the heating of the sunflower oil during the production of Grillin' CB-200 SF (e.g. aldehydes) could not be detected using the plate incorporation assay and requested a repetition of the assay applying the pre-incubation method. The applicant did not provide the additional information requested because 'OECD 471 TG did not specifically mention testing sunflower oil (or the components thereof)' and the condition for testing in the pre-incubation method was considered 'not to mimic real life heating or use of sunflower oil for human consumption'. The Panel considered these justifications as not valid because even though the OECD TG 471 does not always require the application of the pre-incubation method, some compounds were mentioned in the OECD test guideline 471, including aldehydes and allyl compounds, that may be detected more efficiently using the pre-incubation method as well as 'special cases', such as volatile chemicals, for which alternative procedures are strongly recommended.

Since the applicant declined to provide these data, no conclusions can be drawn regarding the potential of Grillin' CB-200 SF to induce gene mutations in bacteria.

In vitro *micronucleus assay*

The *in vitro* micronucleus assay was carried out according to OECD Test Guideline 487 (OECD, 2014) and following GLP. Whole blood cultures from healthy donors were treated with Grillin' CB-200 SF following two experimental conditions: a short treatment with and without S9-mix (4 + 20 h recovery) and a continuous treatment without S9-mix (24 + 0 h recovery). Cytochalasin B (final concentration of 6 μg/mL) was added to each culture after short treatment periods, while in the continuous treatment, cultures were treated with the test article in the presence of cytochalasin B. Appropriate vehicle (acetone) and positive controls were used. All positive controls induced a statistically significant increase of micronucleus frequency and the system was considered sensitive and valid. Two thousand cells were scored per concentration. Based on the result of a dose-finding assay, the concentrations tested in the micronucleus assay were 10, 25 and 50 μg/mL in the 4 and 24-h treatments without S9-mix, and 25, 50, 75 and 100 μg/mL in the 4-h treatment with S9-mix. Precipitate was observed at the highest concentrations tested both in the presence and absence of S9-mix. Cytotoxicity was observed up to 17% relative to vehicle controls. No statistically significant increase in the frequency of micronucleated binucleated cells (MNBN) was observed in the 4 and 24-h treatments without S9-mix. Following short treatment in the presence of metabolic activation, a statistically significant increase ($p > 0.05$, Fisher's Exact test) of MNBN was observed at 75 and 100 μg/mL; the values of MNBN (1.3%) were above the upper limit in the 95th percentile reference control range (0–0.82%).

These results were not reproduced in a repeat experiment performed with the short treatment (4 + 20 h) in the presence of metabolic activation at 25, 50 and 100 μg/mL, where no cytotoxicity nor a statistically significant increase of MNBN relative to vehicle control was observed at any concentration tested. Based on the contrasting findings of the study, the Panel requested a repetition of the micronucleus assay to clarify the equivocal effects observed. Furthermore, the Panel noted that the historical control values of the laboratory were not appropriate since the ranges for negative and positive historical controls were overlapping. Since the applicant did not provide the additional data

requested, no conclusions can be drawn on the potential of Grillin' CB-200 SF to induce chromosome damage in mammalian cells.

Further details on the two above listed studies are given in Appendix C.

In addition to the two studies described above, the applicant has submitted a series of studies performed with some of the α,β-unsaturated aldehydes which have been identified within the volatile fraction of Grillin' CB-200SF. These substances have been evaluated by EFSA in FGE.200 (EFSA CEF Panel, 2014b) and in FGE.203 (EFSA CEF Panel, 2014a), for which additional genotoxicity data have been requested. Therefore, the Panel considered that these additional data do not change the conclusions on the *in vitro* genotoxic potential of Grillin' CB-200SF.

In vivo

Grillin' CB-200SF has not been tested under *in vivo* conditions. Instead, the applicant has taken the approach to provide data on a number of substances found in Grillin' CB-200SF. As is the case for the *in vitro* studies, the substances tested are mostly from FGE.200 (EFSA CEF Panel, 2014b) and FGE.203 (EFSA CEF Panel, 2014a), for which EFSA currently has a request for additional genotoxicity data, respectively, as a genotoxic potential cannot be excluded based on the existing data package.

The Panel noted that these *in vivo* studies do not allow to conclude on the genotoxicity of Grillin' CB-200SF.

3.5.2. Conclusion on genotoxicity

Overall, the Panel concluded that the *in vitro* and *in vivo* data set provided by the applicant for Grillin' CB-200SF is insufficient to evaluate the genotoxic potential of the flavouring.

In addition, the Panel noted that for eight flavouring substances identified as volatile constituents of Grillin' CB-200SF (FL-no: 05.037, 05.060. 05.070. 05.171. 05.076. 05.081. 05.109 and 13.162), additional genotoxicity data are required to rule out a concern for genotoxicity (Appendix A).

3.5.3. Absorption, distribution, metabolism and excretion

The applicant provided descriptions of the metabolism of volatile substances belonging to 'congeneric groups' listed in Section 3.1.4. (Red Arrow Products Company LLC, 2015).

These data provided for selected volatile constituents only, were considered to be insufficient by the Panel to support the evaluation of Grillin'CB-200SF.

3.5.4. Acute toxicity

No information was provided by the applicant on acute toxicity for Grillin' CB-200SF.

3.5.5. Short-term and subchronic toxicity

No short-term and subchronic toxicity studies have been performed with Grillin' CB-200SF.

The applicant only presented data on some volatile substances: 2,4-decadienal (Damske et al., 1980; NTP, 2011), 2-hexenal (Gaunt et al., 1971), 1-octene (Til et al., 1988, report not provided by the applicant), two of which have been identified in the flavouring.

The Panel concluded that the data provided are not sufficient to support the evaluation of Grillin' CB-200SF.

3.5.6. Chronic toxicity and carcinogenicity

No chronic toxicity or carcinogenicity studies have been performed with the flavouring Grillin' CB-200SF itself.

The applicant only referred to data on 2,4-hexadienal (NTP, 2003), as representative substance for the volatile constituents identified in the flavouring.

In addition, the applicant referred to data from a 2-year feeding study with rats administered diets containing 15% of soybean oil (hydrogenated to an iodine value of 70 and 108, respectively) that had been used under practical restaurant-type conditions for frying at 182°C, 8 h daily for a total of 84 and 60 h, respectively (Nolen et al., 1967). A similarly treated, hydrogenated soybean oil (iodine value 108) containing 1.6 ppm methylsilicone, was heated for 216 h at 182°C. Also, cotton oil (heated 49 h) and lard (heated 116 h) were used. The authors reported no changes in the toxicological parameters checked, which included histopathology and clinical-chemical measurements in urine and blood. A

decreased growth in the heated oil-groups as compared to rats that received only the fresh hydrogenated soybean oil (iodine value 108) was observed after 2 and 12 months, which, according to the authors, may be related to decreased absorbability as a result of heating. Similar results were obtained in a 50-week feeding study with four dogs administered a diet containing 15% partially hydrogenated soybean oil (iodine value 107) used under practical restaurant-type conditions for frying (182°C) for 56 h (Nolen, 1973) (Appendix D).

3.5.7. Reproductive and developmental toxicity

No reproductive or developmental toxicity studies have been performed with Grillin' CB-200SF as such.

The applicant only provided data on developmental toxicity studies on two volatiles substances (1-hexene (Gingell et al., 1999) and 1-tetradecene (report not provided by the applicant).

In addition, the applicant presented data from a two-generation study with rats administered diets containing 15% partially hydrogenated soybean oil (iodine value 107) that had been used under practical restaurant-type conditions for frying at 182°C for 56 h (Nolen, 1972). According to the authors, there was no evidence of deleterious effects on the reproductive parameters, nor were any teratogenic effects observed (Appendix D).

3.5.8. Conclusion on toxicity

A substantial portion of the flavouring remains unidentified. No toxicity studies have been performed with the flavouring itself. Considering that the volatile fraction of the flavouring amounts to 3.5%, the Panel concluded that the data provided for some of the volatile constituents (see Sections 3.5.5, 3.5.6 and 3.5.7) are not sufficient to demonstrate the safety of Grillin' CB-200SF.

The Panel also considered the referred data on feeding studies with partially hydrogenated soybean oil that had been used under practical restaurant-type conditions for frying (at 182°C for 49–216 h) as not suitable to demonstrate the safety of Grillin' CB-200SF. The Panel considered, in particular, the time–temperature conditions as not comparable.

Several compound classes are known to be formed upon thermo-oxidation of fats and oils. In addition to polymerisations resulting in dimeric and higher oligomeric triglycerides, the formation of monomeric oxidised triglycerides has been reported. Glycerol-bound epoxy-, hydroxy- and keto-fatty acids are the main types of oxidation products (e.g. Dobarganes and Márquez-Ruiz, 2006). A few quantitative data on the formation of these oxidation products are available; for example, a total of 1.23 g/100 g of epoxy-, keto- and hydroxy-acids have been reported in high oleic sunflower oil subjected to thermo-oxidation for 10 h at 180°C (Marmesat et al., 2008). However, the kinetics of their formation as a function of the applied temperature is not known.

The soybean oil used for the feeding studies had been partially hydrogenated before the heat-treatment which might result in a reduced susceptibility to oxidation reactions.

It is well known that reaction rates may increase exponentially as a function of temperature and it is also very likely that, at these high temperatures at which Grillin' CB-200SF is produced, different chemical reaction pathways may occur than under conditions of restaurant-type food processing.

In addition, the heat-treatment of sunflower oil in the course of the production of Grillin' CB-200SF involved the injection of air into the reactor which might result in increased oxidation rate.

Therefore, Grillin' CB-200SF cannot be considered equivalent to the heated oils used in the feeding studies.

4. Conclusions

The Panel concluded that the *in vitro* and *in vivo* data provided by the applicant for Grillin' CB-200SF are insufficient to evaluate the genotoxic potential of the flavouring.

In addition, for eight volatile compounds identified in Grillin' CB-200SF (FL-no: 05.037, 05.060, 05.070, 05.171, 05.076, 05.081, 05.109 and 13.162), additional genotoxicity data are required, according to their pending evaluations as flavouring substances.

A substantial portion of the flavouring remains unidentified.

The Panel considered the data on feeding studies with partially hydrogenated soybean oil that had been treated under restaurant-type conditions for frying as not suitable to demonstrate the safety of Grillin' CB-200SF. The Panel considered, in particular, the time–temperature conditions employed to produce these oils as not comparable to those applied to produce Grillin' CB-200SF.

The Panel concluded that on the basis of the data provided by the applicant the safety of Grillin' CB-200SF cannot be established.

Documentation provided to EFSA

1) Red Arrow Products Company LLC, Oct 2015 The safety evaluation of flavourings 'other than flavouring substances': Grillin' CB-200SF. Unpublished report submitted by Red Arrow Products Company LLC.
2) Red Arrow Products Company LLC, Jan 2017. Responses to the request of additional information on the product Grillin' CB-200SF [FL-no: 21.004], (EFSA-Q-2016-00003). Including Exhibit A1 to A9. Unpublished data submitted to Red Arrow Products Company LLC.

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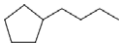
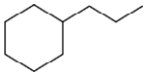
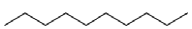
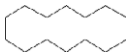
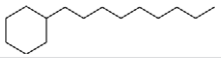
Abbreviations

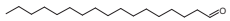
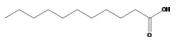
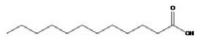
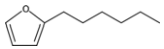
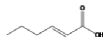
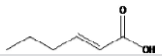
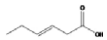
APET	Added Portions Exposure Technique
bw	body weight
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CFR	US Code of Federal Regulations
DATA	Evidence Management Unit, EFSA
DG SANCO	Directorate General for Health and Consumers
EFFA	European Flavour Association
EINECS	European Inventory of Existing Commercial chemical Substances
FAO	Food and Agriculture Organization of the United Nations
FFA	free fatty acids
FGE	Flavouring Group Evaluation
FL-no	FLAVIS number
GC	gas chromatography
GLP	Good Laboratory Practice
GMO	genetically modified organisms
GSFA	General Standard for Food Additives
HS-SPME	headspace solid phase microextraction
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MNBN	micronucleated binucleated cells
MS	mass spectrometry
MSDI	Maximised Survey-derived Daily Intake
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PAHs	polycyclic aromatic hydrocarbons
PCB	polychlorinated biphenyl
SCF	Scientific Committee on Food
SPET	Single Portion Exposure Technique
TFA	total fatty acids
USDA	United States Department of Agriculture
VOC	volatile organic compound
WHO	World Health Organization

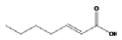
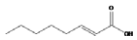
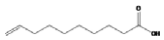
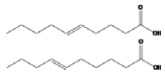
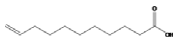
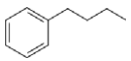
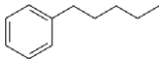
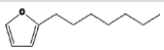
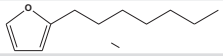
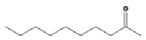
Appendix A – Volatile constituents of Grillin' CB-200SF

Table A.1: Summary of evaluation status for the volatile constituents of Grillin' CB-200SF, some of which are also used as flavouring substances and evaluated by EFSA

Constituents of Grillin' CB-200SF (no of isomers)	Union List substance name (FL-no)	CASrn	Chemical structure	EFSA conclusion on the union list substance	Comments
Octane	–	111-65-9			
Octene isomer	1-Octene [01.070]	111-66-0		(a)	(f)
Nonane	–	111-84-2			
Nonene isomer	–	–	Unspecified isomer		
Butyl cyclopentane	–	2040-95-1			
Propyl cyclohexane	–	1678-92-8			
Nonadiene	2,4-Nonadiene [01.078]	71030-52-9		(b)	(f)
Decane	–	124-18-5			
Decene isomers (2)	–	–	Unspecified isomer		
Butyl cyclopentene	–	–	Unspecified isomer		
Propyl cyclohexene	–	–	Unspecified isomer		
Undecane	–	1120-21-4			
Butyl cyclohexene isomers (2)	–	–	Unspecified isomer		
Undecene isomers (4)	–	–	Unspecified isomer		
Dodecane	Dodecane [01.038]	112-40-3		(a)	
Pentyl cyclohexene isomers (2)	–	–	Unspecified isomer		
Hexyl cyclopentene isomers (2)	–	–	Unspecified isomer		
Dodecene isomers (5)	Dodec-1-ene [01.037]	25378-22-7		(b)	(f)
Undecadiene isomers (4)	–	–	Unspecified isomer		
Tridecane	–	629-50-5	$CH_3–(CH_2)_{11}–CH_3$		
Tridecene isomers (3)	–	–	Unspecified isomer		
Dodecadiene isomers (4)	–	–	Unspecified isomer		
Tridecadiene isomers (3)	–	–	Unspecified isomer		
Tetradecane	Tetradecane [01.057]	629-59-4		(a)	

Constituents of Grillin' CB-200SF (no of isomers)	Union List substance name (FL-no)	CASrn	Chemical structure	EFSA conclusion on the union list substance	Comments
Tetradecene	–	–	Unspecified isomer		
Hexadecene	–	–	Unspecified isomer		
Octyl cyclopentene	–	–	Unspecified isomer		
Tetradecadiene isomers (2)	–	–	Unspecified isomer		
Pentadecane	Pentadecane [01.054]	629-62-9		(a)	
Cyclotetradecane	–	295-17-0			
Pentadecene isomers (2)	–	–	Unspecified isomer		
Nonyl cyclopentene	–	–	Unspecified isomer		
Octyl cyclohexene isomers (2)	–	–	Unspecified isomer		
Hexadecane	–	–	Unspecified isomer		
Nonyl cyclohexane	–	2883-02-5			
Hexadecene isomers (2)	–	–	Unspecified isomer		
Nonyl cyclohexene isomers (3)	–	–	Unspecified isomer		
Hexadecadiene isomers (2)	–	–	Unspecified isomer		
Tetradecadiene	–	–	Unspecified isomer		
Heptadecane	–	629-78-7	CH_3–$(CH_2)_{15}$–CH_3		
Heptadecene isomers (2)	–	–	Unspecified isomer		
Decyl cyclohexene	–	–	Unspecified isomer		
Nonadecene	–		Unspecified isomer		
Octadecene	–	–	Unspecified isomer		
Nonadecene isomers(2)	–	–	Unspecified isomer		
2*H*-Pyran-2-one	–	504-31-4			
Heptanal	Heptanal [05.031]	111-71-7		(a)	
Nonanal	Nonanal [05.025]	124-19-6		(a)	
Acetic acid	Acetic acid [08.002]	64-19-7		(a)	
Decanal	Decanal [05.010]	112-31-2		(a)	
Hexanoic acid	Hexanoic acid [08.009]	142-62-1		(a)	

Constituents of Grillin' CB-200SF (no of isomers)	Union List substance name (FL-no)	CASrn	Chemical structure	EFSA conclusion on the union list substance	Comments
Heptanoic acid	Heptanoic acid [08.028]	111-14-8		(a)	
Pentadecanal	–	2765-11-9			
Octanoic acid	Octanoic acid [08.010]	124-07-2		(a)	
Nonanoic acid	Nonanoic acid [08.029]	112-05-0		(a)	
Heptadecanal	–	629-90-3			
Decanoic acid	Decanoic acid [08.011]	334-48-5		(a)	
Undecanoic acid	Undecanoic acid [08.042]	112-37-8		(a)	
Dodecanoic acid	Dodecanoic acid [08.012]	143-07-7		(a)	
2-Propenal	–	107-02-8			
2-Heptenal	2-Heptenal [05.070]	2463-63-0		(c)	
2-Hexylfuran	–	3777-70-6			
2,4-Hexadienal	Hexa-2(*trans*),4(*trans*)-dienal [05.057]	142-83-6		(d)	(f)
2-Octenal	Oct-2-enal [05.060]	2363-89-5		(c)	
2-Nonenal	Non-2-enal [05.171]	2463-53-8		(c)	
2-Decenal	Dec-2-enal [05.076]	3913-71-1		(c)	
2-Undecenal	2-Undecenal [05.109]	2463-77-6		(c)	
Pentenoic acid	Pent-4-enoic acid [08.048]	591-80-0		(a)	(f)
	(E)-Pent-2-enoic acid [08.107]	13991-37-2		(a)	
2,4-Decadienal	2,4-Decadienal [05.081]	2363-88-4		(d)	
2-Dodecenal	2-Dodecenal [05.037]	4826-62-4		(c)	
Hexenoic acid	2-Hexenoic acid [08.119]	1191-04-4		(a)	(f)
	Hex-2(*trans*)-enoic acid [08.054]	13419-69-7		(a)	
	Hex-3-enoic acid [08.050]	4219-24-3		(a)	

Constituents of Grillin' CB-200SF (no of isomers)	Union List substance name (FL-no)	CASrn	Chemical structure	EFSA conclusion on the union list substance	Comments
Heptenoic acid	*trans*-2-Heptenoic acid [08.123]	10352-88-2		(a)	(f)
Octenoic acid	2-Octenoic acid [08.114]	1871-67-6		(a)	(f)
Nonenoic acid	–	–	Unspecified isomer		
Heptadecenal	–	–	Unspecified isomer		
Decenoic acid	Dec-2-enoic acid [08.073]	3913-85-7		(a)	(f)
	Dec-3-enoic acid [08.074]	15469-77-9		(a)	
	Dec-4-enoic acid [08.075]	26303-90-2		(a)	
	Dec-9-enoic acid [08.065]	14436-32-9		(a)	
	Dec-(5- and 6)-enoic acid [08.068]	72881-27-7		(a)	
Undecenoic acid isomers (2)	Undec-10-enoic acid [08.039]	112-38-9		(a)	(f)
Styrene	Vinylbenzene [01.015]	100-42-5		(b)	
Butyl benzene	–	104-51-8			
Pentyl benzene	–	538-68-1			
Benzaldehyde	Benzaldehyde [05.013]	100-52-7		(a)	
Naphthalene	Naphthalene [01,053]	91-20-3		(b)	
Phenol	Phenol [04.041]	108-95-2		(a)	
2-Methylfuran	2-Methylfuran [13.030]	534-22-5		(b),(e)	
Heptylfuran	2-Heptylfuran [13.069]	3777-71-7		(e)	(f)
2-Octylfuran	2-Octylfuran [13.162]	4179-38-8		(e)	
2-Decanone	Decan-2-one [07.150]	693-54-9		(a)	

Constituents of Grillin' CB-200SF (no of isomers)	Union List substance name (FL-no)	CASrn	Chemical structure	EFSA conclusion on the union list substance	Comments
2-Undecanone	Undecan-2-one [07.016]	112-12-9		(a)	
Nonen-3-ol	Non-1-en-3-ol [02.187]	21964-44-3		(a)	(f)

FL-no: FLAVIS number; CASrn: CAS Registry Number.
(a): No safety concern at the estimated level of intake based on the MSDI approach.
(b): No longer supported by Industry.
(c): Evaluation in FGE.200, additional genotoxicity data are required.
(d): Evaluated in FGE.203Rev1, additional genotoxicity data are required.
(e): Evaluated in FGE.13Rev2 or FGE.67Rev1, additional genotoxicity data are required.
(f): The constituent of Grillin' CB-200SF, as reported by the applicant, is the unspecified isomer which is not identical to the corresponding specific isomer included in the Union list for flavourings. Therefore, footnotes (a) or (b) or (d) or (e), as appropriate, are only fully applicable to the substance present in the Union List.

Appendix B – Use Levels and Exposure Calculations

Table B.1: Normal and maximum occurrence levels for refined categories of foods and beverages for Grillin' CB-200SF

CODEX code	Food categories[a]	Standard portions[b] (g)	Occurrence level as added flavouring substance (mg/kg)		Occurrence level from other sources[c] (mg/kg)		Combined occurrence level from all sources[e] (mg/kg)	
			Normal	Maximum	Average[d]	Maximum	Normal	Maximum
01.2	Fermented and renneted milk products (plain), excluding food category 01.1.2 (dairy-based drinks)	200	100	500	0	0	100	500
01.4	Cream (plain) and the like	15	100	400	0	0	100	400
01.5	Milk powder and cream powder and powder analogues (plain)	30	100	400	0	0	100	400
01.6	Cheese and analogues	40	100	1,000	0	0	100	1,000
01.7	Dairy-based desserts (e.g. pudding, fruit or flavoured yoghurt)	125	100	1,000	0	0	100	1,000
02.1	Fats and oils essentially free from water	15	100	1,000	0	0	100	1,000
02.2	Fat emulsions mainly of type water-in-oil	15	100	1,000	0	0	100	1,000
02.3	Fat emulsions mainly of type water-in-oil, including mixed and/or flavoured products based on fat emulsions	15	100	1,000	0	0	100	1,000
02.4	Fat-based desserts excluding dairy-based dessert products of category 1.7	50	100	1,000	0	0	100	1,000
03.0	Edible ices, including sherbet and sorbet	50	100	1,000	0	0	100	1,000
04.2.2	Processed vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweed, and nut and seed purees and spreads (e.g. peanut butter) and nuts and seeds	200	100	1,000	0	0	100	1,000
05.1	Cocoa products and chocolate products, including imitations and chocolate substitutes	40	100	500	0	0	100	500
05.2	Confectionery, including hard and soft candy, nougats, etc., other than 05.1, 05.3 and 05.4	30	100	500	0	0	100	500
05.3	Chewing gum	3	100	500	0	0	100	500
06.3	Breakfast cereals, including rolled oats	30	100	500	0	0	100	500
06.4	Pastas and noodles and like products (e.g. rice paper, rice vermicelli, soya bean pastas and noodles)	200	100	1,000	0	0	100	1,000
06.6	Batters (e.g. for breading or batters for fish or poultry)	30	100	1,000	0	0	100	1,000

CODEX code	Food categories[a]	Standard portions[b] (g)	Occurrence level as added flavouring substance (mg/kg)		Occurrence level from other sources[c] (mg/kg)		Combined occurrence level from all sources[e] (mg/kg)	
			Normal	Maximum	Average[d]	Maximum	Normal	Maximum
06.7	Pre-cooked or processed rice products, including rice cakes (oriental type only)	200	100	1,000	0	0	100	1,000
07.2	Fine bakery wares (sweet, salty, savoury) and mixes	80	100	1,000	0	0	100	1,000
08.1	Fresh meat, poultry and game	200	100	1,000	0	0	100	1,000
08.2	Processed meat, poultry and game products in whole pieces or cuts	100	100	1,000	0	0	100	1,000
08.3	Processed comminute meat, poultry and game products	100	100	1,000	0	0	100	1,000
08.4	Edible casings (e.g. sausage casings)	1	100	1,000	0	0	100	1000
09.1.1	Fresh fish	200	100	1,000	0	0	100	1,000
09.2	Processed fish and fish products, including molluscs, crustaceans and echinoderms	100	100	1,000	0	0	100	1,000
09.3	Semipreserved fish and fish products, including molluscs, crustaceans and echinoderms	100	100	1,000	0	0	100	1,000
09.4	Fully preserved, including canned or fermented, fish and fish products, including molluscs, crustaceans and echinoderms	100	100	1,000	0	0	100	1,000
10.2	Egg products	100	100	1,000	0	0	100	1,000
10.3	Preserved eggs, including alkaline. salted and canned eggs	100	100	1,000	0	0	100	1,000
10.4	Egg-based desserts (e.g. custard)	125	100	500	0	0	100	500
11.3	Sugar solutions and syrups, and (partially) inverted sugars, including molasses and treacle, excluding products of food category 11.1.3 (soft white sugar, soft brown sugar, glucose syrup, dried glucose syrup, raw cane sugar)	30	100	500	0	0	100	500
11.4	Other sugars and syrups (e.g. xylose, maple syrup, sugar toppings)	30	100	500	0	0	100	500
12.10	Protein products other than from soybeans	15	100	1,000	0	0	100	1,000
12.2	Herbs, spices, seasonings and condiments (e.g. seasoning for instant noodles)	1	100	1,000	0	0	100	1,000
12.3	Vinegars	15	100	500	0	0	100	500

CODEX code	Food categories[a]	Standard portions[b] (g)	Occurrence level as added flavouring substance (mg/kg)		Occurrence level from other sources[c] (mg/kg)		Combined occurrence level from all sources[e] (mg/kg)	
			Normal	Maximum	Average[d]	Maximum	Normal	Maximum
12.4	Mustards	15	100	1,000	0	0	100	1,000
12.5	Soups and broths	200	100	1,000	0	0	100	1,000
12.6	Sauces and like products	30	100	1,000	0	0	100	1,000
12.7.a	Salads 120 g (e.g. macaroni salad, potato salad) excluding cocoa- and nut-based spreads of food categories	120	100	1,000	0	0	100	1,000
12.9	Soybean-based seasonings and condiments	15	100	1,000	0	0	100	1,000
12.9.1	Fermented soya bean products (e.g. miso)	40	100	1,000	0	0	100	1,000
13.3	Dietetic foods intended for special medical purposes (excluding food products of category 13.1 'Infant formulae, follow-up formulae and other formulae for special medical purposes for infants')	200	100	1,000	0	0	100	1,000
13.4	Dietetic formulae for slimming purposes and weight reduction	200	100	1,000	0	0	100	1,000
13.5	Dietetic foods (e.g. supplementary foods for dietary use), excluding products of food categories 13.1 (Infant formulae, follow-up formulae and other formulae for special medical purposes for infants), 13.2–13.4 and 13.6	200	100	1,000	0	0	100	1,000
14.1	Other non-alcoholic ('soft') beverages (expressed as liquid)	300	100	1,000	0	0	100	1,000
14.2.1	Beer and malt beverages	300	100	1,000	0	0	100	1,000
14.2.3	Grape wines	150	100	1,000	0	0	100	1,000
14.2.5	Mead	150	100	1,000	0	0	100	1,000
14.2.6	Distilled spirituous beverages containing more than 15% alcohol	30	100	1,000	0	0	100	1,000
15.1	Snacks, potato-, cereal-, flour- or starch-based (from roots and tubers, pulses and legumes)	30	100	1,000	0	0	100	1,000
15.2	Processed nuts, including coated nuts and nut mixtures (with e.g. dried fruit)	30	100	1,000	0	0	100	1,000
15.3	Snacks – fish based	30	100	1,000	0	0	100	1,000

CODEX code	Food categories[a]	Standard portions[b] (g)	Occurrence level as added flavouring substance (mg/kg)		Occurrence level from other sources[c] (mg/kg)		Combined occurrence level from all sources[e] (mg/kg)	
			Normal	Maximum	Average[d]	Maximum	Normal	Maximum
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) – foods that could not be placed in categories 01–15	300	100	1,000	0	0	100	1,000

(a): Most of the categories reported are the sub-categories of Codex GSFA (General Standard for Food Additives) used by the JECFA in the SPET technique (FAO/WHO, 2008). In the case of category 13.2 (complementary foods for infants and young children), further refined categories have been created so that a specific assessment of dietary exposure can be performed in young children.

(b): For Adults. In case of foods marketed as powder or as concentrates, occurrence levels must be reported for the reconstituted product, considering the instructions reported on the product label or one of the standard dilution factors established by the JECFA (FAO/WHO, 2008):

- 1/25 for powder used to prepare water-based drinks such as coffee, containing no additional ingredients,
- 1/10 for powder used to prepare water-based drinks containing additional ingredients such as sugars (ice tea, squashes, etc.),
- 1/7 for powder used to prepare milk, soups and puddings,
- 1/3 for condensed milk.

(c): As natural constituent and/or developed during the processing and/or as carry over resulting from their use in animal feed.

(d): In order to estimate normal values in each category, only foods and beverages in which the substance is present in significant amount will be considered (e.g. for the category 'Fresh fruit' 04.1.1., the normal concentration will be the median concentration observed in all kinds of fruit where the flavouring substance is known to occur).

(e): As added flavouring or from other sources. The normal and maximum combined occurrence levels of the substance will be assessed by the applicant either by adding up occurrence levels from added use to that from other sources or by expert judgment based on the likelihood of their concomitant presence. This will be done both for normal use levels and for maximum use levels.

Calculation of the dietary exposure – 'Added Portions Exposure Technique' (APET)[5]

Chronic dietary exposure

The chronic APET calculations are based on the combined normal occurrence level by adding the highest contributing portion of food and highest contributing portion of beverages (either among soft drinks or alcoholic beverages) (see Table 4). The APET calculation for children is performed by adding the highest contributing portion of food and the highest contributing portion of beverages (among soft drinks). Furthermore, in the APET calculation for children the portion sizes listed in Table B.1 are adjusted by a factor 0.63 to take into account the smaller portion sizes consumed by children.

Adults

On the basis of normal occurrence level from added flavourings

Solid food: The maximum intake will be from category 16.0 (Composite foods (e.g. casseroles, meat pies, mincemeat) – foods that could not be placed in categories 01–15) with the normal combined occurrence level of 30 mg/adult per day.

Beverage: The maximum intake will be from categories 14.1 (Other non-alcoholic ('soft') beverages (expressed as liquid)) and 14.2.1 (Beer and malt beverages) with the normal combined occurrence level of 30 mg/adult per day.

The total APET will be 6 mg/adult per day corresponding to 1 mg/kg bw per day for a 60-kg person.

Children (3-year-old child of 15 kg body weight)

Solid food: The maximum intake will be from category 16.0 (Composite foods (e.g. casseroles, meat pies, mincemeat) – foods that could not be placed in categories 01–15) with the normal combined occurrence level of 35 × 0.63 = 18.9 mg/child per day.

Beverage: The maximum intake will be from category 14.1 (Other non-alcoholic ('soft') beverages (expressed as liquid)) with the normal combined occurrence level of 30 × 0.63 = 18.9 mg/child per day.

The total APET will be 37.8 mg/child per day corresponding to 2.5 mg/kg bw per day for a 15-kg child.

Conclusion

The higher of the two values among adults and children, expressed per kg/bw per day, should be used as the basis for the safety evaluation of the candidate substance, i.e. the value of 1.26 mg/kg bw per day for a 15-kg child should be compared to the appropriate no observed adverse effect level (NOAEL) for the candidate substance.

Infants and young children

The estimate to infant exposure is currently under consideration by EFSA.

Acute dietary exposure

The calculation is based on the maximum use levels and large portion size, i.e. three times standard portion size (see Table 5). Although the substance is not intended to be used in food categories specifically intended for infants and toddlers, these could still be exposed through consumption of foods from the general food categories, which may contain the substance. However, at present, there is no generally accepted methodology to estimate exposure in these age groups resulting from consumption of foods from the general categories. The APET calculation for children the portion sizes listed in Table B.1 is adjusted by a factor of 0.63 to take into account the smaller portion sizes consumed by children.

Adults

The highest contribution comes from three portions of one of the following categories for which a highest exposure of (3 × 300 g) × 1,000 mg/kg = 900 mg/adult day could be estimated: 16.0 (Composite foods (e.g. casseroles, meat pies, mincemeat) – foods that could not be placed in

[5] The APET has been calculated based on the occurrence levels in the food sub-categories reported in the above table, with the exclusion of categories 13.2 (complementary foods for infants and young children).

categories 01–15), 14.1 (Other non-alcoholic ('soft') beverages (expressed as liquid)) and 14.2.1 (Beer and malt beverages).

Children (3-year-old child of 15 kg body weight)

The highest contribution comes from three portions of one of the following categories for which a highest exposure of (3 × 300 g) × 0.63 × 1,000 mg/kg = 567 mg/child day could be estimated: 16.0 (Composite foods (e.g. casseroles, meat pies, mincemeat) – foods that could not be placed in categories 01–15) and 14.1 (Other non-alcoholic ('soft') beverages (expressed as liquid)).

Infants and young children

Acute dietary exposure is not calculated for infants and young children.

Appendix C – Genotoxicity data

Table C.1: Summary of genotoxicity data (*in vitro*)

Chemical name FL-no	Test system *in vitro*	Test object	Concentrations of substance and test conditions	Result	Reference	Comments
Grillin' CB-200 SF [21.004]	Reverse mutation	*Salmonella* Typhimurium TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2 *uvrA*	1.5–5,000 μg/plate	Inconclusive[(a)]	Red Arrow Products Company LLC (2015)	The study was performed in accordance with OECD TG 471, with two separate experiments, ± S9, using the plate incorporation method. Precipitate was observed at 500 μg/plate and above
	Micronucleus induction	Human peripheral blood lymphocytes	10–100 μg/mL	Inconclusive[(a)]	Red Arrow Products Company LLC (2015)	The study was performed in accordance with OECD TG 487. Concentrations tested were in the 4-h + S9: 25, 50, 75 and 100 μg/mL 4-h and 24-h -S9: 10, 25 and 50 μg/mL

(a): Due to the lack of requested data, a conclusion cannot be drawn on a possible genotoxic effect of Grillin' CB-200SF (see Section 3.5.1 for details).

Appendix D – Developmental toxicity and chronic toxicity data on thermally oxidised oleic acid-based oils as provided by the applicant

Developmental toxicity study on thermally oxidised oleic acid-based oils

Two generations of male and female rats were maintained on diets containing 15% of either a freshly hydrogenated soybean oil (iodine value 107) or hydrogenated soy bean oil heated to 182°C for 56 h under practical restaurant-type frying conditions. The oil was stored frozen after addition of butylated hydroxytoluene (0.39 ppm) plus butylated hydroxyanisol (0.31 ppm). The first two litters of each generation were permitted to be born naturally. During the third pregnancy of each generation, one-half of the females were sacrificed on day 13 of gestation and inspected for early embryonic death. The remaining females were sacrificed on day 21 of gestation, and the fetuses were examined for either skeletal or soft tissue abnormalities. There was no evidence of any deleterious effects on the reproductive parameters nor any teratogenic effects due to either hydrogenated soybean oil (Nolen, 1972).

Chronic toxicity on thermally oxidised oleic acid-based oils

Groups of male and female rats (50/sex per group) were maintained on diets containing 15% of soybean oil (65–66% oleic acid) partially hydrogenated to iodine values of 70 and 108, respectively, that been heated at 182°C, 8 h daily for a total of 84–60 h, respectively, under practical restaurant-type frying conditions (Nolen et al., 1967); a similarly treated, hydrogenated soybean oil (iodine value 108) containing 1.6 ppm methylsilicone, was heated for 216 h at 182°C. Also, cotton oil (heated 49 h) and lard (heated 116 h) were used. The oils were stored frozen after addition of butylated hydroxytoluene (0.39 ppm) plus butylated hydroxyanisol (0.31 ppm).

Study diets were prepared fresh each week and kept refrigerated until dispensed into the feeding cups. Feeding was carried out three times per week, and any feed remaining in the cups was discarded, so that the longest period that any of the feed was unrefrigerated after mixing was 3 days. Untreated hydrogenated soybean oil was used in the control diet. Weekly measurement of body weight, food intake and food efficiency uptake and biweekly measurement of fat absorption showed no significant difference between test and control groups after 2 years. Haematological examination, clinical chemistry determinations, and urine and faeces analysis failed to reveal significant differences between test and control groups. Histopathological examinations of thymus, heart, lung, liver, stomach, pancreas, spleen, adrenal, kidney, mesenteric lymph nodes, ileum, gonads, and any apparent neoplasms exhibited no evidence of lesions that could be associated with administration of the test diet (Nolen et al., 1967).

In a study in dogs, a similar partially hydrogenated soybean oil (iodine value 107) was used. It was kept at 182°C under practical restaurant-type frying conditions until it reached the end of its useful frying life (56 h). This used oil, or a fresh oil control, was fed to groups of two male and two female dogs at levels of 15% in a semipurified diet. Their effects were compared to those of a commercial dog feed from shortly after weaning until the dogs were 54 weeks old. There was no apparent difference in the growth of female dogs fed the diets. The male dogs fed the diet with used fat grew about the same as those fed the commercial dog feed, but both groups had reduced growth compared to dogs fed the diet with fresh fat. As in the rat studies, this reduced rate of growth for males was attributed to the lower absorbability of the used fat compared to the fresh. Otherwise, clinical examinations showed no significant differences between test and control animals. Histopathological examination revealed no lesions that could be attributed to administration of the test material (Nolen, 1973).

Appendix E – Methodology

The definition of 'other flavouring', referred to in Article 3(2)(h) of Regulation (EC) No 1334/2008 is 'a flavouring added or intended to be added to food in order to impart odour and/or taste and which does not fall under the definitions of Article 3(2)(b) – (g) of Regulation (EC) No 1334/2008', and the data requirements for its safety evaluation can be found in the EFSA scientific opinion: 'Guidance on the data required for the risk assessment of flavourings to be used in or on foods' (EFSA CEF Panel, 2010), Part B. IV. 'Information to be supplied with an application for the authorisation of Other Flavourings'.

It is difficult to anticipate what kind of materials will undergo an evaluation as 'Other Flavourings', which suggests that the standard evaluation template is flexible. As a general approach, the following data should be provided:

- full description of the production process, with emphasis on the parameters that might influence the composition of the flavouring;
- identification and quantification of the substances present in the flavouring;
- specifications of the flavouring;
- exposure and toxicological data required to perform a risk assessment of the flavouring.

Appendix F – Flow diagram for the production of Grillin' CB-200SF (confidential)