SCIENTIFIC OPINION

Scientific Opinion on safety of smoke flavour Primary Product - Scansmoke R909[1]

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

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ABSTRACT

This opinion concerns the safety of the smoke flavouring Primary Product Scansmoke R909. The Panel considered the technical and analytical data provided acceptable to characterise the Primary Product and to demonstrate its batch-to-batch variability and stability. Two *in vivo* genotoxicity tests were negative and sufficient to eliminate the concerns over the *in vitro* genotoxicity. The Panel derived a NOAEL of 1250 mg/kg bw/day from a 90-day study in rats. Based on this NOAEL and on the intake data calculated with the use levels of the Primary Product Scansmoke R909 provided by the applicant for the 18 food categories, the margins of safety would amount to 100 and 160 for the intake estimates based on the upper use levels, and to 350 and 420 when normal use levels are considered. When assuming the use in traditionally smoked products only, the margins of safety would amount to 210 and 300 for the intake estimates based on the upper use levels, and to 520 and 735 when normal use levels are considered. The fact that these margins of safety based on a 90-day toxicity study are inadequate, and in addition, data on reproduction and developmental toxicity and long term studies are absent, it is concluded that the uses and use levels for the Primary Product in a wide range of product categories would require a larger margin of safety. The Panel concludes that the margins of safety are insufficient and that the use of Primary Product Scansmoke R909 at the proposed uses and use levels is of safety concern.

KEY WORDS

Smoke flavouring, Primary Product, Scansmoke R909.

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1 On request from the European Commission, Question No EFSA-Q-2005-259, adopted on 26 November 2009.

2 Panel Members: Arturo Anadón, David Bell, Mona-Lise Binderup, Wilfried Bursch, Laurence Castle, Riccardo Crebelli, Karl-Heinz Engel, Roland Franz, Nathalie Gontard, Thomas Haertlé, Trine Husøy, Klaus-Dieter Jany, Catherine Leclercq, Jean-Claude Lhuguenot, Wim Mennes, Maria Rosaria Milana, Karla Pfaff, Kettil Svensson, Fidel Toldrá, Rosemary Waring, Detlef Wölfle. Correspondence: cef-unit@efsa.europa.eu

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* The CEF correspondence email address has been updated.

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SUMMARY

The European Food Safety Authority has been asked to provide scientific opinions on the safety of smoke flavouring Primary Products used or intended for use in or on foods. This opinion concerns a smoke flavouring Primary Product, named Scansmoke R909.

The raw material consists of 90% beech (*Fagus sylvatica*) and 10% oak (*Quercus robur*) wood. Wood of other species might be present in quantities less than 1%. No other ingredients are used.

Water functions as the solvent of the Primary Product Scansmoke R909. The solvent-free fraction amounts to 19.5 wt. %. The amount of the volatile fraction determined by GC was 14.1 wt. % of the Primary Product. 13.6 wt. % (corresponding to 96 % of the volatile fraction) were identified which is in compliance with Commission Regulation (EC) 627/2006. The fraction of unidentified mass has been estimated as 5.9 wt. %. The mass of identified constituents corresponds to 70 % of the solvent-free mass. This is in compliance with Commission Regulation (EC) 627/2006.

Except for benzo[*j*]fluoranthene, the concentrations of the polycyclic aromatic hydrocarbons (PAHs) listed in Annex 2 of the EFSA Guidance document have been provided. In addition, the contents of fluorene, phenanthrene, anthracene, fluoranthene and pyrene have been determined. The levels of benzo[*a*]pyrene and benzo[*a*]anthracene are below their respective limits of 10 and 20 µg/kg given in Regulation (EC) No. 2065/2003. Scansmoke R909 had consistently low levels of PAHs in the batches tested. Although the concentration of benzo[*j*]fluoranthene, one of the PAHs known to be carcinogenic, was not provided, the Panel concluded that based on the reported levels of other carcinogenic PAHs, benzo[*j*]fluoranthene levels would be expected to be similarly low.

The Panel considered the data provided on batch-to-batch variability and on stability of the Primary Product as sufficient.

The genotoxic potential of the Scansmoke R909 was tested in three *in vitro* and two *in vivo* genotoxicity assays. All genotoxicity studies were conducted according to current OECD guidelines and in compliance to GLP. Scansmoke R909 is considered mutagenic *in vitro* in mouse lymphoma cells in the MLTK assay while *in vivo* a negative result was obtained from a mouse micronucleus assay and no indication of unscheduled DNA synthesis was observed in hepatocytes from male rats.

Overall, it is concluded that Scansmoke R909 is genotoxic *in vitro* in the mouse lymphoma assay, whereas two *in vivo* genotoxicity tests are negative and sufficient to eliminate the concerns over the *in vitro* genotoxicity.

The Primary Product was investigated in a 90-day study in rats performed according to the current OECD guideline and in compliance with GLP. Scansmoke R909 was administered in the diet at concentrations of 5, 12 and 20 g/kg resulting in 316, 800 and 1253 mg/kg bw/day in males and 498, 1129 and 1672 mg/kg bw/day in females. The No-Observed-Adverse-Effect Level (NOAEL) was 1250 mg/kg bw/day, the highest dose level tested.

The applicant provided two data sets for use levels, one submitted originally in 2005, and the second in April 2009, after consulting with clients and seeking more detailed information on the actual use levels. For transparency reasons both the initially provided data from 2005 and the updated data from 2009 were considered.

In order to estimate dietary exposure to the Primary Product Scansmoke R909, the CEF Panel used two different methodologies, developed by the Panel specifically for smoke flavourings. Dietary exposure estimates were calculated by assuming that the Primary Product is present at the normal or upper use levels provided by the applicant for the 18 food categories as outlined in Commission Regulation 1565/2000.

Considering the initial data provided on use levels in 2005 dietary exposures from all sources were 14.9 and 25.0 mg/kg bw/day, when assuming that the Primary Product is present at the upper use levels and from 11.2 to 20.0 mg/kg bw/day when normal use levels are considered.

Considering the updated information on use levels from 24 April 2009 dietary exposures from all sources were 7.9 and 12.1 mg/kg bw/day, when assuming that the Primary Product is present at the upper use levels, 3.0 and 3.6 mg/kg bw/day when normal use levels are considered.

The impact on exposure of authorizing the Primary Product only in traditionally smoked food products was also assessed.

Considering the initial data on use levels provided in 2005 the highest exposure estimates, provided by the SMK-EPIC model, were 7.2 and 9.6 mg/kg bw/day when using normal and upper use levels, respectively. With the SMK-TAMDI model these figures were 5.0 and 6.7 mg/kg bw/day, respectively

Considering the updated information on use levels from 24 April 2009 the highest exposure estimates, provided by the SMK-EPIC model, were 2.4 and 6.0 mg/kg bw/day when using normal and upper use levels, respectively. With the SMK-TAMDI model these figures were 1.7 and 4.2 mg/kg bw/day, respectively.

Since the data on use levels originally provided in June 2005 have been updated by the applicant in April 2009, and according to the applicant, these reflecting better the actual uses und use levels, the Panel drew its conclusions based on the margins of safety calculated with these recent data.

Based on the use levels calculated with the new data provided by the applicant on 24 April 2009 the margins of safety as compared to the NOAEL of 1250 mg/kg bw/day derived from the 90-day toxicity study in rats amount to 100 and 160 for the intake estimates based on the upper use levels, and to 350 and 420 when normal use levels are considered.

When dietary exposure estimates are based on use in only traditionally smoked foods the margins of safety using the two smoke flavour exposure estimates, SMK-EPIC and SMK-TAMDI, respectively would amount to 210 and 300 based on the upper use levels and to 520 and 735 when normal use levels are considered.

Considering that these margins of safety based on a 90-day toxicity study are inadequate, and in addition, data on reproduction and developmental toxicity and long term studies are absent, it is concluded that the uses and use levels for the Primary Product in a wide range of product categories would require a larger margin of safety.

The Panel concludes that the margins of safety are insufficient and that the use of Primary Product Scansmoke R909 at the proposed uses and use levels is of safety concern.

It is outside the remit of the Panel to decide whether, despite the low margins of safety, the use of Primary Product Scansmoke R909 might be approved for traditionally smoked products, at use levels specified, to replace smoking.

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BACKGROUND

Smoking is a process traditionally applied to certain perishable foods such as fish and meat. It was originally used for preservation purposes. In addition the process results in sensory changes (colour and flavour) which impart characteristic sensory properties to such foods. With the development of other methods of preservation this function of smoking decreased in importance over time and the sensory aspects prevailed.

Nowadays, smoke flavourings are added to various foods either to replace the smoking process or to impart smoke flavour to foods which are not traditionally smoked.

Smoke flavourings are produced by controlled thermal degradation of wood in a limited supply of oxygen (pyrolysis) and subsequent condensation of the vapours and fractionation of the resulting liquid products. The resulting Primary Products (primary smoke condensate and primary tar fractions) may be further processed to produce smoke flavourings applied in or on foods.

The Regulation (EC) No 2065/2003 of the European Parliament and the Council (EC, 2003) established Community procedures for the safety assessment and the authorisation of smoke flavourings Primary Product intended for use in or on foods. As stated herein the use of a Primary Product in or on foods shall only be authorised if it is sufficiently demonstrated that it does not present risks to human health. A list of Primary Products authorised to the exclusion of all others in the Community for use as such in or on food and/or for the production of derived smoke flavourings shall therefore be established after the European Food Safety Authority (EFSA) has issued an opinion on each Primary Product.

The Guidance on submission of a dossier on a smoke Flavouring Primary Product for evaluation by EFSA (EFSA, 2005) lays down the administrative, technical and toxicological data required.

TERMS OF REFERENCE

The EFSA is required by Article 8 of Regulation (EC) No. 2065/2003 of the European Parliament and of the Council on smoke flavourings used or intended for use in or on foods to carry out risk assessments and deliver a scientific opinion on the safety of Primary Products.

ASSESSMENT

1. Introduction

The following evaluation only applies to the Primary Product Scansmoke R909 manufactured strictly in conformity with the specified process and meeting the chemical specifications described in this opinion.

In accordance with the guidance document (EFSA, 2005), data on the manufacturing process, the composition, intended use levels and toxicological tests have been submitted. The latter include a 90-day oral subchronic toxicity study and three *in vitro* genotoxicity tests. Two *in vivo* genotoxicity tests have also been provided.

2. Information on existing authorisations and evaluations

According to the applicant, there are no existing authorisations of the Primary Product Scansmoke R909.

3. Technical data

3.1. Manufacturing process

3.1.1. Source materials for the Primary Product

The raw material consists of 90% beech (*Fagus sylvatica*) and 10% oak (*Quercus robur*) wood. Wood of other species might be present in quantities less than 1%. No other ingredients are used. According to a certificate provided by the supplier the wood used is not subjected to chemical treatment.

3.1.2. Method of manufacture of the Primary Product

Pieces of dried wood are pyrolysed in a series of connected retorts. The produced smoke condensate is further processed by distillation and air stripping to form the Primary Product.

The process has been described in detail and key operation parameters have been provided.

3.2. Identity of the Primary Product

3.2.1. Trade names of the Primary Product

The trade name of the Primary Product is Scansmoke R909.

3.2.2. Physical state of the Primary Product

The Primary Product Scansmoke R909 is a liquid with an average density of 1.03 g/ml.

3.3. Chemical composition

3.3.1. Overall characterisation

The overall characterisation of the Primary Product is as follows:

3.3.1.1. Solvent-free fraction

Water functions as the solvent of the Primary Product Scansmoke R909. In the batch used for the toxicological studies (03/2004) a water content of 80.5 wt. % was determined by Karl Fischer titration. Thus, the solvent-free fraction of the Primary Product amounts to 19.5 wt. %.

3.3.1.2. Volatile fraction

The Primary Product was analysed by capillary gas chromatography (GC). Mass spectrometry (MS) was used for identification and flame ionisation detection (FID) for quantification. The amount of the volatile fraction determined by GC was 14.1 wt. % of the Primary Product. 13.6 wt. % (corresponding to 96 % of the volatile fraction) were identified which is in compliance with Commission Regulation (EC) 627/2006 (Figure 1).

3.3.1.3. Unidentified constituents

The fraction of unidentified mass has been estimated as the water-free mass minus the mass of the identified volatile compounds: 19.5 wt. % - 13.6 wt. % = 5.9 wt. %. The mass of identified constituents (13.6 wt. %) corresponds to 70 % of the solvent-free mass (Figure 2).

This is in compliance with Commission Regulation (EC) 627/2006 (EC, 2006).

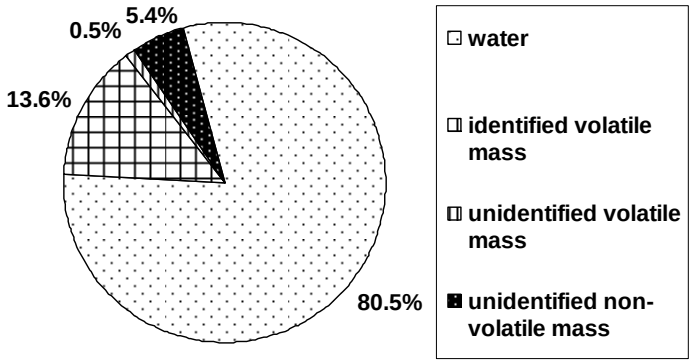

Figure 1. **Overall composition of Scansmoke R909 (wt. % of Primary Product)**

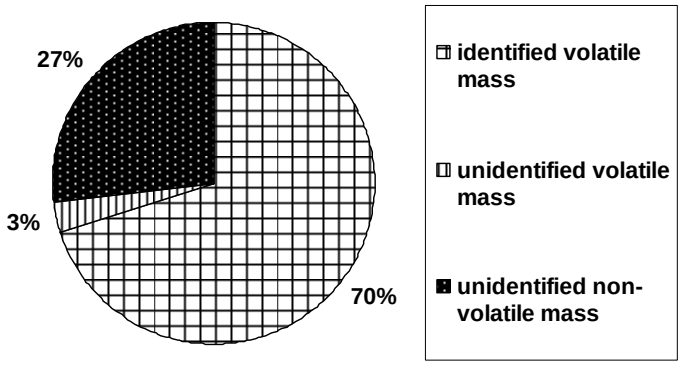

Figure 2. **Composition (%) of the solvent-free fraction of Scansmoke R909**

3.3.2. Chemical description of the Primary Product

The Primary Product has been characterised according to the parameters listed in Table 1.

Table 1. **Description of major parameters of the Primary Product Scansmoke R909**

Batch	07/04	08/04	09/04	10/04	11/04	12/04	01/05	Mean	Rel. SD (%)
Phenols, as syringol [mg/g]	6.5	7.6	7.0	7.5	7.1	7.0	-[a)]	7.1	5.6
Acids, as acetic acid [%]	11.3	11.5	12.1	12.8	12.0	10.7	10.9	11.6	6.3
Carbonyls, as furfural [%]	6.5	6.4	7.1	7.0	6.7	6.2	-[a)]	6.7	5.3
Staining-Index at 440 nm	18.3	17.4	20.9	19.6	19.7	16.3	16.4	18.4	9.6
Staining-Index at 495 nm	19.1	18.7	22.1	21.6	21.3	18.2	18.8	20.0	8.1
pH	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	0
Water [%]	78.2	80.4	79.7	78.7	80.4	81.5	81.9	80.1	1.7
Non volatile residues [wt.%]	1.3	1.6	1.4	1.2	1.2	1.0	1.3	1.3	14.5

[a)] No data provided

For the batch used for the toxicological studies (03/2004) the heavy metal contents listed in Table 2 have been reported.

Table 2. **Heavy metal contents of Scansmoke R909 (batch 03/2004)**

Mercury (Hg) [mg/kg]	< 0.05
Lead (Pb) [mg/kg]	< 0.1
Arsenic (As) [mg/kg]	0.11
Cadmium (Cd) [mg/kg]	0.025

3.3.3. Identification and quantification of Primary Product constituents

3.3.3.1. Principal constituents

Table 3 shows the 20 principal constituents (expressed as wt. % of the dry matter) determined by GC and GC/MS in the Primary Product.

Table 3. **Principal constituents of the Primary Product Scansmoke R909 (batch 03/2004)**

Compound	Concentration [wt. % of dry matter]
Acetic acid	42.1
Propanoic acid	7.1
Hydroxypropanone	6.9
2-furaldehyde	2.5
1-hydroxy-2-butanone	2.0
Syringol	1.8
2-hydroxy-3-methyl-2-cyclopentene-3-one	1.4
Guaiacol	0.7
Hydroxyacetaldehyde	0.6
(5H)-furan-2-one	0.4
4-methyl guaiacol	0.4
Levoglucosan	0.4
g-butyrolactone	0.3
Phenol	0.3
4-methyl syringol	0.3
p-cresol	0.2
3-methyl-2-cyclopentene-1-one	0.2
Anhydrosugar	0.2
Maltol	0.1
o-cresol	0.1

In total 46 compounds have been determined by GC. They amount to 69.6 wt. % of the dry matter, corresponding to 13.6 wt. % of the Primary Product.

3.3.3.2. Content of Polycyclic Aromatic Hydrocarbons (PAHs)

Except for benzo[*j*]fluoranthene, the concentrations of the polycyclic aromatic hydrocarbons (PAHs) known to be carcinogenic and/or genotoxic, listed in Annex 2 of the EFSA Guidance document (EFSA, 2005) have been provided. In addition, the contents of fluorene, phenanthrene, anthracene, fluoranthene and pyrene have been determined (in contrast to the others, these five are not considered to be carcinogenic and/or genotoxic). The analyses were performed by an external accredited laboratory; the method used was equivalent to the method developed by the Joint Research Center of the European Commission (Simon *et al*., 2006a and b) and fulfilled the performance criteria of Commission Regulation (EC) No 627/2006 (EC, 2006), except for the analyte benzo[*j*]fluoranthene. The concentrations of the 19 PAHs determined in the batch (02/2004) of the Primary Product used for the toxicological studies are listed in Table 4. The levels of benzo[*a*]pyrene and benzo[*a*]anthracene are below their respective limits of 10 and 20 µg/kg given in Regulation (EC) No. 2065/2003 (EC, 2003).

Table 4. **Concentrations of PAHs in the Primary Product Scansmoke R909 (batch 03/2004)**

PAHs	Concentration [µg/kg]
Chrysene	0.5
Benzo[*a*]anthracene	<0.5
5-Methylchrysene	<0.5
Cyclopenta[*cd*]pyrene	<0.5
Benzo[*b*]fluoranthene	<0.5
Benzo[*k*]fluoranthene	<0.5
Benzo[*a*]pyrene	<0.5
Indeno[*1,2,3-cd*]pyrene	<0.5
Dibenzo[*a,h*]anthracene	<0.5
Benzo[*ghi*]perylene	<0.5
Dibenzo[*a,e*]pyrene	<1
Dibenzo[*a,h*]pyrene	<1
Dibenzo[*a,i*]pyrene	<1
Dibenzo[*a,l*]pyrene	<1
Fluorene	39
Phenanthrene	17
Anthracene	7.7
Fluroanthene	4.1
Pyrene	4.9

3.3.4. Batch-to-batch variability

The applicant demonstrated the batch-to-batch variability of the Primary Product as follows:

- Variability of the parameters listed in Table 1 for seven batches.

- Variability of the 46 individual components determined by GC-analysis including the principal constituents listed in Table 3. The average relative standard deviation was 11 %. For some constituents, e.g. 2,4-dimethylphenol (content 0.05 wt. % of dry matter) no variation was observed; for others, such as 2-furaldehyde (2.3 wt. % of dry matter) and vanillin (0.02 wt. % of dry matter) relative standard deviations of 54 and 56 %, respectively, were determined.

- Variability of the PAHs listed in Table 4 in five batches. For the measured PAHs listed in Annex 2 of the EFSA guidance document the concentrations were consistently <1 and <0.5 µg/kg (the concentrations of chrysene were also consistently ≤ 0.5 µg/kg).

The Panel considered the data provided on the batch-to-batch-variability of the Primary Product as sufficient.

3.3.5. Stability

Batch 03/2004 was subjected to GC analysis five times from December 2004 to June 2005 (information on the storage conditions was not provided). The contents (wt. % of dry matter) and the standard deviations were determined for 50 components. The average relative standard deviation was 55 %. Individual values ranged from 9 and 7 %, respectively, for the major constituents acetic acid (average content 46.1 wt. % of dry matter) and hydroxypropanone (average content 7.8 wt. % of dry

matter) to 200 % for minor constituents, such as dimethyl-2-cyclopenten-1-one (0.03 wt. %). The data provided for the 20 principal constituents are shown in Table 5.

The Panel considered the data provided as sufficient to demonstrate the stability of the Primary Product.

Table 5. **Data on the stability of the Primary Product Scansmoke R909 (batch 03/2004)**

Compound	12/2004 (wt. %)[a]	02/ 2005 (wt. %)[a]	03/2005 (wt. %)[a]	06/2005 (wt. %)[a]	Relative Standard Deviation (%)
Acetic acid	42.1	50.3	48.7	43.5	9
Propanoic acid	7.1	8.4	8.2	5.7	17
Hydroxypropanone	6.9	8.1	7.8	7.8	7
2-furaldehyde	2.5	2.9	2.8	2.5	8
1-hydroxy-2-butanone	2.0	2.6	2.6	2.5	11
Syringol	1.8	2.2	2.1	2.3	11
2-hydroxy-3-methyl-2-cyclopentene-3-one	1.4	1.7	1.7	2.1	16
Guaiacol	0.74	0.92	0.86	0.87	9
Hydroxyacetaldehyde	0.64	0.76	0.52	0.56	37
(5H)-furan-2-one	0.43	0.54	0.52	0.56	12
4-methyl guaiacol	0.41	0.56	0.55	0.4	19
Levoglucosan	0.36	0.55	0.5	0.57	18
g-butyrolactone	0.31	0.36	0.41	0.31	12
Phenol	0.29	0.36	0.35	0.31	9
4-methyl syringol	0.27	0.31	0.32	0.34	10
p-cresol	0.23	0.13	0.15	0.08	38
3-methyl-2-cyclopentene-1-one	0.21	0.28	0.28	0.30	15
Anhydrosugar	0.15	0.24	0.23	0.33	30
Maltol	0.13	0.19	0.20	0	60
o-cresol	0.13	0.15	0.15	0.14	7

[a] data refer to dry matter of the Primary Product

3.3.6. Specifications

The specifications given by the applicant for the Primary Product are listed in Table 6.

Table 6**. Specifications of the Primary Product**

Acids (expressed as acetic acid)	10.5 – 12.5 %
Smoke flavour compounds*	5 - 10 mg/g
pH	2.0 - 2.5
Specific gravity (at 20° C)	1.02 - 1.04 g/ml
Residue on evaporation	1 - 2 %
Benzo[*a*]pyrene	< 10 µg/kg
Benzo[*a*]anthracene	< 20 µg/kg
Mercury (Hg)	< 0.1 mg/kg

Lead (Pb)	< 0.1 mg/kg
Arsenic (As)	< 0.1 mg/kg
Cadmium (Cd)	< 0.1 mg/kg

- assumed to correspond to "phenols" as described in section 3.3.2

4. Proposed uses

Normal and upper use levels as described originally by the applicant in June 2005 for the Primary Product in each of the 18 food categories as outlined in Commission Regulation (EC) No 1565/2000 (EC, 2000) are reported in Table 7a.

Table 7a. **Normal and upper use levels of Primary Product in food categories as outlined in Commission Regulation (EC) No 1565/2000 (Data provided in June 2005)**

Food categories		Use level (g/kg)	
		Normal	Upper
1	Dairy products, excluding products of category 2	0	0
2	Fats and oils, and fat emulsions (type water-in-oil)	0	0
3	Edible ices, including sherbet and sorbet	0	0
4.1	Processed fruits	0	0
4.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	3*	3
5	Confectionery	0	0
6	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	0	0
7	Bakery wares	0	0
8	Meat and meat products, including poultry and game	3	4
9	Fish and fish products, including molluscs, crustaceans and echinoderms	3	4
10	Eggs and egg products	0	0
11	Sweeteners, including honey	0	0
12	Salts, spices, soups, sauces, salads, protein products etc.	4*	4
13	Foodstuffs intended for particular nutritional uses	0	0
14.1	Non-alcoholic ("soft") beverages, excl. dairy products	0	0
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts	1*	1
15	Ready-to-eat savouries	3	4
16	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 1 – 15	0.99	1.33

* The Upper use level is here used because the applicant declared to be unable to provide a Normal use level.

After consulting with their users and seeking more detailed information on the actual use the applicant provided updated use levels for the different food categories on 24 April 2009. These data are presented in Table 7b.

Table 7b. **Normal and upper use levels of Primary Product in food categories as outlined in Commission Regulation (EC) No 1565/2000 (Data provided on 24 April 2009)**

Food categories		Use level (g/kg)	
		Normal	Upper
1	Dairy products, excluding products of category 2	0	0
2	Fats and oils, and fat emulsions (type water-in-oil)	0	0
3	Edible ices, including sherbet and sorbet	0	0
4.1	Processed fruits	0	0
4.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	0	0
5	Confectionery	0	0
6	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	0	0
7	Bakery wares	0	0
8	Meat and meat products, including poultry and game	1	2.5
9	Fish and fish products, including molluscs, crustaceans and echinoderms	1	2.5
10	Eggs and egg products	0	0
11	Sweeteners, including honey	0	0
12	Salts, spices, soups, sauces, salads, protein products etc.	≤ 2§	≤ 4^
13	Foodstuffs intended for particular nutritional uses	0	0
14.1	Non-alcoholic ("soft") beverages, excl. dairy products	0	0
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts	0.05	0.25
15	Ready-to-eat savouries	1	2.5
16	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 1 – 15	0.33	0.83

§ The following normal use levels for the breakdown of the food category 12 "Salts, spices, soups, sauces, salads, protein products etc." were provided by the applicant and used to assess the exposure: 2 g/kg for Herbs, spices, seasonings and condiments (food category 12.2), 0.5 g/kg for Soups and broths (food category 12.5) and Sauces and like products (food category 12.6) and 0 g/kg for the remaining subgroups.

^ The following upper use levels for the breakdown of the food category 12 "Salts, spices, soups, sauces, salads, protein products etc." were provided by the applicant and used to assess the exposure: 4 g/kg for Herbs, spices, seasonings and condiments (food category 12.2), 2 g/kg for Soups and broths (food category 12.5) and Sauces and like products (food category 12.6) and 0 g/kg for the remaining subgroups.

5. Dietary exposure assessment

In order to estimate dietary exposure to the Primary Product Scansmoke R909, the CEF Panel used two different methodologies developed by the Panel specifically for smoke flavourings (EFSA, 2009).

The Smoke Theoretical Added Maximum Daily Intake (SMK-TAMDI) is an adaptation of the Theoretical Added Maximum Daily Intake (TAMDI) method used by the Scientific Committee on Food (SCF) to assess exposure to single flavourings (Scientific Committee for Food, 1995). As for the TAMDI, the SMK-TAMDI also assumes that the hypothetical consumer will daily consume a fixed amount of flavoured solid foods and liquids. However, in the SMK-TAMDI a single group "Beverages" is used for liquids whereas solid foods are divided in "traditionally smoked solid foods" and "other solid foods not traditionally smoked".

The European Prospective Investigation into Cancer and Nutrition (EPIC) study is one of the few cases in which the consumption levels of "smoked meat" were assessed and published for different

European countries (Linseisen *et al*., 2006). The CEF Panel used consumption data from the EPIC study to estimate the potential cumulative dietary exposure to smoke flavourings. The Smoke flavouring EPIC model (SMK-EPIC) is based on a number of assumptions, in particular it assumes that a hypothetical high consumer of smoked meat is also an average consumer of the other traditionally smoked foods and an occasional consumer of smoked foods or beverages from each of the other categories.

Dietary exposure estimates were calculated by assuming that the Primary Product is present at the normal or upper use levels provided by the applicant for the 18 food categories as outlined in Commission Regulation 1565/2000. When the normal use levels are used, the SMK-TAMDI can be considered as an adaptation of the modified TAMDI (mTAMDI), the method used by the AFC Panel (EFSA, 2004) to screen and prioritise flavouring substances.

Details of the methodologies are described in the dietary exposure document (EFSA, 2009).

The applicant provided two data sets for use levels, one submitted originally in 2005, and the second in April 2009, after consulting with clients and seeking more detailed information on the actual use levels.

Dietary exposure estimates calculated by means of the above mentioned methods are reported in Table 8a and b. For transparency reasons both initially provided data from 2005 and updated data from 2009 were considered.

Considering the initial data provided on use levels in 2005, dietary exposures from all sources were 14.9 and 25.0 mg/kg bw/day, when assuming that the Primary Product is present at the upper use levels, 11.2 and 20.0 mg/kg bw/day when normal use levels are considered (Table 8a).

Considering the updated information on use levels from 24 April 2009 dietary exposures from all sources were 7.9 to 12.1 mg/kg bw/day, when assuming that the Primary Product is present at the upper use levels, 3.0 and 3.6 mg/kg bw/day when normal use levels are considered (Table 8b).

The impact on exposure of using the Primary Product only in traditionally smoked food products was also assessed. Out of the above mentioned 18 food categories, “Dairy products, excluding products of category 2”, “Meat and meat products, including poultry and game” and “Fish and fish products, including molluscs, crustaceans and echinoderms” were considered as “Traditionally smoked solid foods”.

Considering the initial data on use levels provided in 2005 the highest exposure estimates, provided by the SMK-EPIC model, were 7.2 and 9.6 mg/kg bw/day when using normal and upper use levels, respectively. With the SMK-TAMDI model these figures were 5.0 and 6.7 mg/kg bw/day, respectively (Table 8a).

Considering the updated information on use levels from 24 April 2009 the highest exposure estimates, provided by the SMK-EPIC model, were 2.4 and 6.0 mg/kg bw/day when using normal and upper use levels, respectively. With the SMK-TAMDI model these figures were 1.7 and 4.2 mg/kg bw/day, respectively (Table 8b).

Dietary exposures to the Primary Product were also estimated by the applicant using average food consumption data derived from the UK National Diet and Nutrition Survey (NDNS) in adults aged 16-64 (Henderson *et al*., 2002). The dietary exposure calculated by the applicant resulted to be equal to 5.9 mg/kg bw/day. This estimate is obtained by assuming that only 25% of food consumed is flavoured with the Primary Product at the upper use levels.

Table 8a. **Summary of the dietary exposure estimates to the Primary Product (Data provided in June 2005)**

Methodologies		Dietary exposure (mg/kg bw/day)	
		Normal use levels	Upper use levels
SMK-TAMDI	Traditionally smoked food	5.0	6.7
	Other foods not traditionally smoked	10.0	13.3
	Beverages (alcoholic or non-alcoholic)	5.0	5.0
	Total dietary exposure	20.0	25.0
SMK-EPIC	Traditionally smoked food	7.2	9.6
	Other foods not traditionally smoked	3.3	4.6
	Beverages (alcoholic or non-alcoholic)	0.7	0.7
	Total dietary exposure	11.2	14.9
Applicant	Dietary exposure	-*	5.9

*Not provided

The new data provided by the applicant led to the following figures for dietary exposure.

Table 8b. **Summary of the dietary exposure estimates to the Primary Product (Data provided on 24 April 2009)**

Methodologies		Dietary exposure (mg/kg bw/day)	
		Normal use levels	Upper use levels
SMK-TAMDI	Traditionally smoked food	1.7	4.2
	Other foods not traditionally smoked	1.7	6.7
	Beverages (alcoholic or non-alcoholic)	0.3	1.3
	Total dietary exposure	3.6	12.1
SMK-EPIC	Traditionally smoked food	2.4	6.0
	Other foods not traditionally smoked	0.5	1.7
	Beverages (alcoholic or non-alcoholic)	0	0.2
	Total dietary exposure	3.0	7.9
Applicant	Dietary exposure	-*	-*

*Not provided

6. Toxicology

6.1. Identity of the test material

The batch 03/2004 of Scansmoke R909 was used for the toxicity studies, except for the *in vivo* UDS assay in which batch 07-06 was used.

6.2. Subchronic toxicity

A 90-day oral toxicity study of Scansmoke R909 was performed in CRL (WI) BR rats (Lab International Centre Hungary Ltd., 2005a). The study was conducted according to the current OECD guideline 408 (1998) and in compliance with GLP. The Primary Product was administered in the diet at concentrations of 5, 12 and 20 g/kg resulting in 316, 800 and 1253 mg/kg bw/day in males and 498, 1129 and 1672 mg/kg bw/day in females.

No mortality occurred during the study. No effects attributable to the test item were detected by clinical observation. No eye alterations were found. The changes observed in haematological, clinical chemistry and urinalysis parameters were not dose-dependent and were according to the study authors within the historical control ranges for this rat strain. Therefore, these effects were not considered test-item related

The food intake was lower in females of all dose groups (up to about 30% lower in the high dose group compared to controls), however, this effect was only statistically significant in females in the highest dose group at single time points. A decrease of food consumption was not observed in males.

The body weights were lower in females of all dose groups compared to controls at the end of the study (up to 10 % lower in females of the high dose group). The body weight gain in the whole study period (week 1 – 13) was depressed in female rats in all dose groups, however, these effects were statistically significant only in the low and high dose groups and were not dose-related. The body weight gain in females of the high dose group was 74% compared to that of the controls. The authors of the study report considered the alteration in body weight gain relevant in female high dose group. However, although the decrement in body weight gain is more than 10% the Panel did not consider this effect of toxicological relevance because the effect could likely be due to the observed decrease in food intake.

Alterations in organ weights, either absolute or relative to the body or brain weight, were observed both for females and males. In males, decreases of epididymides and adrenal gland weights were observed. The alterations seen in female animals concerned the reduction of the brain, kidney, ovary and spleen weights. Increases in liver and heart weights were not statistically significant.

Since these changes in organ weights were not clearly dose-related and since the authors of the study report stated that they were within historical control ranges, these alterations were not considered of toxicological relevance. Neither test item-related effects were observed by macroscopic examination of organs nor were any substance-related effects detected in organs subject to histopathologic examination.

The Panel noted that the observed decrement of weight gain in the highest dose group was associated with a reduced food intake probably due to unpalatability.

In the absence of any pathological sequels the effect was not considered to be adverse.

Thus, the No-Observed-Adverse-Effect Level (NOAEL) was taken to be the highest dose tested of 20 g/kg diet (equal to 1253 mg/kg bw/day in males and 1672 mg/kg bw/day in females). The lower value

from these two figures (rounded to 1250 mg/kg bw/day) was taken for the calculation of the margins of safety.

6.3. Genotoxicity

The genotoxic potential of the Scansmoke R909 was tested in three *in vitro* and two *in vivo* genotoxicity assays. All genotoxicity studies were conducted according to current OECD guidelines and in compliance to GLP. This in line with the requirements of Regulation (EC) 2065/2003 and Guidance on submission of a dossier on a Smoke Flavouring Primary Product for evaluation by EFSA.

The Primary Product did not induce gene mutations in a bacterial assay which was performed using *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and the *Escherichia coli* strain WP2 uvrA (Lab International Centre Hungary Ltd., 2005b). The experiments have been carried out in the presence and absence of a metabolic activation system prepared from enzyme-induced rat liver. Phenobarbitone and ß-naphthoflavone were used for enzyme-induction. The assay was in accordance with OECD guideline 471 (1997).

Scansmoke R909 induced statistically significant and dose-related increases in the mutant frequency in mouse lymphoma cells in the MLTK assay (performed in accordance with OECD guideline 476 (1997)) both in the absence (up to 4.9-fold at 0.85 mg/ml resulting in a Relative Survival of 26%) and presence of metabolic activation (up to 4.3-fold at 1.4 mg/ml resulting in a Relative Survival of 24%) (Lab International Centre Hungary Ltd., 2005c). Both large and small colonies were induced at similar rates with and without metabolic activation (with small colonies somewhat predominating) suggesting that the genotoxic effects observed may be due to both clastogenicity and the induction of gene mutations in this assay. The metabolic activation system was prepared from rat liver.

The Primary Product did not induce chromosomal aberrations in Chinese Hamster Ovary cells *in vitro* in an assay performed in accordance with OECD guideline 473 (1997) (Lab International Centre Hungary Ltd., 2005d). The experiments have been carried out in the presence and absence of a metabolic activation system. The type of S9-fraction was not reported, however, since the assay has been performed in the same laboratory as the bacterial assay it could be assumed that the metabolic activation system used was prepared from enzyme-induced rat liver likewise.

In vivo, the Primary Product was tested in a mouse micronucleus assay performed in accordance with OECD guideline 474 (1997) (Lab International Centre Hungary Ltd., 2005e). It was administered orally to male and female mice at dose levels of 500, 1000 and 2000 mg/kg. After exposure to the Primary Product a statistically significant increase in the percentage of micronucleated polychromatic erythrocytes (MNPCE) in bone marrow of female mice at the lowest dose at 24 hours (1.75-fold compared to control) was reported. However, a dose-related increase was not observed as at 1000 mg/kg the increase was 1.4-fold and not significant and at 2000 mg/kg there was no increase at all. In addition, there was no change in MNPCE in the males at this time point at any dose. At 48 hours, a dose-related slight increase in male mice (up to 1.6-fold compared to control at the highest dose level) was seen, but this increase did not reach statistical significance. At 48 hours in females, there was a slight but statistically non-significant increase, but only at the mid-dose. The Panel noted that the data were not consistent between dose levels, time points and sexes and that the magnitude of these changes was very small. In addition, increases in MNPCE at later time points (i.e. after 48 hrs) are normally associated with indications of cytotoxicity but no such toxicity (recorded as changes in PCE/NCE ratios) was observed. Based on this variability and the lack of consistence between changes in MNPCE and (absence of) changes in PCE/NCE ratios, the Panel concluded that this study does not provide evidence for genotoxicity of the Primary Product *in vivo*.

Scansmoke R909 was tested *in vivo* in an unscheduled DNA synthesis (UDS) assay which was performed in compliance with GLP (Research Laboratory, 2007). UDS was assessed in hepatocytes of Sprague Dawley rats following oral gavage administration of Scansmoke R909 on two separate occations (the second dose being administered 14 hours after the first dose and 2 hours before

perfusion). This study design deviated slightly from the OECD guideline 486 (1997) with respect to dosing and sampling. However, the protocol was considered acceptable. Scansmoke R909 was administered at dosages of 600 and 2000 mg/kg bw. Under the conditions of this study, Scansmoke R909 did not induce UDS *in vivo*.

In summary, Scansmoke R909 is considered mutagenic *in vitro* in mouse lymphoma cells in the MLTK assay while *in vivo* negative results were obtained from a mouse micronucleus assay and an unscheduled DNA synthesis assay.

6.4. Other studies

No other studies on Scansmoke R909 were provided by the applicant.

DISCUSSION

The applicant provided information on the identity, composition, batch-to-batch variability and stability of the Primary Product as requested in the EFSA guidance document.

Except for benzo[*j*]fluoranthene, the concentrations of the polycyclic aromatic hydrocarbons (PAHs) listed in Annex 2 of the EFSA Guidance document have been provided. In addition, the contents of fluorene, phenanthrene, anthracene, fluoranthene and pyrene have been determined. The levels of benzo[*a*]pyrene and benzo[*a*]anthracene are below their respective limits of 10 and 20 µg/kg given in Regulation (EC) No. 2065/2003 (EC, 2003). Scansmoke R909 had consistently low levels of PAHs in the batches tested. Although the concentration of benzo[*j*]fluoranthene, one of the PAHs known to be carcinogenic, was not provided, the Panel concluded that based on the reported levels of other carcinogenic PAHs, benzo[*j*]fluoranthene levels would be expected to be similarly low.

The Panel considered the data provided on batch-to-batch variability and on stability of the Primary Product as sufficient.

The genotoxic potential of the Primary Product was investigated in three *in vitro* and two *in vivo* assays which were performed according to the current OECD guidelines and in compliance to GLP. Scansmoke R909 did not induce gene mutations in bacteria. It induced statistically significant and dose-related increases in the mutant frequency in mouse lymphoma cells in the MLTK assay both in the absence and presence of metabolic activation. Both large and small colonies were induced at similar rates with and without metabolic activation (with small colonies somewhat predominating) suggesting that the genotoxic effects observed may be due to both clastogenicity and the induction of gene mutations in this assay. The Primary Product did not induce chromosomal aberrations in Chinese Hamster Ovary cells *in vitro.* Negative results were obtained in the *in vivo* bone marrow micronucleus assay. An *in vivo* rat liver unscheduled DNA synthesis assay was negative.

Overall, it is concluded that Scansmoke R909 is genotoxic *in vitro* in the mouse lymphoma assay, whereas two *in vivo* genotoxicity tests are negative and sufficient to eliminate the concerns over the *in vitro* genotoxicity.

The Primary Product was investigated in a 90-day study in CRL (WI) BR rats performed according to the current OECD guideline 408 (1998) and in compliance to GLP. The Primary Product was administered in the diet at concentrations of 5, 12 and 20 g/kg resulting in 316, 800 and 1253 mg/kg bw/day in males and 498, 1129 and 1672 mg/kg bw/day in females. No test item-related effects were observed apart from decreased body weight gain in the highest dose group. The Panel noted that the observed decrement of weight gain was associated with a reduced food intake probably due to unpalatability. In the absence of any pathological sequels the effect was not considered to be adverse. Thus, the NOAEL was the highest dose tested of 20 g/kg diet (equal to 1253 mg/kg bw/day in males

and 1672 mg/kg bw/day in females). The lower value from these two figures (rounded to 1250 mg/kg bw/day) was taken for the calculation of the margins of safety (Table 8a and b).

In order to estimate dietary exposure to Scansmoke R909, the CEF Panel used two different methodologies, developed by the Panel specifically for smoke flavourings. Dietary exposure estimates were calculated by assuming that the Primary Product is present at the normal or upper use levels provided by the applicant for the 18 food categories as outlined in Commission Regulation 1565/2000.

After consulting with their users and seeking more detailed information on the actual use the applicant provided updated use levels for the different food categories on 24 April 2009. For transparency reasons both initially provided data from 2005 and updated data from 2009 were considered.

Considering the initial data provided on use levels in 2005 dietary exposures from all sources were 14.9 and 25.0 mg/kg bw/day, when assuming that the Primary Product is present at the upper use levels. When normal use levels are considered, dietary exposures were 11.2 and 20.0 mg/kg bw/day (Table 8a).

Considering the up-dated information on use levels from 24 April 2009 dietary exposures from all sources were 7.9 and 12.1 mg/kg bw/day, when assuming that the Primary Product is present at the upper use levels. When normal use levels are considered, dietary exposure were 3.0 and 3.6 mg/kg bw/day (Table 8b).

The impact on exposure of using the Primary Product only in traditionally smoked food products was also assessed.

Considering the initial data on use levels provided in 2005 the highest exposure estimates, provided by the SMK-EPIC model, were 7.2 and 9.6 mg/kg bw/day when using normal and upper use levels, respectively. With the SMK-TAMDI model these figures were 5.0 and 6.7 mg/kg bw/day, respectively (Table 8a).

Considering the up-dated information on use levels from 24 April 2009 the highest exposure estimates, provided by the SMK-EPIC model, were 2.4 and 6.0 mg/kg bw/day when using normal and upper use levels, respectively. With the SMK-TAMDI model these figures were 1.7 and 4.2 mg/kg bw/day, respectively (Table 8b).

Based on the use levels calculated with the data originally provided by the applicant in June 2005 the margins of safety as compared to the NOAEL of 1250 mg/kg bw/day derived from the 90-day toxicity study in rats amount to 50 and 84 for the intake estimates based on the upper use levels and to 63 and 112 when normal use levels are considered (Table 9a).

When dietary exposure estimates are based on use in only traditionally smoked foods the margins of safety using the two smoke flavour exposure estimates, SMK-EPIC and SMK-TAMDI, respectively would amount to 130 and 187 based on the upper use levels and to 174 and 250 when normal use levels are considered (Table 9a).

Table 9a. **Margins of safety based on the intake calculated with the data provided originally in June 2005**

	Use level	Dietary exposure* (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Margins of safety*
Total dietary exposure	Normal	11.2 / 20.0	1250	112 / 63
	Upper	14.9 / 25.0	1250	84 / 50
Traditionally smoked food	Normal	7.2 / 5.0	1250	174 / 250
	Upper	9.6 / 6.7	1250	130 / 187

* The first figure refers to dietary exposure estimated on the basis of the Smoke-EPIC model; the second one refers to dietary exposure estimated on the basis of the Smoke-TAMDI model.

Based on the use levels calculated with the new data provided by the applicant on 24 April 2009 the margins of safety as compared to the NOAEL of 1250 mg/kg bw/day derived from the 90-day toxicity study in rat amounts to 100 and 160 for the intake estimates based on the upper use levels and to 350 and 420 when normal use levels are considered (Table 9b).

When dietary exposure estimates are based on use in only traditionally smoked foods and on the model providing the highest exposure estimates, the margins of safety using the two smoke flavour exposure estimates, SMK-EPIC and SMK-TAMDI, respectively would amount to 210 and 300 based on the upper use levels and to 520 and 735 when normal use levels are considered (Table 9b).

Table 9b. **Margins of safety based on the intake calculated with the new data provided in April 2009**

	Use level	Dietary exposure* (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Margins of safety*
Total dietary exposure	Normal	3.0 / 3.6	1250	420 / 350
	Upper	7.9 / 12.1	1250	160 / 100
Traditionally smoked food	Normal	2.4 / 1.7	1250	520 / 735
	Upper	6.0 / 4.2	1250	210 / 300

* The first figure refers to dietary exposure estimated on the basis of the Smoke-EPIC model; the second one refers to dietary exposure estimated on the basis of the Smoke-TAMDI model.

The Panel did not anticipate that smoke flavourings would be used in food specifically designed for infants (0-12 months) and children (12-36 months). Therefore the safety of use of Primary Product Scansmoke R909 in such products was not assessed.

Considering that these margins of safety based on the use levels from April 2009 and on a 90-day toxicity study are inadequate, and in addition, data on reproduction and developmental toxicity and long term studies are absent, it is concluded that the uses and use levels for the Primary Product in a

wide range of product categories would require a larger margin of safety. The Panel concludes that the margins of safety are insufficient and that the use of Primary Product Scansmoke R909 at the proposed uses and use levels is of safety concern.

It is outside the remit of the Panel to decide whether, despite the low margins of safety, the use of Primary Product Scansmoke R909 might be approved for traditionally smoked products, at use levels specified, to replace smoking.

CONCLUSIONS

The Panel considered the technical and analytical data provided acceptable to characterise the Primary Product and to demonstrate its batch-to-batch variability and stability.

Scansmoke R909 is considered mutagenic *in vitro* in mouse lymphoma cells in the MLTK assay while *in vivo* a negative result was obtained from a mouse micronucleus assay and no indication of unscheduled DNA synthesis was observed in hepatocytes from male rats. Overall, it is concluded that Scansmoke R909 is genotoxic *in vitro* in the mouse lymphoma assay, whereas two *in vivo* genotoxicity tests are negative and sufficient to eliminate the concerns over the *in vitro* genotoxicity.

The NOAEL derived from a 90-day study in rats is 1250 mg/kg bw/day, the highest dose level tested.

Since the data on use levels originally provided in June 2005 have been updated by the applicant in April 2009, the Panel drew its conclusions based on the margins of safety calculated with these recent data.

Based on the use levels the margins of safety as compared to the NOAEL of 1250 mg/kg bw/day derived from the 90-day toxicity study in rats amount to 100 and 160 for the intake estimates based on the upper use levels and to 350 and 420 when normal use levels are considered.

When dietary exposure estimates are based on use in only traditionally smoked foods the margins of safety using the two smoke flavour exposure estimates, SMK-EPIC and SMK-TAMDI, respectively would amount to 210 and 300 based on the upper use levels and to 520 and 735 when normal use levels are considered.

Considering that these margins of safety based on a 90-day toxicity study are inadequate, and in addition, data on reproduction and developmental toxicity and long term studies are absent, it is concluded that the uses and use levels for the Primary Product in a wide range of product categories would require a larger margin of safety. The Panel concludes that the margins of safety are insufficient and that the use of Primary Product Scansmoke R909 at the proposed uses and use levels is of safety concern.

It is outside the remit of the Panel to decide whether, despite the low margins of safety, the use of Primary Product Scansmoke R909 might be approved for traditionally smoked products, at use levels specified, to replace smoking.

DOCUMENTATION PROVIDED TO EFSA

1. Dossier from Chemviron Carbon (now ProFagus), June 2005.
2. Amendments to the Dossier submitted by Chemviron Carbon.
3. Response from Chemviron Carbon on request for supplemental information.

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ABBREVIATIONS

AFC	Scientific Panel on Additives, Flavourings, Processing aids and Materials in Contact with Food.
bw	body weight
CEF	Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
DMSO	Dimethyl sulfoxide
EC	European Commission
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
EPIC	European Prospective Investigation into Cancer and Nutrition
FID	Flame Ionisation Detection
GC-MS	Gas Chromatography/Mass Spectrometry
GLP	Good Laboratory Practice
mTAMDI	modified TAMDI
MCPE	Micronucleated Polychromatic Erythrocytes
MLTK	Mouse Lymphoma Tyrosine Kinase
NOAEL	No-Observed-Adverse-Effect Level
NOEL	No-Observed-Effect Level
OECD	Organisation for Economic Cooperation and Development
PAHs	Polycyclic Aromatic Hydrocarbons
PCE/NCE	Polychromatic Erythrocytes/ Normochromatic Erythrocytes
SCF	Scientific Committee on Food
SMK-EPIC	Smoke flavouring EPIC model
SMK-TAMDI	Smoke Theoretical Added Maximum Daily Intake
TAMDI	Theoretical Added Maximum Daily Intake
UDS	Unscheduled DNA Synthesis
UK NDNS	United Kingdom National Diet and Nutrition Survey
WBC	White Blood Cells Counts