European Food Safety Authority

EFSA Journal 2012;10(7):2830

SCIENTIFIC OPINION

Scientific opinion on the safety of smoke flavouring Primary Product SmokEz C-10 - 2012 Update[1]

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

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The EFSA CEF Panel updated the safety assessment of the smoke flavouring Primary Product SmokEz C-10. In 2009, the Panel concluded that the margins of safety for this Primary Product were insufficient and the proposed use levels were considered of safety concern. After the opinion of 2009 the Panel received new data, i.e. new use levels, chemical data and a new 90-day toxicity study, which resulted in this update of the previous opinion. The new chemical data provided demonstrate that the test material used in the new 90-day toxicity study is representative of the Primary Product evaluated by EFSA. Based on the findings from the 90-day study submitted in 2009 and from the newly submitted one, the Panel derived a NOAEL for Primary Product SmokEz C-10 of 535 mg/kg bw/day based on body weight changes, relative kidney weight changes and changes in parameters indicative for changes in kidney function at dietary concentrations of 1350 mg/kg feed (equal to 801 mg/kg bw/day in males) and higher. Based on newly submitted normal use levels, the margins of safety are 56 and 68 (total dietary exposure) and 58 and 80 (use in traditionally smoke foods only) depending on the exposure scenario used. Given that these margins of safety are based on a 90-day toxicity studies, and given the absence of data on reproduction, developmental toxicity and of long term studies, it is concluded that the uses and use levels of Primary Product would require a larger margin of safety. The Panel concluded that the proposed use of the Primary Product at the uses and use levels specified is of safety concern.

KEY WORDS

Smoke flavouring, Primary Product, SmokEz C-10.

[1] On request from the European Commission, Question No EFSA-Q-2012-00452, adopted on July 4th, 2012.

[2] Panel members: Iona Pratt, Ulla Beckman Sundh, Mona-Lise Binderup, Leon Brimer, Laurence Castle, Karl-Heinz Engel, Roland Franz, Nathalie Gontard, Trine Husøy, Rainer Gürtler, Klaus-Dieter Jany, Catherine Leclercq, Jean-Claude Lhuguenot, Wim C. Mennes, Maria Rosaria Milana, Maria de Fatima Pocas, Kettil Svensson, Fidel Toldrá, Detlef Wölfle. Correspondence: cef@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Flavourings: Ulla Beckman Sundh, Leon Brimer, Wilfried Bursch, Angelo Carere, Karl-Heinz Engel, Henrik Frandsen, Rainer Gürtler, Frances Hill, Trine Husøy, Catherine Leclercq, Wim Mennes, Gerard Mulder, Gerrit Speijers and Harriet Wallin for the preparatory work on this scientific opinion and EFSA staff: Davide Arcella, Cristina Croera, Andrea Terron and Anne Theobald for the support provided to this scientific opinion.

Suggested citation: EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF); Scientific Opinion on the safety of smoke flavouring Primary Product SmokEz C-10 – 2012 Update. EFSA Journal 2012;10(7):2830. [21 pp.] doi:10.2903/j.efsa.2012.2830. Available online: www.efsa.europa.eu/efsajournal

SUMMARY

Following a request from the European Commission (EC), the Panel on Food Contact Materials, Enzymes, Flavourings and Processing aids (CEF), of the European Food Safety Autority (EFSA) re-evaluated the safety of the smoke flavouring Primary Product SmokEz C-10 based on new data (new use levels, chemical data and a new 90 day toxicity study) submitted by the applicant in accordance with Regulation (EC) No 2065/2003 of the European Parliament and the Council on smoke flavourings intended for use in or on foods. The other information required for the evaluation of the Primary Product SmokEz-C10, in accordance with the Guidance document (EFSA, 2005), is available in the previous opinion published on 12 June 2009 (EFSA, 2009a).

In the opinion published in 2009, the CEF Panel concluded that in the 90-day toxicity study with SmokEz C-10 treatment-related effects were observed in both male and female rats at a dietary level of 4.5% (equivalent to a mean intake of 2600 mg/kg bw/day in males and 2800 mg/kg bw/day in females) and in female rats at a dietary level of 1.5% (equivalent to a mean intake of 900 mg/kg bw/day). The no-observed-adverse-effect level (NOAEL) was considered by the Panel to be 300 mg/kg bw/day, based on increased kidney weights in female rats at higher intake levels.

Based on the use levels data calculated with the data provided by the applicant in 2009 for total dietary exposure (traditionally and non-traditionally smoked food), the margins of safety as compared to the NOAEL of 300 mg/kg bw/day in female rats derived from the 90-day toxicity study, amount to 9 and 14 for the intake estimates based on the upper use levels, and to 24 and 32 when normal use levels were considered. When assuming the use of Primary Product SmokeEz C-10 in traditionally smoked products only, the margins of safety would amount to 21 and 36 based on the upper use levels and to 44 and 72 when normal use levels were considered.

The CEF Panel considered that these margins of safety based on a 90-day toxicity study were inadequate, and that, in addition, data on reproduction and developmental toxicity as well as long term studies were absent. The CEF Panel concluded that the margins of safety were insufficient and that the use of Primary Product SmokEz C-10 at the proposed uses and use levels was of safety concern.

The applicant has performed a new 90-day toxicity study in the rat and has submitted the results for evaluation by EFSA. As compared with the previous application, the applicant has modified the proposed normal and upper use levels of the Primary Product SmokEz C-10 for the 18 food categories as outlined in Commission Regulation (EC) No 1565/2000. Accordingly EFSA has updated its former exposure assessment for SmokEz-C10.

The present opinion should be read in conjunction with the EFSA opinion of 2009, since this update only contains the new data provided by the applicant (chemical data, proposed normal and upper use levels and a 90-day toxicity study) and their evaluation by the CEF Panel. The other (chemical and toxicological) information required for the evaluation of smoke flavourings is available in the previous opinion and is still considered to apply to this product.

The chemical data provided demonstrate that the test material used in the new 90-day toxicity study is representative of the Primary Product evaluated by EFSA (EFSA, 2009a). No additional data were provided on batch-to-batch variability and chemical stability during shelf life described for the Primary Product in the opinion of 2009.

The Primary Product SmokEz C-10 has therefore been investigated in two 90-day subchronic toxicity studies in Wistar rats (10/sex/group). Animals were treated via the diet up to 4500 mg/kg feed in the first study and up to 2250 mg/kg feed in the second newly submitted study. Based on the findings in both 90-day studies the Panel derived a NOAEL for Primary Product SmokEz C-10 of 535 mg/kg bw/day based on body weight changes, relative kidney weight changes and changes in parameters indicative for changes in kidney function at dietary concentrations of 1350 mg/kg feed (equal to 801 mg/kg bw/day in males) and higher.

In order to estimate dietary exposure to the Primary Product SmokEz C-10, 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 SmokEz C-10 is present at the use levels provided by the applicant for the 18 food categories as outlined in Commission Regulation (EC).

Based on normal use levels, dietary exposure estimates from all sources were 7.9 and 9.6 mg/kg bw/day. Based on upper use levels these exposure estimates were 10.3 and 12.1 mg/kg bw/day. The two estimates based on normal use levels and the two estimates based on upper use levels were calculated according to the SMK-TAMDI and SMK-EPIC methodologies, respectively.

Based on normal use levels, dietary exposure estimates from traditionally smoked foods only were 6.7 and 9.2 mg/kg bw/day. Based on upper use levels these exposure estimates were 8.3 and 11.6 mg/kg bw/day. The two estimates based on normal use levels and the two estimates based on upper use levels were calculated according to the SMK-TAMDI and SMK-EPIC methodologies, respectively.

The Panel re-calculated the margins of safety for the estimated exposure to Primary Product SmokEz C-10 as the ratio between the NOAEL of 535 mg/kg bw/d, derived from two 90-day toxicity studies, and the estimated human dietary exposure, both expressed as mg/kg bw/day.

Based on these data it is concluded that when assuming that the Primary Product SmokEz C-10 is present at the normal use levels provided by the applicant for the 18 food categories, the margins of safety for the intake estimates as compared to the NOAEL of 535 mg/kg bw/day, identified in the 90-day toxicity studies in rats, amount to 56 and 68. When assuming the use of Primary Product SmokEz C-10 in traditionally smoked products only, the margins of safety would amount to 58 and 80.

Based on these data it is concluded that when assuming that the Primary Product SmokEz C-10 is present at the upper use levels provided by the applicant for the 18 food categories, the margins of safety for the intake estimates as compared to the NOAEL of 535 mg/kg bw/day, identified in the 90-day toxicity studies in rats, amount to 52 and 44. When assuming the use of Primary Product SmokEz C-10 in traditionally smoked products only, the margins of safety would amount to 46 and 64.

However, given the fact that:

i) these margins of safety are based on 90-day toxicity studies,
ii) the absence of data on reproduction and developmental toxicity and
iii) the absence of long term studies,

it is concluded that the uses and use levels of Primary Product SmokEz C-10 would require a larger margin of safety. Despite the increase in the margin of safety compared with the previous opinion due to the submission of an additional 90-day study and due to revised use levels provided by the applicant, the Panel concluded that the proposed use of the Primary Product SmokEz C-10 at the uses and use levels specified is of safety concern.

To decide whether despite the low margins of safety the use of Primary Product SmokEz C-10 might be approved for traditionally smoked products, at use levels specified, to replace smoking, is outside the remit of the Panel.

The Panel did not anticipate that smoke flavourings would be used in food specifically designed for infants (0-12 months) and young children (12-36 months). Therefore the safety of use of Primary Product SmokEz C-10 in such products was not assessed.

TABLE OF CONTENTS

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The European Parliament and Council Regulation (EC) No 2065/2003[4] provides the basis for securing a high level of protection for human health and the interests of consumers in relation to smoke flavourings used or intended for use in or on foods. It furthermore lays down a procedure for the evaluation and authorisation of primary smoke condensates and primary tar fractions and for the establishment of a list of primary smoke condensates and tar fractions to the exclusion of all others and their conditions of use.

The European Food Safety Authority (EFSA) was asked to provide scientific opinion on the safety of the product SmokeEz C-10. In its opinion adopted on 14 May 2009 EFSA stated that SmokeEz C-10 is genotoxic *in vitro*, but not *in vivo*. The NOAEL derived from a 90-day study was considered by the Panel to be 300 mg/kg bw/day based on increased kidney weights in female rats at higher intake levels. EFSA concluded that the margin of safety is insufficient and that the use of the Primary Product SmokeEz C-10 at the proposed uses and use levels is of safety concern.

Based on the conclusions drawn by EFSA, the applicant has repeated a 90-day study and proposed new use levels.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The European Commission requests the European Food Safety Authority to carry out a safety assessment of the smoke flavouring primary product SmokEz C-10 based on a new 90-day study, new use levels and new chemical data submitted by the applicant in accordance with Regulation (EC) No 2065/2003[4] of the European Parliament and the Council on smoke flavourings intended for use in or on foods.

[4] Regulation (EC) No 2065/2003 of the European Parliament and of the Council of 10 November 2003 on smoke flavourings used or intended for use in or on foods. OJ L 309, 26.11.2003, p. 1-8.

ASSESSMENT

1. INTRODUCTION

The European Food Safety Authority (EFSA) has been asked by the European Commission (EC) to reconsider its safety assessment on the smoke flavouring Primary Product SmokEz C-10 based on evaluation of a new 90-day toxicity study submitted by the applicant in accordance with Regulation (EC) No 2065/2003 of the European Parliament and the Council on smoke flavourings intended for use in or on foods.

In the opinion published by EFSA in 2009 on the safety of smoke flavouring Primary Product SmokEz C10 (EFSA, 2009a), the CEF Panel concluded that the margins of safety calculated on the basis of a no-observed-adverse-effect-level (NOAEL) identified from a 90-day toxicity study, and on dietary exposure estimates (normal or upper use levels) from all food sources (18 food categories) as well as from only traditionally smoked foods, were insufficient and that the use of Primary Product SmokEz C-10 at the proposed uses and use levels was of safety concern.

The applicant has performed a new 90-day toxicity study and has submitted the results for evaluation by EFSA. The petitioner has also proposed new use levels and new chemical data.

The present opinion does not replace but complements the previous one published on 12 June 2009 (EFSA, 2009a), and therefore both documents should be read in conjunction. This opinion only refers to the new information received from the applicant and to its impact on the safety assessment of the Primary Product SmokEz C10, *i.e.* chemical data on the material used in the new 90-day study, a new 90-day toxicity study and new information on use levels. The newly submitted data specifically include (i) the chemical analysis of the principal constituents and polycyclic aromatic hydrocarbons (PAHs) content of the material tested (demonstrating that this material is representative of the Primary Product previously assessed by EFSA), (ii) a new 90-day toxicity study and (iii) new proposed use levels.

With respect to the other information submitted by the applicant prior to 2009 in accordance with the Guidance document (EFSA, 2005), the reader should refer to the opinion of 2009. The latter contains complementary chemical and toxicological data that still hold true for this Primary Product.

1.1 Summary of the previous opinion on the safety of the smoke flavouring Primary Product SmokEz C-10 (EFSA, 2009a)

The original summary taken from the opinion published by EFSA in 2009 on the safety of the smoke flavouring Primary Product SmokEz C-10 (EFSA, 2009a) is given below.

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 SmokEz C-10.

The Primary Product SmokEz C-10 is obtained from mixed wood species. The average proportions reported by the applicant are as follows: maple (Acer saccharum) 51 %, oak (Quercus alba) 29 %, hickory (Carya ovata) 16 % as primary sources and ash (Fraxinus americana), birch (Betula papyrifera and Betula alleghaniensis), wild black cherry (Prunus serotina), and beech (Fagus grandifolia) as secondary sources (3 %).

The production of SmokEz C-10 comprises the following steps: (i) wood lots received are combined prior to pyrolysis and dried, (ii) pyrolysis of the saw dust in a rotary calciner reactor with continuous feeding in an inert atmosphere, (iii) condensing of the hot vapours, (iv) separation of tar, filtration and conditioning of the Primary Product. The applicant has provided essential parameters of the manufacturing process.

The water content of the primary product is 67 wt. %. The volatile fraction identified by capillary gas chromatography analysis accounts for 22 wt. % of the Primary Product. 19 wt. % (corresponding to 86 % of the volatile fraction) were identified which is in compliance with Commission Regulation (EC) 627/2006. The total identified mass (21 wt. % of the Primary Product) corresponds to 64 % of the solvent-free fraction which is in compliance with Commission Regulation (EC) 627/2006.

The contents of 12 of the 15 PAHs listed in Annex 2 of the EFSA guidance document (EFSA, 2005) have been determined in SmokEz C-10 by an external accredited laboratory using the US-Environmental Protection Agency (EPA) method 3510/8270-GC/MS. According to the applicant, the analyses of 5-methylchrysene, cyclopenta[cd]pyrene and dibenzo[a,e]pyrene were not performed because the respective calibration standards were not available at the time of the analysis. The levels of benzo[a]pyrene and benzo[a]anthracene are below their respective limits of 10 and 20 ìg/kg given in Regulation (EC) No. 2065/2003 (EC, 2003). Although the concentrations of 5-methylchrysene, cyclopenta[cd]pyrene and dibenzo[a,e]pyrene, PAHs known to be carcinogenic, were not provided, the Panel concluded that based on the reported levels of other carcinogenic PAHs, the levels for 5-methylchrysene, cyclopenta[cd]pyrene and dibenzo[a,e]pyrene would be expected to be similarly low.

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.

SmokeEz C-10 showed negative results in a S. typhimurium reverse mutation assay in strains TA1535, TA1537, TA 1538, TA98 and TA 100, both in the absence and presence of S9. The Panel noted that this non-GLP study, carried out in 1977, did not comply with current test guidelines, but did not consider that it was necessary to request the applicant to repeat the study, given that the other two in vitro studies submitted on SmokEz C-10 gave clearly positive results.

Positive results were obtained in the mouse lymphoma L5178Y tk+/- assay, primarily at cytotoxic concentrations of SmokEz C-10, with relatively more small than large colonies being formed. In a test for chromosomal aberrations in Chinese Hamster Ovary (CHO), cells SmokEz C-10 showed evidence of clastogenic activity in both the absence and presence of S9.

The in vivo bone marrow micronucleus assay was negative without significant depression of the PCE/NCE ratio and an in vivo rat liver unscheduled DNA synthesis test was also negative.

Overall, it is concluded that SmokEz C-10 is genotoxic in vitro in the mouse lymphoma assay and the chromosomal aberration assay whereas two in vivo genotoxicity tests are negative and sufficient to eliminate the concerns over the in vitro genotoxicity.

In the 90-day toxicity study with SmokEz C-10 treatment-related effects were observed in both males and females at a dietary level of 4.5% (equivalent to a mean intake of 2600 mg/kg bw/day in males and 2800 mg/kg bw/day in females) and in female rats at a dietary level of 1.5% (equivalent to a mean intake of 900 mg/kg bw/day). The no-observed-adverse-effect level (NOAEL) was considered by the Panel to be 300 mg/kg bw/day, based on increased kidney weights in female rats at higher intake levels.

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.

Use levels of the Primary Product provided by the applicant in 2009, based on finished food product weight, range from 0.2 g/kg (fats and oil) to 5 g/kg (dairy products, meat, fish). Dietary exposure to the Primary Product was not assessed by the applicant.

In order to estimate dietary exposure to the Primary Product SmokeEz C-10, 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 (EC).

Considering the initial data provided on use levels in 2005, the dietary exposure from all sources ranges from 23.9 to 26.0 mg/kg bw/day, when assuming that the Primary Product is present at the upper use levels, and from 10.9 to 13.0 mg/kg bw/day, when normal use levels are considered.

Considering the updated information on use levels from 28 April 2009, the dietary exposure from all sources ranges from 22.2 to 33.8 mg/kg bw/day, when assuming that the Primary Product is present at the upper use levels, and from 9.3 to 12.5 mg/kg bw/day, when normal use levels are considered.

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, resulting from the SMK-EPIC model, were 7.3 and 14.5 mg/kg bw/day when using normal and upper use levels, respectively. With the SMK-TAMDI model these figures were 4.2 and 8.3 mg/kg bw/day, respectively.

Considering the updated information on use levels from 28 April 2009 the highest exposure estimates, resulting from the SMK-EPIC model, were 6.8 and 14.5 mg/kg bw/day when using normal and upper use levels, respectively. With the SMK-TAMDI model these figures were 4.2 and 8.3 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, the Panel drew its conclusions based on the margins of safety calculated with these recent data.

Based on the intake data calculated with the new data provided by the applicant on 28 April 2009 for total dietary exposure (traditionally and non-traditionally smoked food), the margins of safety as compared to the NOAEL of 300 mg/kg bw/day in female rats derived from the 90-day toxicity study amount to 9 and 14 for the intake estimates based on the upper use levels and to 24 and 32, when normal use levels are considered.

When assuming the use of Primary Product SmokeEz C-10 in traditionally smoked products only the margins of safety would amount to 21 and 36 based on the upper use levels and to 44 and 72 when normal use levels are considered.

Considering that these margins of safety based on a 90-day toxicity study are inadequate, and that, in addition, data on reproduction and developmental toxicity as well as long term studies are absent, it is concluded that the uses and use levels of the Primary Product SmokEz C-10 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 SmokEz C-10 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 SmokEz C-10 might be approved for traditionally smoked products, at use levels specified, to replace smoking.

2. TECHNICAL DATA

2.1. Identity of the Primary Product

The batch of the Primary Product SmokEz C-10 used for the additional 90-day oral toxicity study is C10-10020398. It was manufactured on October 2, 2010.

2.1.1 Source materials for the Primary Product

Table 1 shows the wood materials used to produce batch C10-10020398 of the Primary Product employed for the additional 90-day study and batch C10-05044209 employed for the 90-day study in the previous opinion (EFSA, 2009a).

Table 1: Proportions of wood used to produce batch C10-10020398 of the Primary Product and batch C10-05044209 employed for the 90-day in the previous opinion (EFSA, 2009a).

Lot	Maple (%) (*Acer saccharum*)	Oak (%) (*Quercus alba*)	Hickory (%) (*Carya ovata*)	Secondary Woods (%)[a)]
C10-10020398	58	28	10	4
C10-05044209	45	39	13	3

[a)] ash (*Fraxinus americana*), birch (*Betula papyrifera* and *Betula alleghaniensis*), wild black cherry (*Prunus serotina*) and beech (*Fagus grandifolia*)

The data for batch C10-10020398 are in accordance with the average proportions and ranges of wood materials (maple: 51%, min. 25% - max. 60%; oak: 29%, min. 10% - max. 40%; hickory: 16%, min. 10% - max. 25%; secondary woods: 3%, min. 0% - max. 15%), previously reported by the applicant (EFSA, 2009a).

2.1.2 Physical state of the Primary Product

The specific gravity (1.064 g/ml) and the viscosity (2.0 cP at 25°C) are in agreement with average data (1.067 g/ml and 2.1 cP) provided in the previous opinion for the Primary Product SmokEz C-10 (EFSA, 2009a).

2.2 Chemical description of the Primary Product

2.2.1 Overall characterisation

Water functions as solvent of the Primary Product. The batch C10-10020398 had a water content of 67.3 %. This is in agreement with the value (67.0 %) previously reported for SmokEz C10 (EFSA, 2009a).

The applicant provided a list of 50 compounds screened in batch C10-10020398 of the Primary Product by gas chromatography, gas chromatography/mass spectrometry and HPLC with UV detection. For 31 compounds quantitative values were presented, 17 compounds were present below their limits of detection (50 mg/kg), two were reported as not accessible via the applied technique. No analytical details and no data regarding the quantification procedure have been provided.

The identified compounds amount to a total identified mass of 21.9 wt. % of batch C10-10020398. This corresponds to 67% of the solvent-free fraction and is thus in compliance with Commission regulation (EC) 627/2006 (EC, 2006).

2.2.2 Chemical description of the Primary Product

Data have been given on acids, phenols, carbonyls and solids. As shown in Table 2, the data for batch C10-10020398 are in agreement with those provided on batch C10-05044209 employed for the 90-day study in the previous opinion. They also meet the specifications provided for the Primary Product SmokEz C-10 (EFSA, 2009a).

Table 2: Major chemical parameters of the Primary Product SmokEz C-10.

	Batch C10-10020398	**Batch C10-05044209**	**Specifications (EFSA, 2009)**
Total acidity (as acetic acid); wt.%	10.9	9.5	10.5 – 12.0
Carbonyls; wt.%	15.8	12.3	12.0 – 17.0
Phenols (Smoke Flavor Compounds); mg/ml	10.0	11.0	10.0 – 15.0
Solids; °BRIX (g sucrose/100 g solution)	24.8	24.6	not available

2.2.3 Identification and quantification of Primary Product constituents

2.2.3.1 Principal constituents

A comparison of the contents of the 23 principal constituents reported for batch C10-05083301 of the Primary Product in the previous opinion (EFSA, 2009a) and those provided for batch C10-10020398 used for the additional 90-day study is shown in Table 3.

Table 3: Principal constituents of the Primary Product SmokEz C-10.

Constituent	**Batch C10-05083301 (g/kg)**	**Batch C10-10020398 (g/kg)**
Acetic acid	67	89
Acetol (Hydroxypropanone)	26	18
Hydroxyacetaldehyde	18	20
Formic acid	14	17
Methanol	8.1	9.6
Glyceraldehyde	7.0	3.5
Formaldehyde	5.6	1.9
Propionic acid	4.0	3.9
Catechol (2-Hydroxyphenol)	3.5	- [a]
Methyl acetate	3.3	5.3
2,5-Dimethylphenol	2.9	0.1
2-Furaldehyde	2.4	2.6
Acetaldehyde	2.4	1.4
Syringol (2,6-Dimethoxyphenol)	2.2	2.0
Cyclotene	2.0	2.0
Guaiacol (2-Methoxyphenol)	2.0	0.6
p-Cresol	1.8	n.d.[b]
3-Buten-2-one	1.4	n.d.
Acrolein	1.3	n.d.
Methylglyoxal	1.3	n.d.

Ethylene glycol	1.2	4.1
5-Hydroxymethylfurfural	1.1	1.2
Glyoxal	1.1	2.9

[a] according to the applicant, not accessible by the employed analytical method; [b] below the limit of detection: 50 mg/kg

The Panel noted the marked difference in the contents of 2,5-dimethylphenol and the fact that five substances (catechol, p-cresol, 3-buten-2-one, acrolein and methylglyoxal) previously reported as principal constituents in C10-05083301 were not detected in batch C10-10020398.

In the previous dossier submitted to EFSA, GC-based data had been presented on the contents of selected constituents in 13 batches of the Primary Product produced in 2004 and in 24 batches produced in 2005. As shown in Table 4, the contents of major (acetic acid, acetol, hydroxyacetaldehdye) as well as minor constituents (syringol, cyclotene, guaiacol) determined in the batch C10-10020398 were within the previously reported ranges.

Table 4: Batch-to-batch variability of selected constituents in the Primary Product SmokEz C-10.

	batch C10-05083301	**batch C10-10020398**	**13 batches (2004)**		**24 batches (2005)**	
Constituent	***content (g/kg)***	***content (g/kg)***	***range (g/kg)***	***mean (g/kg)***	***range (g/kg)***	***mean (g/kg)***
acetic acid	67	89	80 - 130	100	70 -140	110
acetol (hydroxypropanone)	26	18	26 - 41	32	13 - 25	19
hydroxyacetaldehyde	18	20	17 - 25	21	14 - 22	18
syringol	2.2	2.0	n.a.	n.a.	1.0 – 2.0	1.4
cyclotene	2.0	2.0	1.5 – 2.4	1.9	1.6 – 3.4	2.4
guaiacol	2.0	0.6	0.3 – 0.5	0.4	0.2 – 0.7	0.5

n.a. not available

2.2.3.2 Contents of Polycyclic Aromatic Hydrocarbons (PAHs)

The contents of benzo(a)pyrene and benzo(a)anthracene in the test material SmokEz C-10 (batch 10020398) were reported to be below the detections limits (0.05 and 0.1 ppb, respectively) of the employed methodology (HPLC with fluorescence detection). The contents of these two PAHs are thus below their respective limits of 10 and 20 µg/kg given in Regulation (EC) No. 2065/2003 (EC, 2003).

No data have been provided on other PAHs.

3. PROPOSED USE LEVELS

The revised normal and upper use levels as proposed by the applicant for each of the 18 food categories as outlined in Commission Regulation (EC) No 1565/2000[5] are summarized in Table 5.

[5] Commission Regulation (EC) No 1565/2000 of 18 July 2000 laying down the measures necessary for the adoption of an evaluation programme in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council. OJ L 180, 19.07.2000, p. 8-16.

Table 5: Normal and upper use levels of Primary Product SmokEz C-10 in food categories as outlined in Commission Regulation (EC) No 1565/2000

Food categories		Use levels (g/kg)	
		Normal	**Upper**
1	Dairy products, excluding products of category 2	0.2	0.2
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 (including mushrooms & fungi, roots & tubers, pulses & legumes) and nuts and seeds	0	0
5	Confectionery	0	0
6	Cereals and cereal products, including 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	4.0	5.0
9	Fish and fish products, including molluscs, crustaceans and echinoderms	2.0	3.0
10	Egg and egg products	0	0
11	Sweeteners, including honey	0	0
12	Salts, spices, soups, sauces, salads, protein products etc. 12.1 Salt and sal substitutes 12.2 Herbs, spices, seasonings and condiments 12.3 Vinegars 12.4 Mustards 12.5 Soups and broths 12.6 Sauces and like products 12.7.1 Salads (e.g macaroni salad, potato salad) 12.7.2 Sandwich spreads excluding cocoa and nut based spreads 12.8 Yeast and like products 12.9 Protein products 12.10 Fermented soybean products	2.5 0 2.5 0 0 0 2.5 0 0 0 0 0	3 0 3.0 0 0 0 3.0 0 0 0 0 0
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	0
15	Ready-to-eat savouries	2.5	4.0
16	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 1 - 15	0	0

4. DIETARY EXPOSURE ASSESSMENT

In order to estimate dietary exposure to the Primary Product, the CEF Panel used two different methodologies, namely the Smoke Theoretical Added Maximum Daily Intake (SMK-TAMDI) and the Smoke Flavouring European Prospective Investigation into Cancer and Nutrition (EPIC) model (SMK-EPIC). These methodologies were developed by the Panel specifically for smoke flavourings and are described in detail in the EFSA opinion on dietary exposure assessment methods for smoke flavouring Primary Products (EFSA, 2009b).

As reported in Table 6, dietary exposures to SmokEz C-10 were estimated by both the SMK-TAMDI and SMK-EPIC methodologies, assuming that the Primary Product is present at normal and upper use levels provided by the applicant for the 18 food categories as outlined in Commission Regulation (EC).

Estimated dietary exposure from all sources at normal use levels were 7.9 and 9.6 mg/kg bw/day, according to the SMK-TAMDI and SMK-EPIC methodologies, respectively.

Estimated dietary exposure from all sources at upper use levels were 10.3 and 12.1 mg/kg bw/day, according to the SMK-TAMDI and SMK-EPIC methodologies, respectively.

Table 6: Summary of the dietary exposure estimates to the Primary Product SmokEz C-10 calculated on the basis of the normal and upper use levels.

Methodologies		Dietary exposure (mg/kg bw/day)	
		Normal	Upper
SMK-TAMDI	Traditionally smoked food	6.7	8.3
	Other foods not traditionally smoked	1.3	2.0
	Beverages (alcoholic or non-alcoholic)	0.0	0.0
	Total dietary exposure	7.9	10.3
SMK-EPIC	Traditionally smoked food	9.2	11.6
	Other foods not traditionally smoked	0.4	0.5
	Beverages (alcoholic or non-alcoholic)	0.0	0.0
	Total dietary exposure	9.6	12.1

5. TOXICOLOGY

5.1 Identity of the test material

The batch C10-10020398 was the one used in the new 90-day dietary toxicity study.

5.2. 90-day dietary toxicity studies

In the previous opinion on Primary Product SmokEz C-10, already the results of a 90-day dietary toxicity study were available. From this study a NOAEL of 300 mg/kg bw/day could be derived (see section 1.1). For the present update a second 90-day dietary toxicity study has been submitted. In order to facilitate the comparison of the results from the two studies, the evaluation of the first 90-day study is quoted verbatim from the original opinion on this Primary Product.

5.2.1 First 90-day dietary toxicity study (text taken verbatim from the EFSA 2009 opinion)

A comprehensive 90-day subchronic toxicity study was conducted according to GLP guidelines on SmokEz C-10, batch number 05044209 (TNO, 2005a)[6].

The test material was administered to groups of 10 Wistar rats per sex at 0.45, 1.5 and 4.5% (w/w) in the diet. The intake of study substance per kg body weight per day was calculated from the nominal dietary concentration, the food consumption and the mean body weight in the relevant week, and was equivalent to overall mean intakes of 270, 900 and 2600 mg/kg bw/day in males and 300, 900 and 2800 mg/kg bw/day in females. 2,6-Dimethoxyphenol (2,6-DMP;present at relatively high levels in the test substance) was used as a tracer compound in the diets to calculate the actual content of SmokEz C-10, however analyses to determine the stability of the test material were not undertaken, given that it was a complex mixture.

[6] For reference see previous opinion on C-10

There were no clinical signs of toxicity during the study, and none of the rats died. Neurobehavioural (Functional Observational Battery, FOB) and motor activity assessment showed no evidence of a neurotoxic potential, while ophthalmoscopic examination did not reveal any treatment-related effects. There was however a consistent and statistically significant decrease in body weight gain throughout the study in both males and females at the highest dose level of 4.5% in the diet (11% decrease in body weight gain overall compared with controls in males and 11.4% in females). Body weight was also significantly decreased at several of the assessment times in mid-dose females. Body weight changes were associated with decreased food consumption in the top dose animals and in affected mid-dose females, which was possibly due to palatability of the diet. Water consumption was decreased in high dose males.

Haematological examinations showed statistically significant increases in thrombocyte counts in female rats at both the 1.5 and 4.5% dietary level compared with controls (controls 946 + 30, 0.45% group 971 + 23, 1.5% group 1042 + 18 ($p < 0.05$), 4.5% group 1065 + 34 ($p < 0.01$), all results expressed as x 10^9/l). Clinical chemistry investigations revealed significant decreases in aspartate aminotransferase in these same (female) groups (86% of control at 1.5% and 78% of control at 4.5%). Total plasma protein and also albumin was significantly increased in males at 4.5% (106% and 109% of control, respectively), while females at this level showed significant increases in plasma cholesterol (128% of control) and phospholipids (118% of control) and a significant decrease in plasma creatinine (76% of control). Urinalysis showed a non-significant trend towards increased urinary volumes in both male and female top dose rats.

Female rats at both the 1.5 and 4.5% dietary level showed significantly increased relative liver and kidney weight (relative liver weight 108% of control at 1.5% and 116% of control at 4.5%, relative kidney weight 109% of control at 1.5% and 111% of control at 4.5%). There were however no treatment-related macroscopic or microscopic (histopathological) findings in any group. Overall in this study, females at both the 1.5% and the 4.5% dietary levels (equivalent to 900 or 2800 mg/kg bw/day, respectively) showed evidence of a treatment-related effect, comprising a consistent decrease in body weight gain (only in females receiving 2800 mg/kg bw/day), decreased aspartate aminotransferase and plasma creatinine, increases in plasma cholesterol and phospholipids (only in females receiving 2800 mg/kg bw/day) and increased relative liver and kidney weight. Males receiving 2600 mg/kg bw/day also showed decreased body weight gain and significant changes in some biochemical parameters.

In the opinion of the Panel, the no-observed-adverse-effect level (NOAEL) in this study was therefore 300 mg/kg bw/day (0.45% in the diet) in female rats and 900 mg/kg bw/day in males based on increased kidney weights.

5.2.2 Newly submitted 90-day dietary toxicity study in rats (Grósz, 2012).

A comprehensive 90-day subchronic toxicity study was conducted with SmokEz C-10, batch number 10020398, according to OECD guideline 408 and in compliance with GLP (Grósz, 2012).

The test material was administered to groups of 10 Wistar rats per sex at 0, 0.9, 1.35, 1.8 and 2.25% (w/w) in the diet. The intake of study substance per kg body weight per day was calculated from the nominal dietary concentration, the food consumption and the mean body weights of the animals during the study, and was equal to overall mean intakes of 0, 535, 801, 1115 and 1351 mg/kg bw/day in males and 0, 686, 1133, 1272 and 1824 mg/kg bw/day in females. 2,6-Dimethoxyphenol (2,6-DMP or syringol) was used as a tracer compound in the diets to calculate the actual content of SmokEz C-10. The actual concentrations of the test material in the feed were on average 0, 114, 104, 103 or 106% of the nominal feed concentrations. The stability of the test material in the diets was confirmed by investigation of the 2,6-DMP contents in fresh and frozen diet samples (up to two months of storage).

There were no clinical signs of toxicity during the study, and none of the rats died. Neurobehavioural (Functional Observational Battery, FOB) and motor activity assessment showed no evidence of a neurotoxic potential. Ophthalmoscopic examination did not reveal any treatment-related effects.

Male body weights at the end of the study were slightly lower in the exposed groups as compared to the control animals (-3%, -5%, -4% and -6% in the 0.9, 1.35, 1.8 and 2.25% dose groups, respectively), but statistical significance was not reached. No treatment-related effect on the body weight was observed in the female animals. There was no effect on feed intake and on feed conversion. Water consumption was not monitored.

There was a statistically significant and weakly dose-related increase in red blood cell counts (RBC) in the male animals. Also in all treatment groups the haemoglobin concentration (Hb) and haematocrit (Ht) were increased (no dose response, D-R). The mean corpuscular haemoglobin concentration (MCHC) was not affected. A statistically significant increase in prothrombin time (Pt) was observed (D-R). Table 7 gives an overview of the reported changes in haematological parameters. No consistent changes were observed in other haematological parameters, including thrombocyte counts, in males and in females.

A clear dose-related and statistically significant decrease in plasma creatinine concentrations (m+f) was observed at 1.35% and above. In males also plasma sodium concentrations were decreased (statistically significant and D-R). Plasma phosphate levels were statistically significantly increased at the two highest dose levels in males only. Table 7 gives an overview of the reported changes in blood biochemistry parameters. No other consistent treatment-related changes in clinical chemistry parameters (including total protein, albumin, cholesterol, or lipoproteins) were observed in either sex. No changes were reported in urinary parameters (volume, pH, specific gravity).

No toxicologically relevant macroscopic or microscopic organ changes were observed. In the males, the relative (to body weight) kidney weights were dose-relatedly increased and statistical significance was reached in the 1.8 and 2.25% treatment groups, but no statistically significant changes in absolute or relative (to brain) kidney weights were observed. In the females also a slight increase in relative kidney weight was observed, but here statistical significance was not reached. Also no D-R was obvious. In the females in the 2.25% dose group higher (+/- 20%) absolute and relative (to body weight) thyroid weights were observed as compared to the control females. Liver weights were unaffected in either sex (for quantitative information on the organ weight changes see Table 7).

Table 7: Changes in haematological and blood biochemistry parameters in males and organ weight changes in males (m) and females (f).

	Dose groups (% w/w)				
% in feed	**0**	**0.9**	**1.35**	**1.8**	**2.25**
Haematology					
RBC[1] (10^6/µl; m)	8.5	9.0*	9.1*	9.1*	9.2*
Hb (g/dl; m)	14.7	15.6#	15.6#	15.6#	15.6#
Ht (%; m)	44.8	47.4	47.2#	46.6*	46.6*
Pt (s; m)	21.1	21.2	22*	22.3#	23.4#
Biochemistry					
Creatinine (µM; m)	44.2	39.5	35.1#	34.5#	34.2#
Creatinine (µM; f)	52.6	49.8	40.4#	45.6*	39.6#
Na^+ (mM; m)	149.1	147.5#	147.3#	147.6#	146.3#
PO_4^{3-} (mM; m)	2.5	2.5	2.4	2.7*	2.8*
Organ weights					
kidney (rel; m)	0.53	0.53	0.55	0.58*	0.61#
kidney (rel; f)	0.62	0.64	0.64	0.64	0.66
thyroid (abs; f)	15.0	15.8	16.7	16.1	18.2*
thyroid (rel; f)	0.005	0.006	0.009	0.007	0.010*

[1] RBC: red blood cell counts; Hb: haemoglobin concentration; Ht: haematocrit, Pt: prothrombine time
[2] rel: relative to body weight (%); abs: absolute weight (mg)
* statistically significant P<0.05; # ; statistically significant P<0.01; Duncan's multiple range test.

The study authors noted the following:

- The males in the control group were heavier than normal, and considered the body weight change in the males as unrelated to treatment, because of the absence of a clear dose-response.
- The haematological changes were in the normal ranges for the various parameters studies and no dose- or gender-related changes were observed.
- Although test item-related effects on creatinine, sodium or phosphate cannot be excluded, the parameter values remained within the physiological ranges and correlated findings in other parameters were absent.
- The higher thyroid weight in the high dose females was within the normal range and it was comparable to the thyroid weight in the females of a control group in a simultaneously run 90-day study with a related smoke flavouring substance (SmokEz Enviro 23).

For these reasons the study authors concluded that there were no toxicologically relevant effects in the exposed animals and derived from this study a NOAEL of 2.25%, equal to 1351 mg/kg bw/day in males and 1824 mg/kg bw/day in females. The study authors did not specifically comment on the increased kidney weights in the males.

Where changes were observed in biochemical and haematological parameters, these were in general very small. However, the Panel noted that for none of the effects discussed by the study authors, historical control values were provided in the report, and therefore it is difficult to judge whether the reported changes have any physiological relevance or not. However, similar to the previous study there were effects on body weight and changes in relative kidney weight, haematology and blood biochemistry parameters, which might be indicative of kidney functional changes. The Panel concluded that these changes are treatment –related. However, the Panel concluded that the changes at the lowest dose were so minimal (*e.g.* a reduced plasma creatinine level has no physiological meaning

by itself) that at this dose the changes were not yet adverse. Therefore, the Panel derived a NOAEL of 900 mg/kg feed from the second 90-day study, which is equal to 535 or 686 mg/kg bw/day in males and females respectively. This new study is very comparable to the previous 90-day study and the LOAELs from both studies are comparable, also with respect to severity of observed changes at the respective LOAELs. Therefore, the Panel decided to use the NOAEL of 535 mg/kg bw/day from the second study for the risk assessment of primary product SmokEz C-10 in the present update of this opinion.

6. DISCUSSION

The present opinion describes the results of the evaluation of new data (new use levels, chemical data and a new sub-chronic toxicity study) provided by the applicant on Primary Product SmokEz C-10. The other information required for the evaluation of the Primary Product SmokEz C-10, in accordance with the Guidance document (EFSA, 2005), is available in the previous opinion adopted on 14 May 2009 (EFSA, 2009a).

The Panel noted some inconsistencies between the principal constituents previously described in batch C10-05083301 and those reported in batch C10-10020398. However, taking into account the ranges previously reported for selected constituents in a total of 37 batches and the additional technical information provided, the Panel considered the data acceptable to demonstrate that the material tested in the additional 90-day study (SmokEz C-10, batch 10020398) is representative of the Primary Product evaluated by EFSA in 2009 (EFSA, 2009a).

The Primary Product SmokEz C-10 was investigated in two 90-day subchronic toxicity studies in Wistar rats (10/sex/group). Animals were treated via the diet up to 4500 mg/kg feed in the first study and up to 2250 mg/kg feed in the second newly submitted study. The Panel considered that these two studies are very comparable with respect to study design; dose levels and reported effects. Although the affected parameters were not completely the same in both studies, these changes, especially in the second study, might be indicative of kidney functional changes. The Panel noted that in both studies changes in body weight and kidney-related parameters were observed, but that in the earlier study the females seemed to be more responsive, whereas in the second study the renal effects were observed predominantly, but not exclusively in the males. Despite this sex difference in responsiveness between the studies, the Panel considered it justified to combine the data from the two studies and to derive a NOAEL for Primary Product SmokEz C-10 of 535 mg/kg bw/d. This NOAEL is based on body weight changes, relative kidney weight changes and changes in parameters indicative for changes in kidney function at dietary concentrations of 1.5% (900 mg/kg bw/d) and higher in the first study or 1350 mg/kg feed (equal to 801 mg/kg bw/day in males) and higher in the second study.

In order to estimate dietary exposure to the Primary Product SmokEz C-10, 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 SmokEz C-10 is present at the upper use levels provided by the applicant for the 18 food categories as outlined in Commission Regulation (EC).

Based on normal use levels, dietary exposure estimates from all sources were 7.9 and 9.6 mg/kg bw/day. Based on upper use levels these exposure estimates were 10.3 and 12.1 mg/kg bw/day. The two estimates based on normal use levels and the two estimates based on upper use levels were calculated according to the SMK-TAMDI and SMK-EPIC methodologies, respectively.

Based on normal use levels, dietary exposure estimates from traditionally smoked foods only were 6.7 and 9.2 mg/kg bw/day. Based on upper use levels these exposure estimates were 8.3 and 11.6 mg/kg bw/day. The two estimates based on normal use levels and the two estimates based on upper use levels were calculated according to the SMK-TAMDI and SMK-EPIC methodologies, respectively.

The Panel re-calculated the margins of safety for the estimated exposure to Primary Product SmokEz C-10 as the ratio between the NOAEL of 535 mg/kg bw/day, derived from two 90-day toxicity studies, and the estimated human dietary exposure, both expressed as mg/kg bw/day (Table 8).

Table 8: Margins of safety calculated on the basis of the upper use levels.

	Dietary exposure (mg/kg bw/day)		**NOAEL (mg/kg bw/day)**	**Margins of safety**	
	Normal use levels	Upper use levels		Normal use levels	Upper use levels
Total dietary exposure	7.9[(a)] / 9.6[(b)]	10.3[(a)] / 12.1[(b)]	535	68[(a)] / 56[(b)]	52[(a)] / 44[(b)]
Traditionally smoked food	6.7[(a)] / 9.2[(b)]	8.3[(a)] / 11.6[(b)]	535	80[(a)] / 58[(b)]	64[(a)] / 46[(b)]

(a): if dietary exposure is estimated on the basis of the SMOKE-TAMDI model
(b): if dietary exposure is estimated on the basis of the SMOKE-EPIC model

Based on these data it is concluded that when assuming that the Primary Product SmokEz C-10 is present at the normal use levels provided by the applicant for the 18 food categories, the margins of safety for the intake estimates as compared to the NOAEL of 535 mg/kg bw/day, identified in the 90-day toxicity studies in rats, amount to 56 and 68 (Table 8). When assuming the use of Primary Product SmokEz C-10 in traditionally smoked products only, the margins of safety would amount to 58 and 80 (Table 8).

Based on these data it is concluded that when assuming that the Primary Product SmokEz C-10 is present at the upper use levels provided by the applicant for the 18 food categories, the margins of safety for the intake estimates as compared to the NOAEL of 535 mg/kg bw/day, identified in the 90-day toxicity studies in rats, amount to 52 and 44 (Table 8). When assuming the use of Primary Product SmokEz C-10 in traditionally smoked products only, the margins of safety would amount to 46 and 64 (Table 8).

However, given the fact that:

i) these margins of safety are based on 90-day toxicity studies,
ii) the absence of data on reproduction and developmental toxicity and
iii) the absence of long term studies,

it is concluded that the uses and use levels of Primary Product SmokEz C-10 would require a larger margin of safety. Despite the increase in the margin of safety compared with the previous opinion due to the submission of an additional 90-day study and due to revised use levels provided by the applicant, the Panel concluded that the proposed use of the Primary Product SmokEz C-10 at the uses and use levels specified is of safety concern.

The Panel did not anticipate that smoke flavourings would be used in food specifically designed for infants (0-12 months) and young children (12-36 months). Therefore, the safety of use of Primary Product SmokEz C-10 in such products was not assessed.

CONCLUSIONS AND RECOMMENDATIONS

The European Food Safety Authority (EFSA) has been asked by the European Commission (EC) to reconsider its safety assessment of the smoke flavouring Primary Product SmokEz C-10 based on new data (new use levels, chemical data and a new sub-chronic toxicity study) provided by the applicant on the Primary Product SmokEz C-10. The other information required for the evaluation of the Primary Product SmokEz C-10, in accordance with the Guidance document (EFSA, 2005), is available in the previous opinion published on 12 June 2009 (EFSA, 2009a).

Despite some differences between the principal constituents reported in the previous opinion (EFSA, 2009) and those provided for the batch C10-10020398, the Panel considered the submitted technical data for this batch as acceptable to demonstrate that the material tested in the new 90-day study is representative of the Primary Product SmokEz-C-10.

When considering the new use levels provided by the applicant and assuming application of SmokEz C-10 in foods from all indicated food categories, the resulting margins of safety were 44 and 52 (upper use levels) and 56 and 68 (normal use levels) depending on the exposure scenario used. When assuming the use of Primary Product SmokEz C-10 in traditionally smoked products only, the margins of safety would amount to 46 and 64 (upper use levels) and 58 and 80 (normal use levels). Given i) the fact that these margins of safety are based on a 90-day toxicity study, ii) the absence of data on reproduction and developmental toxicity and iii) the absence of long term studies, it is concluded that the uses and use levels of Primary Product SmokEz C-10 would require a larger margin of safety. Despite the increase in the margin of safety compared with the previous opinion due to the submission of an additional 90-day toxicity study and due to revised use levels provided by the applicant, the Panel concluded that the proposed use of the Primary Product SmokEz C-10 at the uses and use levels specified is of safety concern.

To decide whether despite the low margins of safety the use of Primary Product SmokEz C-10 might be approved for traditionally smoked products, at use levels specified, to replace smoking, is outside the remit of the Panel.

The Panel did not anticipate that smoke flavourings would be used in food specifically designed for infants (0-12 months) and young children (12-36 months). Therefore, the safety of use of Primary Product SmokEz C-10 in such products was not assessed.

DOCUMENTATION PROVIDED TO EFSA

1. Additional dietary 90-day sub-chronic toxicity study in Wistar rats (Grósz, 2012) with smoke flavouring Primary Product SmokEz C-10.

2. Revised maximum use levels for SmokEz C-10

3. Identification and characterization of SmokEz C-10 according to Regulation 627/2006 and evidence that the SmokEz C-10 tested in the new 90-day assay is representative of the commercial product.

REFERENCES

EFSA (European Food Safety Authority), 2005. Guidance from the Scientific Panel on Food Additives, Flavourings, Processing aids and Materials in Contact with Food. Guidance on submission of a dossier on a Smoke Flavouring Primary Product for evaluation by EFSA. Adopted on 7 October 2004; Revised on 27 April 2005. http://www.efsa.europa.eu/en/efsajournal/doc/492.pdf

EFSA (European Food Safety Authority), 2009a. Scientific Opinion of the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) on the safety of smoke flavour Primary Product – SmokEz C-10. The EFSA Journal (2009a) 1225, 1-28.

EFSA (European Food Safety Authority), 2009b. Scientific Opinion of the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) on dietary exposure assessment methods for smoke flavouring Primary Products. The EFSA Journal RN-284, 1-30. http://www.efsa.europa.eu/en/efsajournal/doc/248r.pdf

Grósz, 2012. Final report of a 90-day dietary toxicity study with smoke flavours SMOKEZ C-10 and SMOKEZ ENVIRO 23. Performed as part of the study entitled: a 90-day dietary toxicity study with three smoke flavours SMOKEZ C-10, SMOKEZ ENVIRO 23 and SMOKEZ oil in Wistar rats. CiToxLAB Hungary Ltd, Szabadságpuszta, Hungary. Submitted on behalf of Red Arrow Products Co. LLC, Manitowoc, USA.

GLOSSARY / ABBREVIATIONS

bw	body weight
CEF	Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
EC	European Commission
EFSA	European Food Safety Authority
EPIC	European Prospective Investigation into Cancer and Nutrition
GC/MS	Gas Chromatography/Mass Spectrometry
GLP	Good Laboratory Practice
NOAEL	No-Observed-Adverse-Effect Level
OECD	Organisation for Economic Cooperation and Development
PAHs	Polycyclic Aromatic Hydrocarbons
SMK-EPIC	Smoke flavouring EPIC model
SMK-TAMDI	Smoke Theoretical Added Maximum Daily Intake
TAMDI	Theoretical Added Maximum Daily Intake