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SCIENTIFIC OPINION

Statement on the Safety Evaluation of Smoke Flavourings Primary Products: Interpretation of the Margin of Safety[1]

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

European Food Safety Authority (EFSA), Parma, Italy

KEY WORDS

Smoke flavouring, margin of safety, dietary exposure, risk assessment

SUMMARY

EFSA asked its scientific Panel on Food Contact Material, Enzymes, Flavourings and Processing Aids (CEF) for a clarification of the margin of safety (MoS). The Panel has applied this approach for the safety evaluation of smoke flavourings. Because of their complex and incompletely characterised chemical nature and in view of the limited toxicological data available, the Panel considered it inappropriate to allocate an Acceptable Daily Intake (ADI) for these substances. Instead, the Panel calculated a margin of safety based on the No-Observed-Adverse-Effect Level (NOAEL) in a 90-day study and on dietary exposure calculated from use levels provided by the applicant (EFSA, 2009). The margin of safety is the ratio between the NOAEL of the critical effect in the pivotal animal study on the smoke flavouring and the anticipated dietary exposure of consumers to that smoke flavouring.

The initial toxicological dataset requested for the safety evaluation of smoke flavourings consisted of three *in vitro* genotoxicity tests and a subchronic 90-day feeding study. In those cases, where the overall evaluation of the genotoxicity studies *in vivo* did not raise concern and where the 90-day studies were of adequate quality by current standards, the Panel considered that, normally, an additional uncertainty factor of 3-fold in addition to the default uncertainty factor of 100, should be sufficient to cover the limited duration and statistical power of the pivotal study.

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1 On request of EFSA, Question No EFSA-Q-2009-00764, adopted on 26 November 2009.

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3 Acknowledgement: The Panel wishes to thank the members of the Working Group on smoke flavourings for the preparation of this statement: D. Arcella, A. Carere, K.-H. Engel, D.M. Gott, J. Gry, R. Gürtler, D. Meier, I. Pratt, I.M.C.M. Rietjens, R. Simon and R. Walker.

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Whether a specific margin of safety for a particular smoke flavouring is sufficient, is highly dependent on the specific situation (*e.g.* composition, variability and stability, quality of the toxicological data) and default guidance cannot be given. The Panel notes that the determination of what margin of safety is acceptable may also depend on socio-political aspects to be considered by the risk managers.

The Panel wished to stress that the approach adopted in its safety evaluations is specific to the smoke flavouring Primary Products evaluated by the CEF Panel.

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BACKGROUND AS PROVIDED BY EFSA

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 intended for use in or on foods. As stated herein the use of a smoke flavouring 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.

EFSA´s Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) has been asked to assess the safety of the smoke flavourings on the basis of data presented by the applicants. The CEF Panel has adopted so far several opinions on such smoke flavouring Primary Products. For some of the products the Panel expressed concern and concluded that the margins of safety are insufficient and that the use of these Primary Products at the proposed uses and use levels is of safety concern.

The management of food-related risks itself is outside of EFSA remit. However, EFSA acknowledges that for risk managers it is desirable to obtain scientifically based advice on the margin of safety in order to ensure the safe use of smoke flavourings.

TERMS OF REFERENCE AS PROVIDED BY EFSA

In accordance with Article 29 (1) (b) of Regulation No 178/2002, the European Food Safety Authority asks its Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) to give a clarification of the margin of safety in the light of the scientific issues related to this concept, in order to help risk managers to ensure the safe use of the smoke flavouring Primary Products.

EVALUATION

The European Food Safety Authority (EFSA) asked its Panel on Food Contact Material, Enzymes, Flavourings and Processing Aids (CEF) to give a clarification of the margin of safety (MoS) applied in the safety evaluation of smoke flavouring Primary Products in the light of the scientific issues related to this concept.

The CEF Panel has adopted several opinions on smoke flavouring Primary Products. For some of the products the Panel concluded that the margins of safety were insufficient and that the use of these Primary Products at the proposed uses and use levels are of safety concern. The purpose of this statement is to help risk managers to ensure the safe use of the smoke flavouring Primary Products.

Each safety assessment is performed on a case-by-case basis requiring expert judgement of the entire toxicological database. The evaluation is based on the assumption that the product is not genotoxic and that the toxicological studies carried out are relatively contemporary in design and performed to an acceptable standard. The usual process for the safety evaluation of substances added deliberately to food, such as food additives (SCF, 2001), and the subsequent derivation of an Acceptable Daily Intake (ADI) requires an extensive toxicological database, including long-term (2-year) chronic toxicity/carcinogenicity studies and reproductive/developmental toxicity studies in addition to short-term toxicity and genotoxicity studies. The ADI is then most commonly derived using a default uncertainty factor of 100 applied to the No-Observed-Adverse-Effect Level (NOAEL) from the most sensitive of these studies (the pivotal study). The 100-fold factor is considered to represent the product of a 10-fold factor to allow for species differences between the test animal and humans and a 10-fold factor to allow for inter-individual differences.

However in some circumstances, the safety evaluation has been based on more limited data.

In the case of smoke flavours, because they are complex mixtures of variable and incompletely characterised composition, and in view of the limited toxicological data, the Panel considered it inappropriate to allocate an ADI but calculated a margin of safety based on the NOAEL in a 90-day study. The margin of safety is the ratio between the NOAEL of the critical effect in the pivotal animal study on the smoke flavouring and the anticipated dietary exposure of consumers to that smoke flavouring. Various methods of dietary exposure assessment have been tested and especially developed for these products. They are published in a separate opinion on dietary exposure assessment methods for smoke flavouring Primary Products (EFSA, 2009).

For the purpose of calculating the margin of safety, additional uncertainty factors should be considered. The magnitude of the additional uncertainty factors required has been discussed in a number of publications and recommendations have been made with regard to, *e.g.* the extrapolation from short-term studies to chronic exposure (WHO, 1994, 1999; Smith, 2002; European Chemicals Agency, 2008). These factors only address shortcomings in toxicological dataset but not in *e.g.* data on dietary exposure. Additional uncertainty factors have also been applied relating to the quality of the toxicological database on which the evaluation is based; however, in practice, the magnitude of these additional factors has been much more variable, amounting most often to values between 3 and 10, reflecting expert judgement of the overall quality of the database. For substances added deliberately to food, additional work is normally requested from the applicant to address shortcomings in the database.

The EFSA guidelines for the evaluation of smoke flavourings Primary Products (EFSA, 2004) require a limited initial toxicological dataset, consisting of three *in vitro* genotoxicity tests and a subchronic 90-day feeding study, but stress also that "additional toxicological data may be required for assessment of the safety of the Primary Products as necessary" and that applicants "should consider whether any other types of study might also be appropriate". Therefore when evaluating the safety of smoke flavouring Primary Products, the Panel was presented with a toxicological database containing

a 90-day toxicity study in rats and a number of *in vitro* and *in vivo* genotoxicity studies. In those cases, where the overall evaluation of the genotoxicity studies did not raise cause for concern *in vivo* and where the 90-day studies were of adequate quality by current standards, the Panel considered that, normally, an extra uncertainty factor of 3-fold in addition to the default uncertainty factor of 100, should be sufficient to cover the limited duration and statistical power of the pivotal study. However, each safety assessment requires expert judgement and should consider the data package on a case-by-case basis.

CONCLUSIONS AND RECOMMENDATIONS

Where the overall evaluation of the genotoxicity studies did not raise cause for concern *in vivo* and where the 90-day studies were of adequate quality by current standards, the Panel considered that, normally, an extra uncertainty factor of 3-fold in addition to the default uncertainty factor of 100, should be sufficient to cover the limited duration and statistical power of the pivotal study. However, each safety assessment requires expert judgement and should consider the data package on a case-by-case basis.

Whether a specific margin of safety for a particular smoke flavouring is sufficient, is highly dependent on the situation (*e.g.* composition, variability and stability, quality of the toxicological data,) and default guidance cannot be given. The Panel notes that the determination what margin of safety is acceptable may also depend on socio-political aspects to be considered by the risk managers.

The Panel could only make its evaluation on the basis of intake estimates related to the proposed uses and use levels provided by the applicant. In its opinions on the individual smoke flavouring Primary Products, the Panel noted that where the margin of safety is considered insufficient, restriction of the proposed uses or use levels might be applied to increase the margin of safety but considered this to be a risk management issue and outside the remit of the Panel.

The Panel wished to stress that the approach adopted in its safety evaluations is specific to the smoke flavouring Primary Products evaluated by the CEF Panel.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
CEF	Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
NOAEL	No-Observed-Adverse-Effect Level
MoS	Margin of Safety