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OPINION

ON A PROGRAMME FOR THE EVALUATION

OF FLAVOURING SUBSTANCES

(expressed on 2 December 1999)

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SCIENTIFIC COMMITTEE ON FOOD

SCF/CS/FLAV/TASKF/11 Rev.6 Final

Opinion on a Programme for the Evaluation of Flavouring Substances

(expressed on 2 December 1999)

TERMS OF REFERENCE

The Scientific Committee on Food was asked to advise the Commission in setting up an evaluation programme according to Article 4 (1) of Regulation (EC) N° 2232/96¹ for the evaluation of the substances listed in the register of Commission Decision 1999/217/EC²,

- considering the existing guidelines on the evaluation of chemically defined flavouring substances established by the SCF and other guidelines, in particular approaches taken by JECFA and the Council of Europe, and
- taking account of evaluations of chemically defined flavouring substances already performed by the SCF, JECFA and the Council of Europe.

BACKGROUND

In the past, the Scientific Committee on Food developed guidelines for the safety evaluation of flavourings* for use in foodstuffs³. These guidelines set out the views of the SCF regarding the elements to be taken into account in the safety evaluation of flavourings. Until the end of 1995, the SCF addressed 426 flavourings according to these guidelines and adopted 148 evaluations of flavourings⁶. This evaluation programme came to a halt as a consequence of the adoption of Regulation (EC) N° 2232/96.

This Regulation lays down a procedure for the adoption of a list of chemically defined flavouring substances** the use of which shall be authorised to the exclusion of all others in all Member States of the Community. The Regulation foresees the following steps in order to achieve this positive list:

* In this opinion, "flavourings" are understood to mean chemically defined flavouring substances.

** For the purpose of this Regulation 'flavouring substance' means a defined chemical substance with flavouring properties which is obtained:

(i) by appropriate physical processes (including distillation and solvent extraction) or enzymatic or microbiological processes from material of vegetable or animal origin either in the raw state or after processing for human consumption by traditional food-preparation processes (including drying, torrefaction and fermentation),

(ii) by chemical synthesis or isolated by chemical processes and which is chemically identical to a substance naturally present in material of vegetable or animal origin as described in (i),

(iii) by chemical synthesis but which is not chemically identical to a substance naturally present in material of vegetable or animal origin as described in (i).

- Step 1: Member States notify to the Commission a list of chemically defined flavouring substances which may be used in or on foodstuffs marketed in their territory.
- Step 2: The Commission adopts a register comprising flavouring substances the legal use of which in one Member State must be recognised by the other Member States (a safeguard clause enables Member States to ban or restrict the use of a substance if it constitutes a danger to public health).
- Step 3: Within 10 months after the adoption of the register a programme for the toxicological evaluation of these flavouring substances shall be adopted by the Commission in order to check whether the flavouring substances contained in the register comply with the general use criteria given in the annex of the Regulation (no risk to the health; no misleading of consumers; appropriate toxicological evaluation; in case of GMO origin, inclusion of environmental safety evaluation; constant monitoring and re-evaluation whenever necessary). The programme includes the order of priorities for evaluation, time limits and selection of flavouring substances, which shall be subject of scientific co-operation.
- Step 4: Within 5 years after the adoption of the programme for the toxicological evaluation a list of flavouring substances the use of which is authorised to the exclusion of all others by the Commission shall be adopted.

New flavourings may be authorised by the Commission after the substance has been evaluated according to the above-mentioned programme.

The register mentioned above in step 2 has been adopted by Commission Decision 1999/217/EC of 23 Feb 1999². It comprises about 2800 flavourings. According to the Regulation, the programme for the toxicological evaluation shall be adopted by the Commission within 10 months after adoption of the register.

APPROACHES FOR THE SAFETY EVALUATION OF CHEMICALLY DEFINED FLAVOURING SUBSTANCES

Procedures for the safety evaluation of flavourings have been developed by several Committees. Among these are the Committee of Experts on Flavouring Substances of the Council of Europe (CEFS), the Scientific Committee on Food of the European Commission (SCF) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). All these expert groups recognised the large number of flavourings, the limited toxicological database for most individual flavourings, their relatively low use levels and the fact, that many of them have a simple chemical structure, occur naturally in food and have a long history of use. Common features in the approaches are the evaluation of groups of chemically related flavourings, and the use of the knowledge of metabolism and structure-activity relationship of members of the groups. The approaches differ in some important aspects, among others in the method of exposure assessment, the extent of using toxicity data of structurally related compounds and the application of thresholds.

CEFS

Within the Council of Europe, the CEFS has been working for more than 30 years on flavouring substances. The Council of Europe published the recommendations of the CEFS in Volume I of

the fourth edition of the "Blue Book" in 1992⁴. This volume contains guidelines and a re-evaluation of chemically defined flavouring substances, based on the information available in the 1980's.

In contrast to former editions the flavourings were listed according to their chemical structure. The grouping of chemically related substances, in particular compounds belonging to homologous series, e.g. aliphatic alcohols, aldehydes, ketones or acids, had the advantage that toxicological data available for the whole group could be taken into account for the evaluation of the individual flavourings.

390 flavourings were classified in Category A ("flavouring substances which may be used in foodstuffs") and 504 flavourings in Category B ("flavouring substances for which further information is required before the Committee is able to offer a firm opinion on their safety-in-use; these substances can be used provisionally in foodstuffs").

For the majority of flavourings considered by the CEFS toxicological data were not sufficient for an ADI to be allocated. In these cases, upper levels acceptable for foodstuffs (food, beverages, exceptions) and not considered to result in risks to health were set, based on the available information. These levels correspond to the amounts that are technologically necessary to obtain the required flavour, provided that such levels are toxicologically acceptable and are based on reasonable estimation.

Where available, the Acceptable Daily Intake for man (ADI) recommended by JECFA has been utilised. In these cases, the flavouring was classified in Category A without any further evaluation by the CEFS and no upper level is indicated.

SCF

In its opinion of 10 December 1991³ the Committee sets out its views regarding the elements to be taken into account in the safety evaluation of flavours for use in foodstuffs, with particular reference to chemically defined flavouring substances, following Council Directive 88/388/EEC⁵.

In the same opinion, the SCF subdivided the flavourings already evaluated by the CEFS, the Food and Drug Administration (FDA) and the American Flavor and Extract Manufacturers' Association's Expert Panel (FEXPAN) into those considered acceptable (SCF List 1) and those that were only accepted temporarily (SCF List 2). SCF List 1 contained those, which were included in Category A of Volume 1 of the fourth edition of the CE Blue Book and concomitantly considered safe by the FDA and/or the FEXPAN (about 340). SCF List 2 comprised all other flavourings evaluated and found acceptable or temporarily acceptable by one or more of the above-mentioned bodies (about 1160).

The Committee also established guidelines for the evaluation of flavourings for use in foodstuffs. They include principles for the re-evaluation of the flavourings in SCF List 2 for possible inclusion in SCF List 1. According to these principles, a number of criteria such as chemical structure, structure-activity relationships, metabolic fate, use levels and natural occurrence of many flavourings in normal food are taken into account in an integrated approach in addition to existing toxicity data. Furthermore, the guidelines also contain requirements for the flavourings not adequately evaluated elsewhere.

As a first step in the re-evaluation of flavourings in SCF list 1 and 2, the flavourings were divided into groups of chemically related substances, so that toxicological data from one flavouring could be considered in the evaluation of other structurally related flavourings. In

cases where an ADI did not exist and could not be allocated because of insufficient data, maximum levels of use provided by the flavour industry as well as indications of the foods, in which the flavourings are used, have been applied as a basis for suggesting acceptable technological upper limits of use.

The consumer exposure was estimated by three different approaches³:

The first estimate is the TAMDI (Theoretical Added Maximum Daily Intake), which is calculated on the basis of upper use levels and the estimated daily intakes of flavourable beverages, foods and for particular foods (exceptions). The second estimate is the MSDI (Maximum Survey-derived Daily Intake). The MSDI is derived from the annual European production figure for the individual substances as surveyed by the industry. In deriving the MSDI, it is assumed that the production figure only represents 60% of the use in food due to underreporting and that only 10% of the total EU population are consumers. The third estimate, the DINFO (Daily Intake via Natural Food Occurrence) relates exclusively to intake due to the presence of the substance as an intrinsic component of foods. This estimate is based on available analytical data indicating levels of occurrence and estimates of average consumption of the relevant food items.

In 1995, the Committee adopted a first report⁶ on 148 chemically defined flavouring substances and considered it appropriate that 141 of these could be included in a positive list: 122 evaluated as safe in use (Category 1) and 19 as temporarily safe in use (Category 2). For 2 flavourings there was insufficient data to provide assurance of safety (Category 3). 1 flavouring was not acceptable due to evidence of toxicity (Category 4) and 4 flavourings could not be listed in categories 1 - 4 as being mixtures or not being used as flavours (Category N)³.

These evaluations of the SCF made use of the FLAVIS database. This database lists 2577 chemically defined flavourings of which 1558 were assigned to 14 chemical groups and were given individual numbers.

JECFA

Prior to 1995, JECFA had only occasionally evaluated flavourings and had applied the conventional ADI approach. In 1995, a new procedure was considered at the 44th meeting^{7, 8} and subsequently applied in an adjusted version to the evaluation of large groups of chemically defined flavouring substances^{9, 10}.

This procedure is a stepwise approach that integrates information on intake from current uses, structure-activity relationships, metabolism and, when needed, toxicity. One of the key elements in the procedure is the subdivision of flavourings into three structural classes (I, II, III) for which human exposure thresholds that are not considered to present a safety concern have been specified.

Class I contains flavourings that have simple chemical structures and efficient modes of metabolism which would suggest a low order of oral toxicity. Class II contains flavourings that have structural features that are less innocuous, but are not suggestive of toxicity. Class III does comprise flavourings that have structural features that permit no strong initial presumption of safety, or may even suggest significant toxicity⁹. The human exposure thresholds for these structural classes of 1800, 540 or 90 µg/person/day, respectively, are derived from a large database containing subchronic and chronic animal studies of 613 substances representing a range of industrial chemicals, pharmaceuticals, food substances, environmental and consumer

chemicals. They were calculated using a 100-fold safety factor from the 5th centile of either the no-observed-effect levels (NOELs) from chronic studies or of one third of the NOELs from subchronic studies.

In the first step of the procedure, the flavourings are assigned to one of the structural classes. The further steps address the following questions: can the flavourings be predicted to be metabolised to innocuous products; do their exposures exceed the human exposure threshold for the structural class or in certain cases the threshold of concern of 1.5 µg/person/day; are the flavourings or their metabolites endogenous; does a NOEL exist on the flavourings or on structurally related substances?

In addition, JECFA, in its current evaluation practice, takes into account the whole toxicological background information for the groups of chemically related compounds, to which the individual flavourings belong, in order to assure that these data are consistent with the results of the procedure. Furthermore, JECFA does not apply its procedure to flavourings with existing unresolved problems of toxicity. Therefore, the right is reserved to use alternative approaches when data on specific flavourings warranted such actions^{9,10}.

In the exposure assessment part of the procedure the MSDI model is used for estimation of intake^{9,10}. To date, the intake estimates have been derived from annual production figures from surveys in Europe and the USA. In using these survey data to estimate intakes of flavourings, it is assumed that only 60% of the total use had been reported and that the total amount destined for use in food is consumed by only 10% of the population.

JECFA recommends, however, that further consideration of intake should be given to flavourings for which there are high reported levels of use in some foods or beverages, but low intakes when calculated from production data. This would be particularly important for flavourings with intakes calculated to be only slightly below one of the threshold criteria¹⁰.

Until now, JECFA has evaluated 626 flavourings using this procedure. Of these flavourings, 620 were concluded to be of "no safety concern" at current estimated levels of intake. The evaluation of six flavourings was postponed pending consideration of further information and for one flavouring further data were required. For the 626 flavourings, however, only limited specifications could be prepared, almost half of those being tentative as certain necessary information was lacking.

DISCUSSION

The safety evaluations of flavourings by the described procedures applied by the Scientific Committee on Food of the European Commission (SCF), the Committee of Experts on Flavouring Substances of the Council of Europe (CEFS) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) raise some important issues, i.e. the adequacy of intake estimates, the acceptance of a threshold concept, and the potential relevance of genotoxicity.

With respect to the issue of intake estimates, it should be noted that the TAMDI approach, which is a rather conservative exposure assessment, sometimes overestimates the mean intake by orders of magnitude. In contrast, the MSDI model may underestimate the intake by certain groups of consumers - although compensated somewhat by the assumptions concerning

underreporting and that only 10% of the population consume flavoured foods and beverages. The MSDI model does not take into account the consumption pattern of population sub-groups. It does neither consider geographic variations in the use of the flavourings nor the fact that a specific flavouring substance can be used only in one or very few food categories, consumed only locally or by a limited number of persons. Furthermore, it is known that at least for some flavourings there may be a great variation in the periodically reported production volumes. This variation can be orders of magnitude for a specific flavouring¹¹. This would be particularly important for flavourings with intakes only slightly below the threshold criteria within the evaluation procedure¹⁰.

A more appropriate intake estimate could be performed using a stepwise procedure. This could start with both the MSDI and TAMDI and, when needed, the TAMDI results could be refined by exclusion of food categories in which the flavour is not present and by inclusion of maximum use levels for specific food categories. Prerequisite for such a stepwise procedure would be that the flavour industry and the Member States provide detailed data on global and specific maximum levels of use and on the type and consumed amounts of flavoured food categories.

A second important issue is the applicability of the concept of thresholds of concern. When the Committee had to consider the threshold of regulation concept in relation to food contact materials¹², firm conclusions could not be reached, because it appeared necessary to conduct an up-to-date review of existing data covering endpoints of concern which may give rise to effects at low doses, such as neurotoxic, immunotoxic, endocrinologic and developmentally toxic events. However, in the case of the JECFA procedure for flavouring substances, it should be taken into account that the use of human exposure thresholds is preceded by consideration of chemical structure and metabolism in relation to likely toxicity. Although the Committee has not formally endorsed the values for human exposure thresholds used by JECFA, it considers that they offer a reasonable and pragmatic approach for flavourings.

The third issue is the potential genotoxicity of flavourings, which is not explicitly addressed in the JECFA procedure. In its opinion on the threshold of regulation concept¹² the Committee stated that it may be worthwhile considering whether it is desirable to set two separate threshold values - one for substances known to be non-genotoxic and a second for substances whose genotoxic potential is unknown. The Committee continued that setting a threshold for substances whose general toxic potential is unknown would undoubtedly require further fundamental studies addressing the issue of thresholds for the expression of genotoxic activity and may or may not be achievable in the long term. This consideration still holds true for flavourings and therefore these substances should be at least examined for structural alerts for genotoxicity.

CONCLUSION

In considering the existing guidelines on the safety evaluation of chemically defined flavouring substances, the Committee recognises that the most up-dated and systematic procedure is presently applied by JECFA. The Committee considers this procedure is a pragmatic approach and, in principle, is prepared to use this approach for chemically defined flavouring substances within the evaluation programme of the Commission.

The Committee recommends, however, that the intake estimation needs further consideration and should be based not only on production data but should also take into account the results of other intake assessments. The Committee notes that JECFA recommends further consideration of intake in certain cases as well. Furthermore, flavourings should also be examined for structural alerts of potential genotoxicity. This is in accordance, at least partly, with the current practice of JECFA, in which genotoxicity data, when available, are included in the consideration as to whether or not the toxicological background information is consistent with the results of the procedure.

In the light of the large number of flavourings that have to be evaluated in the programme and the relatively short period of time in which a list of authorised flavourings has to be adopted, the Committee is of the opinion that the evaluation programme has to make use of safety assessments already performed as much as possible. Although the Committee suggests the above-mentioned developments of the JECFA procedure, it is of the opinion that the flavourings considered acceptable at the current estimated intake by JECFA comply with the criteria given in the annex of the regulation. They can be included in the list of authorised substances without undergoing a separate SCF evaluation for the time being. The Committee is of the opinion, however, that those flavourings that were accepted with the only argument that their estimated intake is lower than the threshold of concern of 1,5 µg/person/day should not be included in the list. In its previous opinion on the scientific basis of the concept of threshold of regulation in relation to food contact materials, the Committee felt that the present scientific knowledge does not allow a definitive conclusion on the existence of a figure for an overall threshold of concern. The issue of the threshold of concern must be reconsidered by the Committee, before a decision on these substances can be made. The Committee is aware that there are ongoing activities in this area and it wishes to keep these under review.

The Committee is of the opinion that the flavourings previously adopted by the SCF in Category 1 and by the CEFS in Category A can also be included in a list of authorised flavourings. The criteria for these categories were stringent enough to consider the substances in those categories to be safe in current use. The total number of flavourings, which according to these suggestions might be included in an authorised list, amounts presently to more than 750.

In evaluating the remaining flavourings, duplication of work should be avoided. Therefore, the Committee considers that it would be mutually advantageous to share the burden by dividing groups of flavourings between JECFA and the SCF, which makes co-ordination of the evaluation programmes essential. The SCF could then concentrate its efforts on flavourings which will not be considered by JECFA and on flavourings prioritised for particular reasons.

Before a co-ordinated evaluation programme for the remaining flavourings of the register can start, a number of preceding steps must be taken: (a) distribution of the flavourings in the register in groups of structurally related compounds, taking into account the system applied by JECFA; (b) elimination of duplicates from the register and corrections of chemical names and CAS numbers; (c) setting up a list of flavourings that have already been accepted by JECFA or classified in the above mentioned categories by SCF and CEFS and compilation of the data used for these safety evaluations; (d) clarification which flavourings will be evaluated by JECFA in the foreseeable part of its programme; (e) provision of up-to-date information by the flavour industry in accordance with Article 4(2) of the Regulation.

Steps (a) - (c) could be performed by taking advantage of the existing FLAVIS-data-base. Step (d) and (e) are tasks of the Commission. All these steps are essential prerequisites for the evaluation programme and therefore have high priority.

The Committee emphasises that the flavourings of the register can only be evaluated when all existing chemical and toxicological information that may be relevant is provided by Industry. This includes data on the chemical identity and purity, the production volume and use levels in specified food categories, the natural occurrence in food as well as toxicological data for the individual flavourings and chemically related compounds.

The Committee recommends that the period until industry has provided the requested information, should be used to evaluate the flavourings in the register that have been suggested for deletion for toxicological reasons by Member States (e.g. estragol, methyl eugenol, vinyl benzene, menthofuran, furfural diethylacetal). The Committee considers this task to have priority.

Until the required information is delivered, time should also be used for the critical reconsideration of existing exposure assessments and for the refinement of exposure models. At this stage, the flavourings already evaluated could also be examined for structural alerts of genotoxicity in order to find out whether certain flavours must be reconsidered.

After submission of the required information all available data must be registered for the individual flavourings. In addition, critical reviews on groups of flavourings and chemically related compounds must be prepared. This will be a time and manpower consuming part of the programme and will go beyond the working capacity of the Committee itself. This part may be the subject of scientific co-operation between Member States. This task is an important prerequisite for the safety evaluation that must be accomplished by the SCF as last step of the programme.

The time period in which the programme could be realised depends also very much on how efficiently an overlap with the evaluations by JECFA can be avoided and how fast the flavour industry can provide the required information.

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REFERENCES

¹ Regulation (EC) No 2232/96 of the European Parliament and of the Council of 28 October 1996 laying down a Community procedure for flavouring substances used or intended for use in or on foodstuffs. Official Journal L 299, 23/11/1996, p. 1 – 4.

² Commission Decision 1999/217/EC of 23 February 1999 adopting a register of flavouring substances used in or on foodstuffs drawn up in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council of 28 October 1996. Official Journal L 084, 27/03/1999, p. 1 – 137.

³ Guidelines for the evaluation of flavourings for use in foodstuffs: 1. Chemically defined flavouring substances. Opinion expressed by the Scientific Committee on Food on 10 December 1991. Reports of the Scientific Committee on Food, 29th Series catalogue no: EUR 14482-EN, Office for Official Publications of the European Community, L-2985 Luxembourg.

⁴ Flavouring substances and natural sources of flavourings. Vol. I – chemically defined flavouring substances, Council of Europe, Maissonneuve, Strasbourg 1992.

⁵ Council Directive 88/388/EEC of 22 June 1988 on the approximation of the laws of the Member States relating to flavourings for use in foodstuffs and to source materials for their production. Official Journal L 184, 15/07/1988, p. 61 – 66.

⁶ Annex 6 to the minutes of the 98th meeting of the Scientific Committee on Food, 21/22 September 1995.

⁷ Evaluation of certain food additives and contaminants. 44th Report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 856, Geneva 1995.

⁸ Toxicological evaluation of certain additives and contaminants in food. Prepared by the Joint FAO/WHO Expert Committee on Food Additives, WHO Food Additives Series 35, Geneva 1996.

⁹ Evaluation of certain food additives and contaminants. 46th Report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 868, Geneva 1997.

¹⁰ Evaluation of certain food additives and contaminants. 49th Report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 884, Geneva 1999.

¹¹ Adams TB et al. The FEMA GRAS assessment of alicyclic substances used as flavour ingredients. Food Chem. Tox. 34 (1996) 763-828.

¹² Opinion of the Scientific Committee on Food on the scientific basis of the concept of threshold of regulation in relation to food contact materials (expressed on 8 March 1996), Reports of the Scientific Committee on Food, 39th Series, catalogue no: GT 07 97644-EN, Office for Official Publications of the European Community, L-2985 Luxembourg.