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EVALUATION OF CERTAIN FOOD ADDITIVES

Sixty-third report of the
Joint FAO/WHO Expert Committee on
Food Additives

World Health Organization
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Monographs containing summaries of relevant data and toxicological evaluations are available from WHO under the title:

Safety evaluation of certain food additives and contaminants. WHO Food Additive Series, No. 54, in preparation. Specifications are issued separately by FAO under the title:

Compendium of food additive specifications, Addendum 13. FAO Food and Nutrition Paper, No. 52, Add. 13, 2004, in preparation.

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

The preparatory work for toxicological evaluations of food additives and contaminants by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is actively supported by certain of the Member States that contribute to the work of the International Programme On Chemical Safety (IPCS). The IPCS is a joint venture of the United Nations Environment Programme, the International Labour Organisation and the World Health Organization. One of the main objectives of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment.

Contents

1. Introduction

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) met in Geneva from 8 to 17 June 2004. The meeting was opened by Dr Margaret Chan, Director of Protection of the Human Environment (PHE), World Health Organization (WHO), on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). She thanked the participants for their invaluable contribution to the work of the Committee.

Dr Chan noted that the work of the Committee plays an important role in the improvement of food safety on a global basis, particularly in developing countries or regions, and that WHO and FAO were committed to strengthening this system. Dr Chan indicated that increased financial resources were to be devoted to the JECFA programme, both by WHO and by FAO.

In this context Dr Chan made reference to a workshop, held in Geneva in early 2004, which had led to a number of recommendations on how to improve the provision of scientific advice by FAO/WHO to Codex and Member States. She noted that FAO and WHO were committed to the implementation of these recommendations and were jointly developing procedural guidelines with a focus on improving transparency, timeliness and consistency. Much of the experience gained through this Expert Committee will facilitate future improvements.

2. General considerations

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955 (*1*), there have been sixty-two previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the basis of the recommendation made at the sixtieth meeting (Annex 1, reference *163*).

The tasks before the Committee were:

— to elaborate further principles for evaluating the safety of food additives and contaminants (section 2);

— to undertake toxicological evaluations of certain food additives and flavouring agents (sections 3 and 4, and Annex 2);

— to review and prepare specifications for selected food additives and flavouring agents (sections 3 and 4, and Annex 2); and

— to undertake a toxicological evaluation of a natural constituent, glycyrrhizinic acid (section 5).

2.1 Modification of the agenda

Monosodium glutamate, thaumatin and thaumatin B were removed from the agenda because data necessary for their evaluation or re-evaluation as flavouring agents were not available. The evaluation of magnesium sulfate was removed from the agenda because the intended use and use levels were not identified to the Committee; however the available data were sufficient to establish tentative specifications for the compound (see section 3).

The natural flavouring complexes bois de rose oil, lemongrass oil and cardamom seed oil were removed from the agenda because discussions on the procedural framework necessary for their evaluation remained to be completed (see general consideration 2.3). The evaluation of these complexes was deferred to a future meeting. For the other two natural flavouring complexes listed in the call for data, cardamom extract and cardamom oleoresin, no data were available to the Committee.

The group of aliphatic and aromatic hydrocarbons used as flavouring agents was divided into two separate groups, aliphatic and alicyclic hydrocarbons, and aromatic hydrocarbons.

2.2 Principles governing the toxicological evaluation of compounds on the agenda

In making recommendations on the safety of food additives and contaminants, the Committee took into consideration the principles established and contained in WHO Environmental Health Criteria, No. 70, *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*), as well as the principles elaborated at subsequent meetings of the Committee (Annex 1, references *77*, *83*, *88*, *94*, *101*, *107*, *116*, *122*, *131*, *137*, *143*, *149*, *152*, *154*, *160*, *166*, including the present one. WHO Environmental Health Criteria, No. 70, contains the most important observations, comments and recommendations made, up to the time of its publication, by the Committee and associated bodies in their reports on the safety assessment of food additives and contaminants.

2.3 The safety evaluation of flavouring agents

2.3.1 *Estimating intake of flavouring agents*

At its fifty-fifth meeting (Annex 1, reference *149*), the Committee considered the use of the per capita × 10 method for estimating the

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intake of flavouring agents according to the Procedure for the Safety Evaluation of Flavouring Agents, as well as alternative procedures (Annex 1, reference *149*). While the Committee concluded that use of this method was appropriate, it acknowledged that it may, in some cases, result in an underestimate of the intake of persons with high levels of consumption of specific foods. At its forty-ninth meeting (Annex 1, reference *131*), the Committee also recognized that further consideration may be required in certain cases where there is conflicting information on intake. At its present meeting, the Committee reaffirmed these conclusions.

The Committee recognized that the estimates of current intake that it uses in evaluating the safety of flavouring agents according to the Procedure are difficult to reconcile with reported maximum use levels for some flavouring agents in different food groups. To help understand the basis for the apparent discrepancy in the information available to the Committee, the Committee requested that industry provide precise data on the use levels of flavouring agents that may be used in food products that are not widely distributed and that may be eaten on a regular basis by specific population groups in specific regions of the world.

The Committee anticipates that estimating the intake of flavouring agents, especially those with particularly low or particularly high production volumes, will be considered in detail at the forthcoming Joint FAO/WHO workshop on exposure assessment to be held in 2004.

Combined exposure

The Committee also recognized that the current procedure to estimate the combined intake for all congeners of one congeneric group of flavouring substances reflects an unlikely situation in which the same individuals are consumers of all the substances. Nevertheless, this results in conservative estimates that allow evaluations to be completed. The Committee therefore recommended the establishment of a working group to develop a more adequate approach, to be discussed at the next meeting of the Committee.

2.3.2 *Flavour complexes derived from natural sources*

At its present meeting, the Committee further considered a possible approach to the safety assessment of complex flavours derived from natural sources (usually from plant material), such as essential oils, oleoresins and solvent extracts. After considering the available data on three of the five flavour complexes originally included on the agenda — derived from essential oils of lemongrass, cardamom seed and rosewood — the Committee defined the information that would

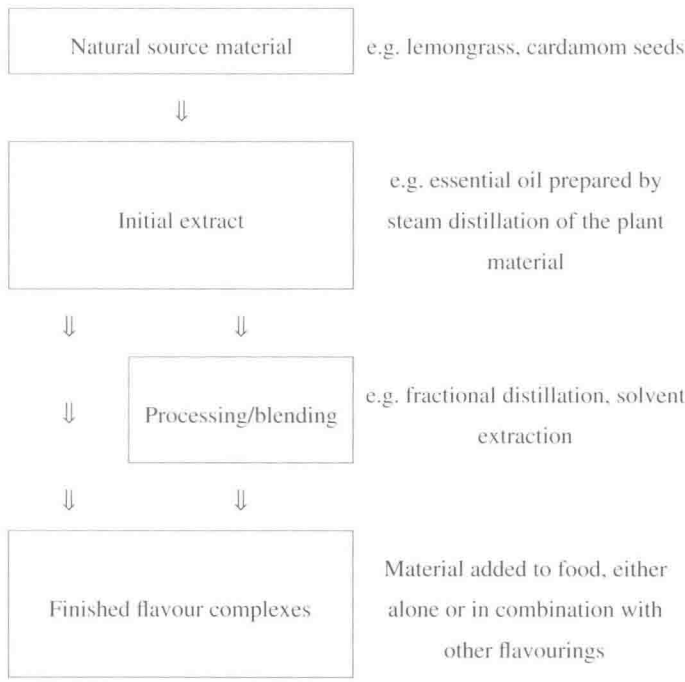
be required in order to test the application of the revised Procedure for the Safety Evaluation of Flavouring Agents (Annex 1, reference *131*), which it had previously adopted for the safety evaluation of chemically-defined flavourings.

Background

Although these flavourings are typically named after the initial extract prepared from the source material, it is common practice for the initial extracts to be processed and refined in a variety of ways, to produce a range of flavour complexes with the specific properties desired for particular food applications. These processes might include distillation, concentration, solvent extraction and blending of extracts from different batches. Processing is generally carried out by flavour companies or, in certain cases, by food manufacturers who use the finished flavours. The progression from source material to finished flavour is illustrated in Figure 1.

The initial extracts are typically prepared from the plant material close to the point of production. Their composition may vary considerably at this level owing to a variety of factors, such as climate,

Figure 1
Progression from source material to finished flavour



geography, genotype and maturity of the source material. The flavour producer aims to supply flavour complexes with consistent technical and olfactory properties. This is primarily achieved by processing and blending to meet a target composition that is monitored by chemical analysis.

Use of the scheme for evaluation of finished flavour complexes is dependent upon:

— information on the composition of the material that is added to food (and hence on the elaboration of a reliable specification that covers the range of finished flavour complexes that may be derived from the initial extracts);

— existing safety evaluations of the individual components and congeneric groups;

— estimates of intake of the finished flavour complexes, and hence of the individual components.

Although the finished flavour complexes are entirely derived from the original extract, using only physical processes such as those described above, their composition is likely to differ quantitatively from that of the initial extracts prepared directly from the source material.

Compositional data necessary to support the safety evaluation of a finished flavour complex

General considerations

The safety evaluations of finished flavour complexes derived from natural sources would be based on the revised Procedure, with particular consideration of the major components and of congeneric groups. The analytical data should be adequate to apply the revised Procedure.

Intake should be taken into account in determining the extent to which chemical characterization and identification of individual components is necessary, beyond that which is necessary to define the flavour characteristics. In applying the Revised Procedure for the Safety Evaluation of Flavouring Agents, the estimated intake of the individual agent is compared with appropriate thresholds of toxicological concern, to determine whether or not the intake represents a safety concern. The same numerical thresholds can be applied to the intakes of individual identified components and of combinations of components, such as occur in congeneric groups, that are present in finished flavour complexes derived from natural sources. The same intake thresholds can also be used as a basis for establishing analytical requirements, as described below.

The human intake thresholds of toxicological concern are of two types: thresholds of 1800, 540 and 90 μg/person per day, which are applied for structural classes I, II and III, and a general threshold of 1.5 μg/person per day, which is applicable to all structural classes. The thresholds for classes I, II and III are based on the lower 5th percentile no-observed-effect level (NOEL) for the structural class, from toxicological studies in animals, divided by the usual 100-fold safety (uncertainty) factor. The general threshold (step B5 of the Procedure) is a pragmatic value based on an estimate of the human intake associated with a lifetime risk of cancer of less than 1 in a million, calculated by linear-extrapolation from animal studies (as described by the Committee at its forty-sixth meeting; Annex 1, reference *122*). Because of the assumptions used in the derivation of this threshold, it is considered to be sufficiently conservative to cover all types of toxicity. The Committee considered that these thresholds can provide the basis for a pragmatic approach to the development of limits of sensitivity for analytical methods, when linked to reliable and validated estimates of intake, which should be derived from long-term average poundage (disappearance data).

Consideration of individual components

Identified components: On the basis of step B5 of the Procedure, the Committee concluded that there would be no significant safety concern if the intake for an identified component in a finished flavour complex derived from natural sources were <1.5 μg/person per day. This threshold can be used to establish a general limit for analytical characterization for components in a finished flavour complex as described in (b) below, based on the estimated intake of the complex. For example, if the estimated daily intake of the finished flavour complex were 150 μg/person per day, then there would be no safety concern for any component present at <1%. Similarly, if the estimated daily intake of the finished flavour complex were 15 μg/person per day, then there would be no safety concern for any component present at <10%. For high-volume finished flavour complexes, the limit for analytical characterization would be set at 0.1–0.5% (see (b) below). Because the threshold is based on lifetime carcinogenicity data, the percentage should be the average value of the available analyses, and not the highest single value.

Unidentified components: The chromatographic analysis of a finished flavour complex is likely to reveal the presence of a large number of unidentified minor components. Previously the Committee has not considered the general threshold of 1.5 μg/person per day for unidentified components. The Committee recognized that application

of the general threshold to an unidentified component could not provide the same reassurance of safety as for structurally defined compounds, but considered that it could be incorporated into a pragmatic approach to establishing analytical requirements for finished flavour complexes derived from natural sources. This threshold combined with the estimated intake of the complex can be used to define a limit for the percentage of a chromatographic peak above which structural characterization would be necessary. For example, if the estimated daily intake of the finished flavour complex were 150μg/person per day, then chemical characterization would be required for any component present at >1%, so that safety evaluation of the component could be undertaken.

Product descriptions and specifications: A key part of the safety assessment would be the preparation of appropriate specifications covering the relevant finished flavour complexes. As with all food additive evaluations, the purpose of specifications for flavour complexes is to identify the material, to ensure that it meets the criteria for safe use, and to encourage good manufacturing practice. Specifications should reflect the materials used throughout the world and should take account of existing specifications drawn up at national or international level, as described in WHO Environmental Health Criteria, No. 70 (*2*).

The Committee noted the existence of internationally agreed specifications prepared by the International Organization for Standardization (ISO) for more than 100 essential oils obtained by steam distillation of plant materials. Essential oils and derived products are numerically the largest group of flavour complexes. ISO standards describe the oils and define the acceptable ranges for various parameters, including the methods for measuring these values. Many of these standards include ranges for the key chemical components, accompanied by typical gas chromatograms that can be used to confirm the identity of the oils. The Committee concluded that it is necessary to take these standards into account when setting specifications for food flavourings, particularly when selecting the parameters to be included and the associated analytical methods.

In order to develop specifications for flavour complexes added to food, and to provide the data necessary for the safety evaluation to proceed, the Committee requires a full description of the range of source materials and processing conditions. Sponsors should also provide the results of appropriate analyses carried out on samples of representative flavour complexes, accompanied by details of the analytical methods (including validation of the methods) and a full

description of each sample, including the source materials and production processes. Sponsors should also address the possible presence of undesirable compounds associated with the source material (or species with which it might be confused) and should provide sufficient information to differentiate the flavour complexes from other products with similar properties.

Standard information in the specifications for finished flavour complexes would include: descriptions of the source material(s), the derivation of the initial extract, and any subsequent processing stages; a physical description of the flavour complexes; information on solubility; and (for liquid products) specific gravity, refractive index and optical rotation.

Specifications developed by the Committee will include the following information on composition, which is essential for the safety evaluation to proceed:

(a) upper and lower concentrations of major characterizing components, including all key constituents identified in relevant ISO standards and any other components considered to be critical for the organoleptic properties of the flavouring.

(b) a list of other components that may be present at or above a given concentration; the concentration will depend on the intake and the relevant threshold of toxicological concern (see above) in the revised Procedure for the Safety Evaluation of Flavouring Agents. Components present in the flavour complex at levels above 0.1–0.5% whose estimated intake exceeds 1.5 µg/day should be characterized if their estimated intake exceeds 1.5 µg/day. The need for more detailed characterization would be determined on a case-by-case basis, depending on the nature of the starting material.

(c) upper limits for any other relevant components, including likely impurities and contaminants or potentially toxic components, such as inherent toxins associated with any part of the source species or with related species with which it might be confused.

The overall scheme for evaluating finished flavour complexes is summarized in Figure 2.

The Committee requested data, in line with the above proposals, on examples of flavour complexes with a range of different constituents and representing different estimated intakes, in order to develop appropriate specifications and to evaluate the application of the revised Procedure to this type of flavouring agent. In particular, in the

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