



## Updated procedure for the safety evaluation of natural flavor complexes used as ingredients in food



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### ABSTRACT

An effective and thorough approach for the safety evaluation of natural flavor complexes (NFCs) was published in 2005 by the Expert Panel of the Flavor and Extract Manufacturers Association (FEMA). An updated procedure is provided here, which maintains the essential concepts of the use of the congeneric group approach and the reliance on the threshold of toxicological concern (TTC) concept. The updated procedure emphasizes more rigorous considerations of unidentified constituents and the genotoxic potential of constituents. The update of the previously established procedure is the first step in a multi-year project to conduct safety re-evaluations for more than 250 NFCs that have uses that are currently considered Generally Recognized as Safe (GRAS) by the FEMA Expert Panel. In addition, this procedure can be more generally employed in the safety evaluation of NFCs.

### 1. Introduction

Natural Flavor Complexes (NFCs) are naturally occurring mixtures derived from plants and other natural sources that are used to flavor foods for human consumption. Many NFCs from commonly used spices and herbs, including black pepper, cinnamon, clove, rosemary, oregano and basil have been used to flavor food for centuries. By the beginning of the 20th century, NFCs were used for a variety of applications, such as use of peppermint and other mint oils for the flavoring of chewing gums and candy and use of citrus oils in soda fountain drinks. Today, NFCs remain important flavoring ingredients in almost all food categories.

The Flavor and Extract Manufacturers Association of the United States (FEMA) began a program in 1959 to assess the safety and generally recognized as safe (GRAS) status of flavoring ingredients under the authority provided by the 1958 Food Additives Amendments to the

Federal Food, Drug, and Cosmetic Act (FFDCA). The FEMA Expert Panel published its first GRAS list in 1965 (Hall and Oser, 1965) including 265 NFCs that are also permitted at 21 Code of Federal Regulations Part 172.510 and 21 Code of Federal Regulations Part 182.20. The Expert Panel has since evaluated numerous chemically-defined flavoring materials for GRAS status including approximately 40 NFCs in recent years. As part of its mission, the Expert Panel continually reviews available safety data and use of all substances determined to be FEMA GRAS.

In the first FEMA GRAS evaluations for NFCs, conclusions on their safety were generally based on their long history of safe use in foods combined with their likely low exposure, based on the principle of self-limitation (i.e. flavor ingredients used at high concentrations are often unpalatable, and thus they are typically used at very low concentrations in food). Recognizing the need for a new safety evaluation procedure for NFCs that applied current scientific knowledge in the fields of

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toxicology, metabolism, biochemistry and analytical chemistry, a scientifically based procedure for the safety evaluation of NFCs based on their chemical composition was developed and published in 2005 (Smith et al., 2005). The procedure requires a comprehensive evaluation of the chemical and biological properties of the constituents. The safety evaluation of cardamom oil demonstrated the application of the procedure (Smith et al., 2004).

The Smith et al., 2005 procedure employs a congeneric group approach for the classification and evaluation of the identified (known) constituents of the NFC under consideration and compares the intake of each congeneric group to the threshold of toxicological concern (TTC) (Cramer et al., 1978; Kroes et al., 2000; Munro et al., 1996) a widely adopted and highly conservative approach to the safety evaluation of food ingredients. Both the European Food Safety Authority (EFSA) and the World Health Organization (WHO) Joint Expert Committee on Food Additives (JECFA) use the TTC approach in their evaluation of flavoring substances (EFSA/WHO, 2016). In the Smith et al., 2005 procedure, the constituents of each congeneric group are related by chemical structure, biochemistry, metabolism and toxicologic potential. The 36 congeneric groups that were described in the original procedure, with some modifications, are listed in Appendix A. Comprehensive, quantitative chemical analyses of each NFC are considered, sorting each identified constituent into its appropriate congeneric group. The structure of each constituent is assessed for toxic potential using the Cramer decision tree (Cramer et al., 1978) which classifies chemical substances into the following classes: Class I (expected low oral toxicity), Class II (less innocuous than Class I but do not contain structural features that provide oral toxicity concern) or Class III (contains structural features which do not permit a presumption of safety). The Cramer decision tree class for each congeneric group is assigned using the highest structural class of any constituent present in the congeneric group. For the NFC under consideration, the range of concentrations of each congeneric group is determined based on multiple analyses. To determine the intake of each congeneric group resulting from consumption of the NFC, the highest percent concentration is multiplied by the NFC intake which is calculated in terms of daily *per capita* intake derived from annual volume of use surveys. The intake of each congeneric group is evaluated against the TTC thresholds for each Cramer Class, 1800 µg/person/day for Class I, 540 µg/person/day for Class II and 90 µg/person/day for Class III (Kroes et al., 2000). For the evaluation of the relatively small percentage of unidentified constituents of an NFC using the Smith et al., 2005 procedure, they are grouped, and approximations of intake of the unidentified constituents are determined in a similar way as for the known congeneric groups. The resulting intake is evaluated against the TTC threshold for Class III, 90 µg/person/day. For both known congeneric groups and unknown constituents of the NFC, if the intake is below the TTC threshold, there is no safety concern. When the intake exceeds the TTC threshold for the respective Cramer class, the procedure calls for the evaluation of the toxicological data for representative members of the congeneric group and/or the NFC. For the evaluation of the unidentified constituents, if their intake is greater via consumption of the food compared to their intake via use of the NFC as added flavoring, further consideration of the unknown portion is not needed and the evaluation of the NFC proceeds to other potential issues that may raise safety concerns.

This manuscript presents an update to the 2005 procedure for the safety evaluation of NFCs. A summary of the revised procedure is outlined in Fig. 1 but the full procedure described here should be used for evaluating NFCs. The original scope of the procedure was for the safety evaluation of essential oils derived from higher plants for the intended use as flavoring substances in food. However, the inherent flexibility and general applicability of the procedure has allowed for the evaluation of a wider range of complex mixtures including those that may be derived from non-botanical sources. While the general approach of the procedure remains the same as that published in 2005, the updated procedure reflects the knowledge obtained through its practical

application over the last decade, including a more rigorous consideration of the unknown fraction and further consideration of the approach to genotoxicity evaluation of constituents, in addition to other minor changes.

## 2. The procedure for the safety evaluation of natural flavor complexes (NFCs)

### Preamble

This procedure provides *guidance* for the safety evaluation of NFCs; it is not to be viewed as a rigid check-list.

The preamble identifies the data that must be available to successfully employ this safety evaluation sequence as described below:

- A. It is essential to provide a complete analytical characterization of the chemical composition of the NFC to be used as a flavoring agent.
- B. The description of the starting material and isolation method must take into account, where relevant:
  - all recognized botanical/natural sources,<sup>1</sup>
  - all relevant geographical sources,
  - all commercially used plant parts,
  - all commercially used degrees of maturity,
  - all commercially used methods of isolation, and
  - the variability inherent in each method of isolation.

These six factors can, and often do, have such an extensive influence on composition that their variation may result in a wholly distinctive product. Therefore, in all cases, it is essential to define these factors to ensure that commercial products conform to the identification that describes the evaluated product.

- C. An NFC identification shall include existing relevant specifications and additional data that assure the identity, purity, technical effect and safety of the commercial product.
- D. Data should be provided on the total exposure to the NFC that includes:
  - a. History of use
  - b. Intake of the natural source of the NFC when that source is itself consumed as a food, and
  - c. Intake of the NFC when it is used as an added flavoring ingredient
  - d. Any other relevant data on individual constituents

**Step 1.** To conduct a safety evaluation of an NFC, the Panel requires that comprehensive analytical data are provided. The analytical methodologies employed should reflect the expected composition of the NFC and provide data that identify, to the greatest extent possible, the constituents of the NFC and the levels (%) at which they are present. It is anticipated that GC-MS and LC-MS would be used for characterization of most NFCs, and that the chromatographic peaks based on peak area of total ion current will be almost completely identified. The percentage of unknowns should be low enough to not raise a safety concern. Other appropriate methods (e.g., Karl Fischer titration, amino acid analysis, etc.) should be employed as necessary. The analytical parameters should be submitted for each type of analysis, including the method of quantitation for both identified and unidentified constituents and libraries, databases and methodology employed for the identification of analytes. The Panel requires data from multiple batches to understand the inherent variability of the NFC.

#### a. Consumption of foods from which the NFCs are derived

Calculate the *per capita* daily intake (PCI) of the NFC based on the annual volume added to food.

<sup>1</sup> A botanical source should be described phylogenetically by family and by genus, species and variety within each family.

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