OVERVIEW OF FLAVOR ADDITIVES
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This paper provides a general characterization of flavor additives, including an overview of how they are regulated within the United States and how they are currently used in organic food production.

I. EXECUTIVE SUMMARY

Flavors are volatile organic chemicals. Most have simple, well-characterized structures with a single functional group (i.e., a chemically reactive subunit) and a low molecular weight. Flavors can be categorized as artificial flavors, spices, and natural flavors. Flavors are regulated by the Food and Drug Administration (FDA) in the United States and are either "generally recognized as safe" (GRAS) substances or food additives, which need to be approved by FDA. Manufacturers that produce flavors that are considered food additives must submit petitions to FDA containing specific information so that the favors can be evaluated for safety when consumed by humans. Although FDA regulates whether flavors are safe for human consumption, they are also of interest to other governmental bodies. Currently, the USDA and the National Organic Standards Board (NOSB) are evaluating the use of natural flavors in organic foods or foods made with organic ingredients.

II. CHARACTERIZATION

Approximately 2,500 chemically defined flavoring substances are in use in either Europe or the United States (Munro et al., 1999). These substances are all volatile organic chemicals, and most have simple, well-characterized structures with a single functional group (e.g., alcohol, ketone) and a low molecular weight (<300 g/mol). Aliphatic acyclic and acyclic alcohols, aldehydes, ketones, carboxylic acids and related esters, lactones, ketals, and acetals comprise more than 700 of the 1,323 chemically defined flavoring substances in the United States. Additional structural categories include aromatic, heteroaromatic, and heterocyclic substances with characteristic organoleptic properties (Munro et al., 1999).

Flavors can further be characterized as artificial flavors, spices, or natural flavors. According to FDA (21 CFR Part 101), artificial flavors, spices, or natural flavors are defined as follows:

Artificial Flavor or Artificial Flavoring: "…any substance, the function of which is to impart flavor, which is not derived from a spice, fruit or fruit juice, vegetable or vegetable juice, edible yeast, herb, bark, bud, root, leaf or similar plant material, meat, fish, poultry, eggs, dairy products, or fermentation products thereof."

Specific artificial flavors are listed in 21 CFR Parts 172.515 and 182.60.

Spice: "…any aromatic vegetable substance in the whole, broken, or ground form, except for those substances which have been traditionally regarded as foods, such as onions, garlic, and celery; whose significant function in food is seasoning rather than nutritional; that is true to name; and from which no portion of any volatile oil or other flavoring principle has been removed."

Specific spices are listed in 21 CFR Parts 182.10 and 184.

Natural Flavor: "…the essential oil, oleoresin, essence or extractive, protein hydrolystate, distillate, or any product of roasting, heating or enzymolysis, which contains the flavoring constituents derived from a spice, fruit or fruit juice, vegetable or vegetable juice, edible yeast, herb, bark, bud, root, leaf of similar plant material, meat, seafood, poultry, eggs, dairy products, or fermentation products thereof, whose significant function in food is flavoring rather than nutritional."

Natural flavors include the natural essence or extractives obtained from plants listed in 21 CFR Parts 182.10, 182.20, and 182.40, as well as those listed in Parts 184 and 172.50.

According to a study by Munro et al. (1998), human exposure to flavors is generally low in the United States. Exposure levels estimated by Munro et al. (1988) are shown in Table 1. These estimates were made with the following assumptions: (1) survey poundage reflects 60 percent of actual use, (2) 10 percent of the population is exposed, and (3) the U.S. population in 1987 was 240 million.

Table 1: Human Exposure to Flavor Ingredients [a] (Munro et al., 1998)

Intake (µg per day)[b]	Number of Flavors	Cumulative Frequency (%)
<0.01	349	26
0.01-0.1	93	33
0.1-1	274	54
1-10	224	71
10-100	204	86
100-1000	111	95
1000-10,000	45	98
10,000-100,000	16	99
>100,000	7	100
Total	1,323	100

a Chemically defined flavoring substances permitted for use in the U.S., excluding botanicals.
b Intake (µg/person/day) = ([annual flavor usage in µg/0.6]/24) X 10^6 persons X 365 days

III. REGULATION

Currently in the United States, flavors are regulated by FDA under authority of the Food Additives and Amendment Act (FAA) of 1958. Under the FAA, FDA is responsible for ensuring the safety of new food additives, including flavors, before they are used in food

products. In the existing regulatory system, all flavors are either GRAS ("generally recognized as safe") substances or flavor additives that must be approved for use by FDA.

A. GRAS Flavors

In response to the FAA, the Flavor and Extract Manufacturers Association of the United States (FEMA) was formed, and the GRAS assessment program was initiated. This assessment program was created because the lengthy new food additive application process was considered unnecessary for the large number of substances with a long history of widespread and apparently safe use. Food Additive Petitions and approval by FDA (see Section III. B.) are not required for GRAS substances.

FEMA consists of a panel of independent experts who are responsible for establishing procedures that help decide whether a flavor qualifies as a GRAS substance and applying these procedures to the safety evaluation of flavor materials being used in the United States. In order to qualify as a GRAS substance, a flavor must meet the following four requirements (Hallagan and Hall, 1995):

1. Safety must be generally recognized by experts.

2. Experts must be qualified by scientific training and experience in evaluating safety.

3. Experts must base their decisions on scientific procedures or through experience based on common use in food if used in food prior to 1958.

4. Determination of a GRAS substance must be based, in part, on the intended conditions of use of the flavoring substance through the calculation of a possible average daily intake and a *per capita* exposure estimate.

To date, there are more than 2,000 materials judged to be GRAS substances by FEMA (Adams and Smith, 2004).

FDA recognizes the work of FEMA and incorporates information provided by the expert panel on the safety of flavoring substances into FDA's flavor database. Additionally, in 1976, FDA recognized the FEMA GRAS lists when giving their opinion on bulk labeling of flavors and in other direct ways (Hallagan and Hall, 1995). Currently, FDA's safety requirements for GRAS substances largely depend on the flavor's historical profile. Affirmation of GRAS status is often based on the common use of the substance in foods prior to 1958 coupled with the lack of known or documented adverse effects. This statement is supported by Section 170.30 of the CFR. Those substances with no documented history prior to 1958 may still qualify as a GRAS substance by FDA; however, the quantity and quality of scientific evidence required is the same as that for a food additive petition. Affirmed GRAS substances that are to be used in new ways or at different concentrations also must have their status re-evaluated by FDA. Like FEMA,

FDA affirms GRAS substances by using an expert advisory panel that reviews the scientific data. Substances lacking strong scientific evidence may be deemed a food additive and subjected to a food additive petition.

B. Flavors Regulated as Food Additives

If a flavor does not qualify as a GRAS substance, a food additive petition must be filed by the petitioner and approved by FDA. In filing for a food additive approval, the petitioner is responsible for providing FDA with information including, but not limited to the following:

- Identification of the food additive;
- Physical, chemical, and biological properties;
- Chemical specifications;
- Manufacturing process description;
- Stability data;
- Intended uses and restrictions;
- Labeling[1];
- Tolerances limitations[2];
- Analytical methods for enforcing chemical specifications;
- Safety studies; and
- Estimate of probable exposure.

A full description of the information to be submitted in a food additive petition is available in 21 CFR Part 571.

A food additive petition must show that the proposed additive performs as it is intended and that it would not cause harmful effects at expected levels of human consumption. FDA is responsible for evaluating food additive petitions and determining whether food additives are safe for human consumption. Generally, this determination is made by examining the following factors:

- History of use or natural occurrence;
- Consumption ratio (i.e., the comparison of natural occurrence to intentional addition), if applicable;
- Exposure levels;
- Inherent toxicity of the substance;
- Toxicological data on the substance or on structurally-related compounds; and
- Metabolism of the substance (either know of forecasted on the basis of data for structurally-related compounds).

[1] Any labeling that will be required by applicable provisions of the Federal Food, Drug, and Cosmetic Act on the finished food by reason of the use of the food additive.

[2] According to 21 CFR Part 571, "If the food additive is one for which a tolerance limitation is required to assure its safety, the level of use proposed should be no higher than the amount reasonably required to accomplish the intended physical or other technical effect, even though the safety data may support a higher tolerance."

FDA's assessment includes a review toxicity data such the results of controlled animal studies. Ideally, a complete range of data, including short- and long-term toxicity studies, as well as studies that examine possible reproductive, carcinogenic, mutagenic, and sensitization characteristics of the flavoring substance would be available for review. Sometimes a complete set of toxicology data is not available. One method of gaining additional insight on a flavor lacking a complete set of data is to evaluate the toxicity of structurally related substances. By evaluating structurally related substances, scientists can try to determine how the compound is absorbed, distributed, and metabolized within the study, and how it may act on target organs in the body. Based on these data and various safety factors, FDA determines a safe exposure level for the color additive.

FDA then compares the safe exposure level to the amount likely to be consumed in food taking into consideration the composition and properties of the substance and the proposed conditions of use. Because the absolute safety of any substance can never be proven, FDA must determine if the additive is safe under the proposed conditions of use, based on the best scientific knowledge available. For more information, see http://vm.cfsan.fda.gov/~dms/opa-cg8e.html.

IV. NON-REGULATORY TOOLS

Cramer et al. (1978) created a decision-tree approach that is used by some agencies to determine which favoring substances are safe for use in food. Documentation could not be found as to whether FDA uses this decision tree approach; however, the information presented by Cramer et al. (1978) is relevant to the understanding of how a flavor could be judged as safe for human consumption. Although it is not implicitly stated that FEMA uses this decision tree, it is included on the FEMA web site.[3] Additionally, a modified version of this decision tree is used by the Joint FAO/WHO Expert Committee on Food Additive (JECFA), an international expert scientific committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). Another modified version of the decision-tree created by Cramer et al. (1978) is listed below, in which flavoring substances are considered safe for their intended use if one of the five numbered decision criteria outlined below is met (Munro et al., 1999).

1a. The favoring substance has a simple structure and is predicted to be metabolized into innocuous products; and

1b. The conditions of intended use do not result in an intake greater than the human exposure threshold for the relevant structural class, indicating a low probability of potential for adverse effects.

2a. The conditions of intended use result in an exposure greater than the human exposure threshold for the relevant structural class; however,

[3] The decision tree may be found under the topic of "growth and development and accomplishments" at http://www.femaflavor.org/html/public/general_info.html.

2b. The favoring substance has a simple structure and is predicted to be metabolized into innocuous products, and it or its metabolites are endogenous human metabolites with no know biochemical regulating function.

3a. The favoring substance has a simple structure and is predicted to be metabolized into innocuous products; and

3b. The conditions of intended use result in an exposure greater than the human exposure threshold for the relevant structural class; however,

3c. There are toxicity data establishing safety under conditions of intended use, or there are toxicity data on 1 or more structurally-related chemicals which provide a NOEL high enough to accommodate any perceived difference.

4a. The metabolic fate of the flavoring substance cannot be confidently predicted on the basis of the structure; however,

4b. The conditions of intended use result in an exposure below the human exposure threshold for the relevant structural class, indicating a low probability of potential adverse effects; and

4c. There are toxicity data establishing safety under conditions of intended use, or there are toxicity data on 1 or more structurally-related chemicals which provide a NOEL high enough to accommodate any perceived difference.

5a. The metabolic fate of the flavoring substance cannot be confidently predicted on the basis of the structure; however,

5b. The conditions of intended use result in an intake below the human exposure threshold of 1.5 µg/day[4], providing assurance that the substance will be safe under conditions of intended use.

IV. USE OF FLAVORS IN ORGANIC FOODS

Flavors are currently on the National List of Allowed and Prohibited Substances for use in organic foods. Flavors were not added to the National List as the result of a petition. Instead, they were included among substances initially placed on the National List when USDA promulgated regulations pursuant to the Organic Food Production Act of 1990. According to 21 CFR Part 205.605, nonagricultural (nonorganic) flavors are allowed as ingredients in or on processed food products labeled as "organic" or "made with organic." Only nonsynthetic flavors (as a group) are listed.

The NOSB has debated the issue of using natural flavors as ingredients in organic foods. Recommendations by the NOSB state that, for organic food (i.e., 95-100 percent organic ingredients), all flavor constituents of the natural flavor must be from natural sources that have not been chemically modified in a way that makes them different from their natural

[4] FDA established a human exposure threshold value for an untested chemical present in food. This value is the intake level below which no risk to public health would be likely to occur (i.e., the human exposure threshold value will present less than a 10^{-6} risk). Currently, the human exposure threshold is 1.5 µg/day and is based on the assumption that an individual consumes 1,500 g of solid food and 1,500 g of liquid food per day (Federal Register, 1995).

state. Additionally, the natural flavor cannot be produced using any synthetic solvent and carrier systems or any artificial preservatives. For foods made with organic ingredients (i.e., 50-95 percent organic ingredients), all of the flavor constituents used in the natural flavor must be from natural sources that have not been chemically modified in such a way that makes them different from their natural chemical state. Additionally, the following conditions must be satisfied:

- The natural flavor does not contain propylene glycol, any artificial preservative, and is not extracted with hexane.

- Manufacturers must provide written documentation in their Organic Handling Plan, which shows that efforts were made toward the ultimate production of an organic natural flavor as listed in the stepwise progression below:

    - Natural flavor constituents and non-synthetic carrier base and preservative agents

    - Organic flavor constituents, organic carrier base, and organic preservative agents

    - Organ flavor constituents extracted using organically produced solvent organic carrier base, and organic preservative agents.

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