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Review

Under the conditions of intended use – New developments in the FEMA GRAS program and the safety assessment of flavor ingredients

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ABSTRACT

In 1995 we published a review describing the scientific and legal bases for the GRAS assessment program for flavor ingredients sponsored by the Flavor and Extract Manufacturers Association of the United States (FEMA) [Hallagan, J.B., Hall, R.L., 1995. FEMA GRAS – A GRAS assessment program for flavor ingredients. Regulatory Toxicology and Pharmacology 21, 422]. This review provides new information related to flavor safety assessment and regulation and is intended to complement our previous report. The FEMA GRAS assessment program is the most extensive and longest running industry-sponsored GRAS program and has established a sound record of scientific rigor and transparency. In this review, in addition to providing general information on the topics of flavor safety assessment and regulation, we explore the effects of recent developments on the four pillars of the FEMA GRAS assessment program: (1) general recognition; (2) among experts qualified by scientific training and experience to evaluate safety; (3) through scientific procedures; (4) under the conditions of intended use in food. We conclude that developments since our last review in 1995 have further strengthened the FEMA GRAS assessment program allowing it to maintain its global leadership role in the safety assessment of flavor ingredients.

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1. Introduction

In 1959, the Flavor and Extract Manufacturers Association of the United States (FEMA) began a program to assess the safety and "GRAS" (generally recognized as safe) status of flavor ingredients under the authority provided by the 1958 Food Additives Amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA). The FEMA program began with an initial flavor industry survey to identify flavor ingredients then in use and to provide estimates of the amounts of these substances used by the flavor manufacturing industry (Hall, 1960). The FEMA Expert Panel began its program for evaluation of the safety of flavor ingredients in 1960 and the new program applied a number of modern techniques of safety evaluation including the use of metabolic studies and structural relationships that had not previously been applied in a significant manner to food ingredients such as flavoring substances (Hall and Oser, 1961).

There have been many significant developments relevant to flavor safety assessment and regulation since we last described the history, and scientific and legal bases for the FEMA GRAS assessment program for flavor ingredients (Hallagan and Hall, 1995). The years since 1995 represented an active period for the FEMA GRAS assessment program during which more than 1000 single chemically defined flavoring substances were evaluated and determined to be "FEMA GRAS." Also during this time, the FEMA Expert Panel thoroughly reviewed and revised their criteria for determining GRAS status for single chemically defined flavor ingredients and natural flavor complexes (Smith et al., 2004, 2005) and published in the peer-reviewed scientific literature detailed reviews of structurally-related groups of flavoring substances. In addition, the Expert Panel also published a number of reports resolving issues associated with the safety and FEMA GRAS status of a number of individual flavoring substances.

Another significant development, although not directly affecting the operations of the FEMA GRAS assessment program, was the implementation in 1997 of the Food and Drug Administration (FDA) voluntary GRAS notification program. The FDA program has provided support for the GRAS concept as a sound regulatory tool and has provided important clarification of some of the key elements of GRAS assessments.

Since 1995, global and regional flavor safety assessment programs such as the programs of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Union (now through the European Food Safety Authority – EFSA) have been implemented using principles consonant with modern safety evaluation programs (JECFA, 1996; Munro et al., 1998, 1999). Thus, these evaluation programs are consistent with those of the FEMA GRAS assessment program and have therefore led, in nearly all instances, to parallel results.

This report provides new information related to flavor safety assessment and regulation and is intended to complement our previous report (Hallagan and Hall, 1995). In addition to providing general information on these topics we explore the effects of recent developments on the four pillars of the FEMA GRAS assessment program: (1) general recognition; (2) among experts qualified by scientific training and experience to evaluate safety; (3) through scientific procedures; (4) under the conditions of intended use in food.

2. Flavor ingredients added to food

The historical role of flavors in food manufacturing was reviewed by Hall and Merwin (1981) who provided several basic definitions. "Flavor" was defined as "... the sum of those characteristics of any material taken in the mouth, perceived principally by the senses of taste and smell and also the general pain and tactile receptors in he mouth, as received and interpreted by the brain." A flavor was defined as "a substance which may be a single chemical entity, or a blend of chemicals of natural or synthetic origin whose primary purpose is to provide all or part of the particular flavor effect to any food or other product taken in the mouth" (Hall and Merwin, 1981).

Flavors may also be called "compounded flavors," and in modern food manufacturing are often mixtures of as many as one hundred or more flavoring substances, some of them complex mixtures themselves, chosen to provide a particular taste sensation. Other flavor ingredients, such as solvents, emulsifiers, flavor modifiers, and antioxidants are required to allow the compounded flavor to function properly in the food to which it is added. Flavor ingredients that impart flavor (i.e. provide an aroma/taste sensation) are referred to as "flavoring substances" and include individual substances referred to as single chemically defined flavoring substances, and natural materials such as extracts, essential oils, and oleoresins that are referred to as natural flavor complexes. FDA has designated all of these substances as "flavoring agents and adjuvants" and defines them as "Substances added to impart or help impart a taste or aroma in food."[1]

There are more than 2400 single chemically defined flavoring substances in use in the United States and they can be of natural or synthetic origin. Although the origin of these substances has no bearing on safety assessment or GRAS status, whether they are of synthetic or natural origin is important for food labeling purposes in the US because FDA distinguishes between the two origins in its flavor and food labeling regulations. FDA provides a definition of "artificial (synthetic origin) flavor" at 21 CFR 101.22(a)(1) and a definition of "natural flavor" at 21 CFR 101.22(a)(3). The primary flavor and food labeling requirements are found at 21 CFR 101.22(g), (h), and (i) (Hallagan, 2004).

There are about 300 natural flavor complexes in use which are themselves complex mixtures of individual single chemically defined flavoring substances. Single chemically defined flavoring substances and natural flavoring complexes each have their own safety assessment procedures employed by the FEMA Expert Panel (Smith et al., 2004, 2005).

Compounded flavors typically contain individual single chemically defined flavoring substances at levels well below 1.0% of the compounded flavor. Natural flavoring complexes may be present in higher concentrations in a compounded flavor but the individual single chemically defined flavoring substances in the natural flavoring complex are, again, typically present in the compounded flavor at <1.0%.

In addition to flavoring substances, flavor adjuvants (e.g. antioxidants, emulsifiers, flavor modifiers, and solvents) may be candidates for FEMA GRAS status within established limits. The Expert Panel stated,

> Often, substances that act as emulsifiers, solvents and preservatives in the preparation of compounded flavors serve the same function in the food supply. In these instances, the Panel evaluates the substance for its GRAS status based strictly on its intended use as a component of a food flavor. In order to complete the GRAS evaluation, the applicant must demonstrate that the substance provides the specified function in flavors under conditions and at levels of use that do not serve other non-flavor functions in the finished food (Waddell et al., 2007).

Compounded flavors are most often added to food during food manufacture at levels below 1.0%. After loss during the food manufacturing process, due to volatilization during blending or heat processing, the concentration of the compounded flavor in the

[1] 21 CFR 170.3(o)(12).

finished food is reduced further below the initial level at which it was added. The end result is that individual single chemically defined flavoring substances are most often present in food as consumed at parts per million levels and lower.

3. The Food and Drug Administration and GRAS assessments

3.1. Statutory authority

In our previous report we reviewed the legal basis for GRAS assessment programs generally, and specifically for the FEMA GRAS assessment program for flavor ingredients (Hallagan and Hall, 1995). Section 201(s) of the FFDCA provides that substances to be added to food are subject to a premarket approval requirement unless the substances are generally recognized as safe (GRAS) by experts under their conditions of intended use.

> The term food additive means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food. if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of intended use...[2]

FFDCA Section 201(s) therefore provides an explicit exemption from the definition of "food additive" that permits an alternate pathway to permission to include certain food ingredients in food. A food ingredient that is generally recognized as safe under its conditions of intended use ("GRAS") can be added to food without the approval by FDA of a food additive petition. FDA's food additive petition requirements are described at 21 CFR Parts 170 and 171.

3.2. The FDA voluntary GRAS notification program

A significant development since our 1995 report with respect to the interpretation of issues associated with GRAS status was FDA's implementation of its voluntary GRAS notification program in 1997.[3] Even though the agency has not issued a final rule and codified the requirements of the program, it has fully implemented it as an on-going regulatory program reflecting agency policy. In doing so FDA has folded its own GRAS affirmation program[4] into the voluntary GRAS notification program.

FDA cited three purposes for issuing the proposed rule for the voluntary GRAS notification program.

> In proposing these changes, FDA is (1) Emphasizing that a GRAS substance is distinguished from a food additive by the common knowledge about the safety of the substance for its intended use rather than by what the substance is, or on the basis of the types of data and information that are necessary to establish its safety; (2) identifying the types of technical evidence of safety that could form the basis of a GRAS determination; and (3) clarifying the role of publication in satisfying the general recognition standard.[5]

While many important legal and regulatory issues related to the interpretation of the GRAS provisions of Section 201(s) were resolved in the courts some time ago (Hallagan and Hall, 1995), the extensive preamble to FDA's voluntary GRAS notification program (FDA, 1997) provided the agency an opportunity to clarify and reinforce a number of relevant principles.

In describing the history of the GRAS provision at FFDCA Section 201(s), the agency stated,

> In enacting the 1958 amendment, Congress recognized that many substances intentionally added to food would not require a formal premarket review by FDA to assure their safety, either because safety had been long established by a long history of use in food or by virtue of the nature of their substances, their customary or projected conditions of use, and the information generally available to scientists about the substances.[6]

Consistent with this principle, FDA explicitly addressed the issues of whether the statute allowed a private party to determine GRAS status, and if so whether the party could conduct an appropriate GRAS assessment, reach the conclusion of GRAS, and market the substance without first informing FDA. The preamble to the 1997 proposed rule stated:

> (A) substance that is GRAS for a particular use may be marketed for that use without agency review and approval. ...Under both the current and the proposed procedures, a manufacturer may market a substance that the manufacturer determines is GRAS without informing the agency.[7]

This statement of agency policy has no effect on the FEMA GRAS assessment program because fully informing FDA of GRAS determinations of flavor ingredients has been part of the FEMA program since its inception more than forty years ago.

The FDA notification program provided the agency with a mechanism for it to publicly acknowledge GRAS assessments performed by private groups given the information available at the time of the assessment. FDA's acknowledgement of GRAS status is published on FDA's website (www.cfsan.fda.gov/~rdb/opa-gras.html) and takes the form of a letter from FDA to the proponent of GRAS status briefly summarizing FDA's interpretation of the data submitted and concluding with a brief statement that FDA "has no questions at this time" regarding the proponent's conclusion that the use of the substance is GRAS. This acknowledgement of GRAS status by FDA has been important as the food industry has become increasingly global by providing a mechanism for food manufacturers to obtain an FDA "approval" for private GRAS assessments that has significant credibility with other national and supranational regulatory agencies.

3.3. Regulation of flavoring substances in the United States

GRAS assessment programs like the FEMA program have often been incorrectly described as "self-regulation" programs. The FEMA program is not a self-regulation program. The FEMA GRAS program operates under statutory authority granted by Congress in 1958 in the Food Additives Amendment to the FFDCA and exists only with the oversight and participation of the Food and Drug Administration. Furthermore, flavoring substances and flavor manufacturing are also subject to numerous other regulatory requirements including the requirements of the Occupational Safety and Health Administration (OSHA) and the Environmental Protection Agency (EPA). For example, flavor manufacturing is subject to the requirements of OSHA's general workplace safety standards (29 CFR Parts 1900-1999) and specifically to OSHA's Hazard Communications Standard (29 CFR 1910.1200). Many single chemically defined flavoring substances are subject to the requirements of the

[2] FFDCA Sec. 201(s).
[3] 62 *Fed. Reg.* 18938. 17 April 1997.
[4] 21 CFR Parts 170 and 184.
[5] 62 *Fed. Reg.* at 18941.
[6] 62 *Fed. Reg.* at 18938, 18939.
[7] 62 *Fed. Reg.* at 18941.

Toxic Substances Control Act (TSCA) administered by EPA. A number of single chemically defined flavoring substances were included in the extensive data review exercise conducted by EPA through the High Production Volume Chemical initiative.

Because of FDA's statutory authority, the explicit listing by FDA of flavoring substances permitted for addition to food is the primary regulatory authority for the use of these substances in the United States. Flavoring substances explicitly regulated by FDA as GRAS substances (21 CFR Parts 182 and 184) and food additives (21 CFR Part 172) may be used only under the conditions of use specified by the agency (i.e. flavoring substances for general use in food consistent with good manufacturing practice). Likewise, the approximately 2000 flavoring substances with FEMA GRAS status but no explicit FDA regulatory status may be used only as flavor ingredients, the conditions of intended use specified by the FEMA Expert Panel and not, for example, as sweeteners.

Within the total of more than 2700 flavoring substances with FEMA GRAS status (both single chemically defined flavoring substances and natural flavor complexes) there are several hundred single chemically defined flavoring substances and natural flavor complexes that are explicitly listed as GRAS by FDA for use as flavoring substances.[8] Several hundred other flavoring substances are listed by FDA as approved food additives.[9] All of these flavoring substances are explicitly permitted for use by FDA as flavoring substances for general use in food in amounts consistent with good manufacturing practice. Of the many flavor ingredients in use in the US only about fifty have FDA regulatory status but not FEMA GRAS status. FEMA GRAS status for these substances has not been sought either because they are not important flavor ingredients or because they are already approved for use by FDA and no public health or business reason exists to obtain FEMA GRAS status. A number of the fifty substances are substances such as ethyl cellulose (21 CFR 172.868) and mono and diglycerides (21 CFR 184.1505) that do not impart flavor but that may be used to formulate compounded flavors. Others impart flavor but are minor-use isomers of FEMA GRAS flavoring substances such as l-carvone (21 CFR 182.60) and l-limonene (21 CFR 182.60). None of the fifty substances is a high-volume flavor ingredient. A list of these flavor ingredients is available from author Hallagan.

The regulatory status of diacetyl (2,3-butanedione), a flavoring substance used to provide a "buttery" flavor to many foods, illustrates the relationship between FDA regulatory status and FEMA GRAS status. Diacetyl is listed by FDA as GRAS for use as a flavoring agent "with no limitation other than current good manufacturing practice."[10] Diacetyl is considered to be FEMA GRAS for use as a flavoring substance under its conditions of intended use (Hall and Oser, 1965). If diacetyl did not have FEMA GRAS status, it could still be added to foods under the existing FDA regulation. Diacetyl has been identified as a potential respiratory hazard in flavor and microwave popcorn manufacturing (FEMA, 2004; Kanwal et al., 2006) but workplace exposure issues are beyond the scope of authority provided by Congress to FDA for regulating flavors and other food constituents. Furthermore, GRAS evaluations, by FEMA or FDA, do not require an assessment of potential inhalation toxicity because the primary route of exposure for GRAS substances is ingestion as constituents of food (FDA, 2007).

Over the years, eight flavor ingredients have had FEMA GRAS status revoked by the Expert Panel: alkanet root extract, brominated vegetable oil, calamus, calamus oil, musk ambrette, 3-nonanon-1-ol, 2-methyl-5-vinylpyrazine, and o-vinylanisole. The flavor industry voluntarily ceased use of a ninth, cinnamyl anthranilate, which was subsequently banned by FDA. In many other instances, use as flavor ingredients for certain substances has been determined to not be appropriate during the Expert Panel's GRAS review process and therefore have never been considered FEMA GRAS. FDA has explicitly designated four flavoring substances as prohibited for use in food: calamus and its derivatives, cinnamyl anthranilate, coumarin, and safrole.[11] None of them have FEMA GRAS status.

Flavor ingredients have not been a significant part of the FDA voluntary GRAS notification program largely because of the strength and wide recognition of the FEMA GRAS program. The fact that a flavor ingredient is FEMA GRAS, and therefore has been assigned a FEMA GRAS number, has commercial value in the flavor and food manufacturing industries. So far, approximately 200 food ingredients have been listed by FDA in the voluntary GRAS notification program but of these, only three are FEMA GRAS flavor ingredients that also are listed by FDA for flavor-related uses: mesquite extract (GRAS Notice No. GRN 000018 for use as a flavoring agent; 1999), trehalose (GRAS Notice No. GRN 000045 for use as a flavor enhancer and other uses; 2000), and beta-cyclodextrin (GRAS Notice No. GRN 000074 for use as a flavor carrier or protectant; 2001).

One other FEMA GRAS flavor ingredient, allyl isothiocyanate, was listed in the FDA voluntary GRAS notification program for use as a "shelf-life extension" and anti-spoilage agent (GRAS Notice No. GRN 000180; 2005). Gamma-cyclodextrin is not FEMA GRAS but was listed by FDA in the voluntary GRAS notification program for use as a flavor carrier, among other uses (GRAS Notice No. GRN 000046; 2000).

4. Elements of the FEMA GRAS assessment program – new developments

4.1. General recognition

4.1.1. Publication of FEMA GRAS decisions, supporting data, and procedures

General recognition of the safety of a food ingredient under its conditions of intended use is a key factor in supporting GRAS status (Hallagan and Hall, 1995). Since 1965, the FEMA Expert Panel has evaluated and determined to be GRAS approximately 2700 flavor ingredients and has achieved general recognition by publishing the identity of all FEMA GRAS flavor ingredients in *Food Technology* (Hall and Oser, 1965, 1970; Oser and Hall, 1972; Oser and Ford, 1973a,b, 1974, 1975, 1977, 1978, 1979; Oser et al., 1984, 1985; Burdock et al., 1990; Smith and Ford, 1993; Newberne et al., 1998, 2000; Smith et al., 1996, 2001, 2003, 2005a; Waddell et al., 2007).

Safety assessment information supporting GRAS status on structurally-related groups of single chemically defined flavoring substances is published in the form of monographs in the peer-reviewed scientific literature (e.g. Adams et al., 2005, 2007). To further enhance the concept of "general recognition" FEMA has provided all safety assessment information supporting GRAS status to FDA for inclusion in its publicly available databases and to allow the agency the opportunity to object to the assignation of GRAS status to any individual flavor ingredient.

Changes in publication vehicles and data gathering strategies resulting from the significant growth of acceptance of the Internet since 1995 may be altering the perception of the general recognition requirement. While the requirement that GRAS determinations, and the information that they are based on, must be published in the open literature has not been officially changed by FDA it has become apparent that publication on the Internet

[8] 21 CFR Parts 182 and 184.
[9] 21 CFR 172.510; 172.515.
[10] 21 CFR 184.1278.
[11] 21 CFR Part 189.

is an increasingly utilized publication vehicle. FDA publishes its voluntary GRAS notification program acknowledgement letters only on the agency's website.

FEMA now publishes its GRAS determinations on the FEMA website (www.femaflavor.org) in addition to publishing them in *Food Technology*. FEMA also continues to publish much information describing how the Expert Panel makes GRAS determinations (Oser and Hall, 1977; Woods and Doull, 1991; Smith et al., 2004, 2005).

4.1.2. Periodic, comprehensive reviews

As we noted (Hallagan and Hall, 1995), GRAS assessment is dynamic and must be re-evaluated to account for new information on flavor ingredients and new perspectives on safety evaluation. This is a key element in meeting the "general recognition" requirement imposed by the statute.[12] The FEMA Expert Panel completed its first systematic review of the GRAS status of flavor ingredients in 1985, known as "GRAS affirmation" resulting in the review of approximately 1200 FEMA GRAS flavor ingredients The Expert Panel began its second systematic review, known as "GRAS reaffirmation" in 1994 and completed it in 2005.

The GRAS reaffirmation process completed in 2005 incorporated a thorough review of all available information relevant to the safety assessment and GRAS status of more than 2000 FEMA GRAS single chemically defined flavoring substances. Flavor ingredients determined to be GRAS during the GRAS reaffirmation process will be re-evaluated during the Expert Panel's next systematic GRAS review. The GRAS reaffirmation process did not result in the revocation of GRAS status for any flavor ingredient. However, as a condition of maintaining GRAS status the Expert Panel required the conduct of toxicological and mechanistic studies of certain flavor ingredients to assure that data sets were as complete as possible. The results of the reaffirmation process are being published in a series of review articles on groups of structurally-related single chemically defined flavoring substances (e.g. Adams et al., 2007).

4.1.3. Focus on certain individual flavoring substances

In addition to its GRAS affirmation and GRAS reaffirmation reviews, the Expert Panel also reviews the GRAS status of flavoring substances for which significant scientific issues are presented or for which new information becomes available. Since 1995, the Expert Panel has been especially active in addressing and resolving issues associated with certain individual flavoring substances. For example, the Expert Panel published its review and assessment of the relevant safety data for the flavoring substances trans-anethole (Newberne et al., 1998; Smith et al., 2005), citral (Smith et al., 2001), cinnamaldehyde (Smith et al., 2003), and cornmint oil (Smith et al., 2005a), among others, and in each instance the Expert Panel's review resulted in the maintenance of GRAS status for these substances for the specified uses.

There are several particularly illustrative examples of the Expert Panel's manner of addressing flavoring substances for which special issues are presented. The Expert Panel's evaluation of the p-allylalkoxybenzene derivatives estragole and methyleugenol demonstrates that detailed investigations of potential mechanisms of action can provide valuable safety assessment information. Based on comparative metabolic, DNA, and protein adduct studies the Expert Panel concluded that while estragole and methyleugenol can form covalently-bound protein and DNA adducts in rodents, it is highly unlikely that there is a significant health risk to humans at current levels of exposure (Smith et al., 2005).

Another example is the Expert Panel's evaluation of process flavors. Process flavors are a class of flavoring substances manufactured by the heat processing of foods or food constituents in the presence of water followed by isolation and purification. The food constituents from which process flavors are manufactured generally contain carbohydrate and protein sources. The final process flavor is a mixture that imparts a savory flavor to foods. Under certain manufacturing conditions, the potential exists that polycyclic heteroaromatic amines (PHAs), which occur naturally in cooked meats, may be formed during process flavor manufacture. A number of PHAs are considered relatively potent animal carcinogens. FEMA, in consultation with FDA, sponsored an extensive analytical testing program during the 1990s to identify the degree to which PHAs may be present in process flavors (Hallagan, 2005). Analyses of model process flavors were conducted for a representative sample of PHAs facilitating an analysis of potential safety issues by the Expert Panel and FDA. The Expert Panel concluded that the potential intake of PHAs from process flavors is negligible when compared to the intake of PHAs from cooked foods and that "process flavors do not present a safety concern under current conditions of use." (Newberne et al., 2000). The data from the FEMA program were provided to FDA and the agency has not proposed any additional regulation of process flavors.

4.2. Among experts qualified by scientific training and experience to evaluate safety

The Expert Panel's internal operational procedures and membership are updated and addressed as needed to assure that the Panel's evaluations maintain the highest standards and are fully consistent with the statutory authority for GRAS assessment programs provided by Congress and implemented by FDA.

The FEMA Expert Panel is a group of experts well-qualified by training and experience in various disciplines relevant to the safety assessment of flavor ingredients. The Expert Panel operates with total independence in its safety evaluations (Hallagan and Hall, 1995). The membership of the Expert Panel has changed significantly since 1995 as members retired and were replaced by the Panel with others equally well-qualified who also brought the expertise that GRAS assessments currently require.

The Panel's current membership reflects the increasing "globalization" of the world – the Panel currently has two members from Europe, one consultant from Japan, and one consultant from Canada. The Panel's membership includes expertise from biochemistry, medicinal chemistry, organic chemistry, pathology, and toxicology.

The Expert Panel is normally comprised of eight members but this number varies from time to time due to retirements and other factors. There are six current members of the Expert Panel with two vacancies that may be filled. The six current members are: Samuel M. Cohen, M.D., Ph.D. of the University of Nebraska Medical Center, Lawrence J. Marnett, Ph.D. of the Vanderbilt University School of Medicine, Philip S. Portoghese, Ph.D. of the University of Minnesota, Ivonne M.C.M. Rietjens, Ph.D. of Wageningen University, Robert L. Smith, Ph.D. of the Imperial College School of Medicine, and William J. Waddell, M.D., Ph.D. of the University of Louisville School of Medicine. Prof. Smith serves as Chair of the Expert Panel.

The broad expertise represented on the Expert Panel is important to address the requirement that experts making GRAS determinations be qualified by scientific training and experience to evaluate the safety of flavoring substances. Also of significance is the fact that the relatively large normal complement of Expert Panel members (eight) provides a sound measure of "general recognition" because all Expert Panel GRAS decisions must be unanimous and unanimity among such a group clearly supports general recognition.

[12] FFDCA Sec. 201(s).

4.3. Through scientific procedures

The Expert Panel's evaluation procedures are regularly updated to address changes in safety assessment approaches and scientific advances. The Panel evaluates and adjusts its procedures to account for the best information available as reflected in the Panel's description of the criteria that it applies to determine the GRAS status of single chemically defined flavoring substances (Smith et al., 2005) and natural flavor complexes (Smith et al., 2004).

Since our last report in 1995, the Expert Panel has revised and made even more transparent their procedures for performing GRAS assessments of single chemically defined flavoring substances (Smith et al., 2005) and natural flavor complexes (Smith et al., 2004). For single chemically defined flavoring substances, the Expert Panel continues to focus on evaluating individual substances within their group of structurally-related substances with emphasis on the metabolism and disposition of members of the group, their available toxicology data, and an estimate of potential exposure (Smith et al., 2005). Information on chemical identity, physical and chemical properties, and production methods is required for these substances. In certain instances, as described in the previous section on general recognition, the Expert Panel may engage in very detailed analyses to address specific issues and may require the collection of additional data.

For natural flavor complexes, the Expert Panel has adopted a procedure for evaluating natural flavor complexes that relies on an analysis of the potential intake of the constituents of the material as related to a threshold of toxicological concern (Smith et al., 2004). Therefore a full characterization of the natural flavor complex is critical. Many of the constituents of commonly used natural flavor complexes are considered GRAS by FEMA and/or FDA. However, the GRAS status of a natural flavor complex does not mean that its constituents are also considered to have GRAS status. Individual constituents of natural flavor complexes may be used in ways different from the use of the natural flavor complex resulting in different levels of intake, and warranting their own, separate GRAS evaluation.

During the past decade, the Expert Panel and the FEMA scientific staff have, as described below, addressed a number of emerging issues such as the role of intake assessments and genotoxicity data in flavor safety evaluations which have become increasingly important as global regulation has moved forward under the World Trade Organization (WTO) Treaties and the responsible implementing international organization, the Codex Alimentarius Commission.

4.3.1. FEMA flavor ingredient poundage surveys

Annual reported poundage data have been collected regularly and represent the volume of each flavor ingredient that "disappears" into the food supply each year. In other words, the annual reported poundage represents the amount of flavor ingredients that are introduced annually into the general food supply.

At one time, flavor ingredient poundage surveys were sponsored by FDA and conducted by a committee of the National Academy of Sciences with the support and participation of FEMA. This arrangement covered poundage surveys in 1972, 1977, 1982 and 1987. The 1987 survey was the last survey sponsored by FDA. In the absence of FDA sponsorship, FEMA has sponsored two comprehensive surveys of poundage disappearance information, one that collected information from 1995 and that was published in 1999 (Lucas et al., 1999), and the most recent FEMA poundage survey composed of poundage data from 2005 (Gavin et al., 2008). The results of both surveys were published by FEMA and provided to FDA.

The most recent poundage data (Gavin et al., 2008) show that volumes of many single chemically defined flavoring substances were modestly increased when compared to the 1995 data (Lucas et al., 1999). This is consistent with the reported gradual increases in overall flavor manufacturing company sales volumes. The flavor manufacturing industry typically shows year-to-year growth in sales volume in the range of 3–5% annually. As the flavor industry develops new flavor ingredients to meet consumer demands, there will always be a delay between when the flavor industry develops and markets new flavor ingredients and when actual poundage data become available through surveys. Depending on the type of flavor ingredient, it takes some time before the market acceptance of a flavor ingredient is evident and reflected in poundage survey data.

Poundage data are used for several important purposes within the FEMA GRAS assessment program. Poundage data from the most recent survey are compared with data from past surveys to identify trends in the use of flavor ingredients. For example, data from the 2005 survey may suggest that a particular flavor ingredient has experienced an increase in use. If the increase is of a significant magnitude (e.g. >100%) then it will be reviewed to assess whether the increase may result in a significant increase in exposure. A substance with a significant annual volume and >100% increase in poundage may result in a potential increase in exposure if it is used in food categories with significant consumption. On the other hand, an increase in poundage of this magnitude may not result in a significant increase in exposure if it is broadly distributed among foods with small portion sizes that are infrequently consumed. Possible significant increases in exposure may warrant a reassessment of GRAS status by the FEMA Expert Panel.

As explained in the next section, one of the most important uses of poundage data is to facilitate a reliable, conservative estimate of exposure through application of the maximized survey-derived daily intake (MSDI) method.

4.3.2. Intake estimates for flavoring substances

Reliable estimates of the intake of flavor ingredients are of critical importance to the safety assessment of the approximately 2700 FEMA GRAS flavor ingredients added to foods. Several methods for estimating the intake of flavor ingredients have been evaluated and considered over the years but one, the maximized survey-derived daily intake (MSDI) method, is generally most appropriate for flavoring substances.

The MSDI method, also known as the "per capita $\times$ 10" (PCIx10) method, has been used for many years as an integral part of flavor safety assessment (JECFA, 1996; Smith et al., 2005; Young et al., 2006). While other methods have been evaluated, they are more resource intensive and most often do not provide significant improvement compared to the MSDI method (Hall and Ford, 1999; Lambe et al., 2002; Young et al., 2006).

Methods to determine estimates of intake are based on information derived from various types of surveys. For example, the MSDI method relies on estimates of the amounts ("poundage") of flavor ingredients sold into the food manufacturing market each year ("disappearance" data). Poundage data are available from flavor manufacturers at relatively modest expense and have been collected regularly by government agencies and the flavor industry as described earlier in this report (Lucas et al., 1999; Gavin et al., 2008).

Unlike the MSDI method, other methods of estimating intake, such as the detailed dietary analysis method (DDA) and the flavorings stochastic model (FSM) rely on information that is far more difficult and expensive to obtain – accurate information on the amounts of flavoring substances added to foods and then consumed (Hall and Ford, 1999; Lambe et al., 2002). This information, often referred to erroneously as "use level" information, is then used together with information on the amount of certain types of foods that people consume.

Accurate, quantitative information on the levels of flavoring substances present in foods as consumed is extremely difficult and expensive to collect. Accurate information on levels of flavors added to foods is generally not known by flavor manufacturers – this information is held by their customers, the food manufacturers, who consider such information to be closely guarded trade secrets. Generally, only the estimates of use levels from the FEMA GRAS assessment process are available. After being added to foods, usually within a compounded flavor or a natural flavor complex, individual single chemically defined flavoring substances are most often present at exceedingly low ppm levels intended to result in the presence of these substances in foods at levels similar to the levels found naturally in foods.

Information on levels of flavoring substances added to foods does not necessarily correlate with levels in foods as consumed. Most flavoring substances are volatile and food processing techniques, most importantly heat processing, result in substantial loss of added flavor ingredients (Young et al., 2006). This loss to volatilization is taken into account by the flavorist when the amounts of flavoring substances to be included in the compounded flavor are determined. In instances involving heat processing, loss to volatilization can be substantial and may reach as much as 80% for some volatile flavoring substances (Young et al., 2006). For example, an optimum concentration for flavor perception by a consumer may be 5 ppm in baked goods, but perhaps 50 ppm must be added to the food before heating to result in the 5 ppm concentration because most of the flavoring substance is lost during baking. Furthermore, due to the sensitivity of human taste perception, many flavoring substances are self-limiting meaning that including more of a flavoring substance in a food does not make the food taste better and may adversely affect taste.

The typical, low concentrations of single chemically defined flavoring substances in foods alleviate concerns related to possible over-exposure. This is especially true in light of the demonstrated low order of toxicity of the vast majority of flavoring substances and their metabolic products which are most often innocuous, simple chemical substances that are commonly found in food naturally and often are endogenous in humans. While any method to estimate exposure should be appropriately conservative, the characteristics of the vast majority of single chemically defined flavoring substances (e.g. simple, innocuous structures; very low concentrations in food; appropriate safety data; extensive safety reviews) demonstrate that excessive conservatism is not warranted.

It was suggested that the theoretical added maximum daily intake (TAMDI) method would yield a more appropriately conservative intake estimate (Arcella and Leclercq, 2005). Cadby compared the MSDI and TAMDI methods and concluded that the MSDI method was best suited for flavoring substances as a "conservative and practical method of estimating exposure" (Cadby, 2004) and that the TAMDI method may in fact generate significant over-estimates of flavoring substances in many instances (Cadby, 1996).

Young et al. (2006) reviewed the primary alternatives to the MSDI method including the possible average daily intake (PADI) method, the theoretical added maximum daily intake (TAMDI), the modified theoretical added maximum daily intake (mTAMDI) methods, and the flavorings stochastic model (FSM) and concluded that the MSDI method is "a conservative yet practical method to estimate the intake of flavoring substances."

In 1995, when the Joint FAO/WHO Expert Committee on Food Additives (JECFA) initiated its current program to evaluate the safety of single chemically defined flavoring substances, JECFA concluded that the MSDI method would be used to estimate the intake of flavoring substances (JECFA, 1996, 1997). In 2007, JECFA evaluated an additional intake estimation method, the "single portion exposure technique" (SPET) as a possible complement to the MSDI method for estimating the intake of flavoring substances (JECFA, 2007). SPET requires the availability of specific use level information for specific foods, information which, as explained previously, is rarely readily available. SPET facilitates an estimate of exposure for a regular consumer of a specific food that contains the flavoring substance of interest. To evaluate the utility of SPET, in 2007 JECFA compared exposure estimates for 57 flavoring substances using SPET and the MSDI methods. JECFA concluded that SPET and the MSDI method provide different and complementary information in that SPET may provide information about exposure to a flavoring substance for a regular daily consumer of a specific food product containing that flavoring substance while MSDI provides a daily exposure estimate for an average consumer (JECFA, 2007).

During its 2008 meeting, JECFA went further in its evaluation of SPET evaluating additional flavoring substances using MSDI and SPET in the context of their threshold of toxicological concern (JECFA, 2008). JECFA concluded,

> The Committee noted that MSDI and SPET estimates of dietary exposure provide different and complementary information. Use of the SPET estimate addresses previous concerns expressed by the Committee about the dietary exposure methodology used in the (safety evaluation) Procedure, because the SPET estimates take account of the possible uneven distribution of dietary exposures to a flavoring agent for consumers of foods containing that substance. The higher value of the two dietary exposure estimates (MSDI or SPET) should be used within the Procedure (JECFA, 2008).

JECFA determined that all future evaluations of flavoring substances would include intake assessments using both MSDI and SPET with the higher value employed in the safety assessment procedure. JECFA also determined that "it would not be necessary to re-evaluate flavoring agents (applying SPET) that have already been assessed using the Procedure" (JECFA, 2008). Until more experience is gained in comparing MSDI and SPET, it remains unclear whether the use of SPET in evaluating flavoring substances will be worthwhile given the likely difficulty and increased expense associated with obtaining the accurate use level information required for SPET. A previous comparison of DDA and MSDI suggests that the use of SPET may not result in significant differences in results compared to MSDI (Hall and Ford, 1999).

Analyses comparing various methods of estimating intake of flavoring substances have repeatedly demonstrated that estimates of intake using the MSDI method are appropriately conservative when compared to the DDA, FSM, PADI, TAMDI and mTAMDI methods (Hall and Ford, 1999; Lambe et al., 2002; Smith et al., 2005; Young et al., 2006). In certain instances involving, for example, atypical highly focused consumption patterns, the use of methods other than MSDI may be warranted. We suggest that because of its reliably conservative results, ease of use, and low resource requirements the MSDI method remains the intake estimation method best suited for general use for flavoring substances.

4.3.3. The interpretation of genotoxicity assays and their relevance to flavor ingredient safety evaluation

The interpretation of genotoxicity assay results has long presented significant questions in the safety evaluation of food constituents (O'Brien et al., 2006; Pottenger et al., 2007). Flavoring substances are typically present in very low levels in foods, often at ppm levels, and the use of genotoxicity data must be carefully evaluated to avoid the assignment of a higher level of risk than the totality of the data would indicate.

The FEMA Expert Panel conducted a review of the appropriate interpretation of genotoxicity assays and summarized their conclusions in their most recent report describing their criteria for

the safety evaluation of single chemically defined flavoring substances (Smith et al., 2005). The Panel concluded that genotoxicity data will remain a part of their evaluation procedure but that it is important to evaluate the relevance of the data in the context of other data more closely related to actual human exposure (Smith et al., 2005). The Panel's conclusion is consistent with the conclusions of a special conference organized to review and evaluate the issues associated with substances that are both genotoxic and carcinogenic (Barlow et al., 2006). The results of the application of the FEMA Expert Panel's approach to the appropriate interpretation of genotoxicity assays is exemplified by the Panel's evaluation of a group of α,β-unsaturated aldehydes and related substances used as flavor ingredients (Adams et al., 2008).

4.3.4. New flavor ingredient technologies

The majority of single chemically defined flavoring substances are, with a small number of exceptions, innocuous, simple chemical substances that are found naturally in food and that are present in food from natural occurrence at levels well in excess of the amounts present through added flavors (Stofberg and Kirschman, 1985).

In the late 1990s it was thought that the application of some of the recently developed biotechnology production processes would become important in the production of flavoring substances. A paradigm for the safety assessment of flavoring substances produced through the use of genetically modified organisms was developed (Hallagan and Hall, 1995a) but has so far been used only once, for the evaluation of the flavor ingredient recombinant thaumatin (Smith et al., 1996). A paradigm for the safety assessment of flavor ingredients derived from plant cell and tissue culture has also been developed (Hallagan et al., 1999) but has not been employed. Flavor manufacturers have generally found that these new production methods are not cost effective and that there remains significant uncertainty whether the end product (i.e. the flavor ingredient) would qualify as "natural" under FDA's definition of natural flavor[13] thereby limiting the value of flavor ingredients produced by these means.

The flavor industry began to explore single chemically defined flavoring substances during the late 1990s that were novel structures not found in nature, some of which were specifically designed to interact with certain taste receptors. While the biological mechanisms involved in these materials are clearly not novel, the materials are and they therefore receive particular attention during GRAS assessment evaluations. The Expert Panel have applied their criteria for single chemically defined flavoring substances (Smith et al., 2005) to these novel substances with the review of supplemental data as necessary in the application of their scientific judgment. Flavoring substances with novel structures recently determined to be FEMA GRAS include 2-isopropyl-N,2,3-trimethyl-butyramide (WS-23), a cooling agent (Smith et al., 1996) and N-(heptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide, a flavor modifier (Smith et al., 2005a).

4.4. "Under the conditions of intended use" in food

Section 201(s) of the FFDCA states that a substance that may be generally recognized as safe, and therefore not be classified as a "food additive" under the statute, must be shown to be safe "under *the* conditions of intended use" in food by experts qualified to "evaluate *its* safety." (Emphasis added). For flavor ingredients, this means use only in food as defined by the statute. FFDCA Sec. 201(f) states, "The term 'food' means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article." Use in consumer products, tobacco and other items is therefore not covered by FEMA GRAS status.

There is little in the legislative history for the Food Additives Amendment that indicates Congress' intent but the specificity of language chosen by Congress (namely "the conditions" and "its safety") suggests the intent to limit the authority to consider food ingredients GRAS to specific uses for each substance. In other words, it is only the specified use of a given substance that is GRAS and not the substance itself. This policy has long been reflected in FDA's regulation of flavor ingredients.

There are several hundred single chemically defined flavoring substances and natural flavor complexes that are considered GRAS by FDA for use as flavoring substances (21 CFR Parts182 and 184) and several hundred others are listed by FDA as approved food additives (21 CFR Part 172). A key aspect of the regulation of all of these substances is that FDA specifies that the regulated use, whether a GRAS substance or a food additive, is as a flavoring substance. For all of these flavoring substances, FDA imposes the requirement that they be used in amounts consistent with good manufacturing practice. For example, for natural and synthetic flavoring substances regulated as food additives, FDA states that, "They are used in the minimum quantity required to produce their intended physical or technical effect and in accordance with all the principles of good manufacturing practice."[14] FDA has defined "good manufacturing practice" to mean that:

> (1) The quantity of a substance added to food does not exceed the amount reasonably required to accomplish its intended physical, nutritional, or other technical effect in food; ... (3) The substance is of appropriate food grade and is prepared and handled as a food ingredient.[15]

The first FEMA GRAS determinations were published in 1965 based in part on a survey of the flavor and food industries initiated in 1959 on flavor ingredients in use shortly after the enactment of the Food Additives Amendments of 1958. The survey collected information on use categories and estimated average use levels in food for flavoring substances then in use. The first FEMA GRAS publication announced an initial list of flavor ingredients considered to be GRAS and explained the significance of the use and use level information reported.

> The figures (uses and use levels) presented and discussed in this report are not tolerances. The word 'tolerance' means a level within the safe range established by scientific procedures but no greater than necessary to achieve the desired effect, and hence above which the substance may not legally be used. In contrast, the figures cited here are averages to which certain flexible principles must be applied. It is the opinion of the Expert Panel that, except where specifically noted, it is neither necessary nor practical to establish tolerances or rigid use limits for the flavoring substances covered by this report. It is clear that the fact that a flavor ingredient may have been reported as used only in certain food categories does not necessarily preclude its use as a substance generally recognized as safe in other categories within the principles stated above (i.e. good manufacturing practice) (Hall and Oser, 1965).

Following the publication of the initial "FEMA GRAS list" in 1965 (Hall and Oser, 1965), FEMA implemented the requirement that applications for FEMA GRAS status for flavoring substances should include descriptions of proposed uses in specific food categories, and estimated average use levels in those categories,

[13] 21 CFR 101.22(a)(3). Also see Hallagan (2004).

[14] 21 CFR 172.510, 172.515.

[15] 21 CFR 182.1(b).

to allow the evaluation of the conditions of intended use as flavoring substances.

The general categories of uses evaluated by the FEMA Expert Panel have been consistent with the categories developed by the National Academy of Sciences (NAS) during the initial surveys of food ingredients conducted by NAS in the early 1960s after enactment of the Food Additives Amendments of 1958. These categories were adopted by FDA in its regulations on food additives and GRAS substances where forty-three categories of foods are listed.[16]

Information on proposed use categories and estimated average use levels in food allows an evaluation of whether the proposed conditions of intended use are consistent with use as a flavoring substance and not indicative of uses to achieve other technical effects in food such as a sweetening effect. This information is provided by the manufacturer/applicant and is published in the FEMA GRAS publications in the journal *Food Technology*. In the case of flavor ingredients determined to be GRAS by the Expert Panel prior to the 1980s, use categories are also published in the FEMA Scientific Literature Reviews available from the US National Technical Information Service. As discussed earlier in this report, use and use level information is not used to develop intake estimates.

After the food manufacturing industry had used the GRAS authority provided by the 1958 Food Additives Amendments for some time, FDA suggested that perhaps the industry had begun to view the requirements for GRAS status in a more liberal manner than intended by Congress, and desired by FDA. FDA expressed concern on this issue in 1974 when the agency stated:

> It has been too often assumed that the GRAS substance may be used in any food, at any level for any purpose. As a result, the uses of some food ingredients have proliferated to the point where the GRAS status was brought into serious question.[17]

The FEMA Expert Panel addressed this issue in 1979 and noted that while it would be highly likely that uses and use levels different from those evaluated by the Expert Panel in an initial GRAS assessment would still fall within "good manufacturing practice" as defined by FDA, "... increases in use levels or proposed new uses should be evaluated to insure continued GRAS status" for use as a flavor ingredient, and summarized its position by stating "... that increased use levels of a GRAS substance or uses in different food categories would still be considered GRAS as long as they do not enhance significantly its overall dietary intake" (Oser and Ford, 1979). This concept was reiterated (Oser et al., 1984) and expanded upon in 1993 when the Expert Panel stated that the

> ...use levels are not intended to be either rigid limits or the highest acceptable (safe) exposures. Rather, they reflect only the proposed uses in the application for GRAS determination and therefore are better viewed as good manufacturing practice (GMP) guidelines. They are, however, the levels of use reviewed by the Panel in their consideration of GRAS status and any other uses resulting in significantly higher exposure should be carefully evaluated to ensure that they still meet the criteria of GRAS (for use as a flavoring substance) (Smith and Ford, 1993).

Since 1996, letters issued by FEMA to successful applicants for FEMA GRAS status have stated, "Significant changes in use levels within an approved category, or use in new food categories, require a reevaluation of this material by the Expert Panel" to assure that the conditions of intended use remain consistent with use as a flavoring substance.

Therefore, both FDA and FEMA require that if a specific use of a substance (e.g. as a flavoring substance) has not been evaluated for GRAS status then that substance is not GRAS for use as a flavoring substance even if the substance is considered GRAS for other uses (e.g. as an emulsifier or preservative for general use in food). FDA reiterated this policy in the preamble to its 1997 voluntary GRAS notification program proposal.

> Importantly, under section 201(s) of the act, it is the use of a substance, rather than the substance itself, that is eligible for the GRAS exemption.[18] (Emphasis added).

4.4.1. Self-limiting flavoring substances

The amounts of flavoring substances added to foods often reflect the fact that many flavoring substances are "self-limiting." As noted by FDA,

> If a substance is added to food above its technologically self-limiting level, the food becomes unpalatable, unappealing or otherwise unfit for consumption....For example, it is generally known that the taste associated with many GRAS synthetic flavoring substances limits the levels at which the flavoring substances can be used to levels below those known to exhibit toxic properties.[19]

Many flavoring substances are self-limiting in their use in food – more does not taste better and the levels of such flavoring substances are kept to the minimum needed to achieve the desired flavor effect consistent with FDA's policy on good manufacturing practices. For example, sulphur-containing flavoring substances such as allyl mercaptan are commonly self-limiting at parts per billion levels. However, other classes of flavoring substances, and some individual flavoring substances within certain chemical classes, are less self-limiting and attention must be paid to assure that safe levels are not exceeded. For example, some of the new flavoring substances that provide a "cooling" effect in certain foods do not exhibit clear self-limiting properties and in these relatively rare instances, more can taste better. The Expert Panel therefore pays careful attention to such structural classes such as the amides, which contain many of the new cooling agents.

4.4.2. Volatility of flavoring substances

As noted previously, significant loss occurs often during the manufacture of foods containing added flavors (Young et al., 2006), and also during the manufacture of the flavor mixture itself. Therefore, even if a flavor formula calls for a flavoring substance to be added to the compounded flavor at a level approaching 1.0% that compounded flavor will typically be incorporated into food at a level of less than 1.0%, thus reducing the level of that individual flavoring substance in the food to less than 0.01% even before any inevitable losses from processing. As can be readily seen from reviewing the usual and maximum use levels for flavoring substances, they are rarely incorporated into foods at levels exceeding a few hundred parts per million. After incorporation into food, loss during processing occurs, often significant, from volatilization. Most flavoring substances are quite volatile, and must be so to enable perception by humans.

The fact that nearly all flavoring substances are at least somewhat volatile (otherwise they would not be perceived) raises the issue of whether potential inhalation exposure through food preparation or manufacture should be part of a safety assessment for the food use of a flavoring substance. This has not been the case in the safety assessment of flavoring substances or any other food ingredients or foods. The FDA "Red Book" (FDA, 2007) does not call for an evaluation of potential inhalation exposure for any food

[16] 21 CFR Sec. 170.3(n).
[17] 39 *Fed. Reg.* 34194. 23 September 1974.
[18] 62 *Fed. Reg.* at 18939.
[19] 62 *Fed. Reg.* at 18948.

ingredients and an evaluation of potential inhalation exposure is not required by JECFA (1996) or any other food safety evaluation body. The Expert Panel's review of the GRAS status of flavor ingredients accounts only for the safety of flavor ingredients under their conditions of intended use when they are ingested as constituents of food. Should food preparation be included within the conditions of intended use of a food ingredient? This question remains to be answered.

The use of volatile flavoring substances to manufacture flavors and foods presents important workplace safety issues (FEMA, 2004). However, the FEMA Expert Panel does not evaluate the safety of flavor ingredients in the flavor or food manufacturing workplaces. Workplace exposures differ significantly, both quantitatively and qualitatively, from exposure through food consumption. Workplace exposures to flavor ingredients can occur at relatively high concentrations in both flavor and food manufacturing and through completely different routes of exposure including dermal and inhalation exposure when compared to exposure by ingestion, the route of exposure evaluated by the Expert Panel. Furthermore, workplace exposures are regulated under separate legal and regulatory authority by agencies not involved in food regulation (e.g. the Occupational Safety and Health Administration in the US Department of Labor).

5. Significant developments in the global safety assessment and regulation of flavor ingredients

Major global and regional safety evaluation programs were initiated in the mid-1990s including the flavoring substance safety evaluation programs initiated by the European Union through its European Food Safety Authority (EFSA) and the FAO/WHO Joint Expert Committee on Food Additives (JECFA). A key aspect of these two programs is that they represent a significant degree of concurrence with the FEMA GRAS program in their safety assessment methodologies (Munro et al., 1998). The E.U., JECFA and FEMA programs represent major progress towards a globally accepted method for the safety assessment of flavoring substances. As with the FEMA program, both the E.U. and JECFA programs review single chemically defined flavoring substances as members of groups of structurally-related substances and focus on the importance of metabolic fate to facilitate an effective and resource-efficient safety review. Like the FEMA program, both programs also use the MSDI method of intake assessment although JECFA will begin using the SPET method in future evaluations of flavoring substances (JECFA, 2008). Also, since 2004 EFSA has employed the mTAMDI method of intake assessment to complement the MSDI method to address the concern that "the MSDI model may underestimate the intake of flavoring substances by certain groups of consumers" (EFSA, 2004).

Beginning in 1996, JECFA implemented a comprehensive safety assessment program for single chemically defined flavoring substances (JECFA, 1996) that is consistent with the principles of safety assessment employed by the FEMA Expert Panel. The goal of the JECFA program is to create an open positive list of flavor ingredients that could be used by the Codex Alimentarius Commission in the development of global food standards pursuant to the World Trade Organization Treaties. So far, more than 1700 single chemically defined flavoring substances have been evaluated by JECFA within structurally-related groups and found to "pose no safety concerns at current levels of intake." JECFA is turning its attention to natural flavor complexes using a safety assessment scheme (JECFA, 2004) consistent with the methods employed by the FEMA Expert Panel (Smith et al., 2004).

The European Union program is being conducted by the European Food Safety Authority (EFSA) and was initiated in the late 1990s with a survey of flavoring substances in use in the European Union much as the effort was begun in the United States in 1959 with the first FEMA survey. An inventory of more than 2800 single chemically defined flavoring substances has been compiled as flavoring substances in use in E.U. member states and will eventually be evaluated by EFSA within 34 structurally-related groups. While this effort has experienced significant delays it may be completed within the next few years.

6. The future of the GRAS concept and the FEMA GRAS program

The GRAS concept is a uniquely American regulatory program. Behind the GRAS concept is a fundamental decision by the US Congress that certain food ingredients may be assigned a lower priority for oversight by FDA. FDA summarized this policy decision in 1992 stating,

> ...Congress recognized that many substances intentionally added to food do not require a formal premarket review by FDA to assure their safety... FDA has traditionally encouraged producers of new food ingredients to consult with FDA when there is a question about an ingredient's regulatory status, and firms routinely do so, even though such consultation is not legally required. If the producer begins to market the ingredient based on the producer's independent determination that the substance is GRAS and FDA subsequently concludes that the substance is not GRAS, the agency can and will take enforcement action to stop distribution of the ingredient and foods containing it on the ground that such foods are or contain an unlawful food additive.[20]

The lack of a legal requirement for FDA oversight of all GRAS determinations is one of the primary, long-standing criticisms of the GRAS concept. While FEMA has sought, and received, FDA oversight of GRAS determinations of flavor ingredients made by the FEMA Expert Panel, GRAS determinations of other types of food ingredients have not always been reported to FDA. Critics of the GRAS concept have cited this as a case of "the fox guarding the chicken coop" (Wenner, 2008). However, the same critics have also acknowledged that with respect to flavors, "flavorings typically have been innocuous chemicals used in small amounts and there is no history of safety problems" (Wenner, 2008).

One opportunity to strengthen the GRAS concept in general is to require that all GRAS determinations be reported to FDA – such a proposal was discussed in Congress in 2008 and may be further explored in the future. Accompanying such a reporting requirement may also be a requirement that all data supporting a GRAS determination be published, or if unpublished, be provided to FDA. It is also important to increase the availability of information related to GRAS food and flavor ingredients. While much information on flavor ingredients is provided to FDA through the FEMA GRAS program, there may not be a sufficient level of knowledge on the part of the public on why they should be fully confident in the safety of the added flavors in their foods. FEMA has implemented various efforts to share information through its website (www.femaflavor.org) and through conventional publications.

Even though the GRAS concept and therefore the FEMA GRAS program are uniquely American, the science behind the FEMA program is not. It will remain important for the FEMA program to continue the type of sophisticated investigations that have facilitated our understanding of the mechanisms of action of a number of flavoring substances such as anethole, furanone derivatives, and the p-allylalkoxybenzene derivatives estagole and methyleugenol (Smith et al., 2005). The FEMA Expert Panel's use

[20] 57 *Fed. Reg.* 22984. 29 May 1992.

of structure–activity relationships, metabolic data, and exposure assessments have become fundamental parts of the flavor safety assessment programs of JECFA, EFSA and others. The acceptance of these safety assessment principles by other evaluative bodies lends much credibility to the FEMA GRAS program and suggests that the program will continue to have the opportunity to maintain its leadership position in flavor safety assessment.

Conflict of interest statement

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