

# FEMA GRAS—A GRAS Assessment Program for Flavor Ingredients

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**The generally recognized as safe (GRAS) assessment program of the Flavor and Extract Manufacturers Association (FEMA) of the United States was initiated in 1959 to provide for the assessment of flavor ingredients as GRAS under the Food Additives Amendment to the U.S. Federal Food, Drug, and Cosmetic Act. FEMA sponsored the formation of an independent panel of experts to perform GRAS assessments and to provide their conclusions to the U.S. Food and Drug Administration, the food and flavor industries, and the public. The program was designed to account for the legal, regulatory, and scientific issues associated with GRAS assessments and has continued to incorporate changes in the law and in science. This review describes the legal and scientific foundation of the FEMA program. © 1995**

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## INTRODUCTION

Congress enacted the Food Additives Amendment (FAA)<sup>1</sup> in 1958 against a background of concern over the safety of substances added to foods to perform various functions. The FAA sharply increased and shifted the responsibilities for ensuring the safety of food ingredients. It placed squarely on industry the burden of demonstrating safety and established a new requirement for premarket approval of food additives as defined in the FAA. When functioning well, the new arrangements created a partnership between the FDA and industry to ensure the safety of food ingredients.

In the years since the enactment of the FAA, the concept of government/industry partnership has been embraced by the Flavor and Extract Manufacturers Association of the United States (FEMA) in its efforts to ensure the safety of the multitude of individual ingredients which are combined to create flavors for addition to food. The mechanism for the operation of the partnership between FDA and FEMA has been the safety assessment program known as "FEMA GRAS."

<sup>1</sup> Pub. L. No. 85-929, 72 Stat. 1784 (1958). Codified at 21 U.S.C. Sec. 348 (1988).

## THE GRAS CONCEPT AND FEMA GRAS

The centerpiece of the FAA is its definition of food additive and an exclusion specifically provided by Congress for substances "generally recognized to be safe," which is commonly known as "generally recognized as safe" (GRAS).<sup>2</sup>

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 its intended use. . . .<sup>3</sup>

The definition removes GRAS substances from consideration as food additives, thereby explicitly excluding them from mandatory premarket approval by FDA and therefore permitting the agency to conserve its limited resources. However, the exclusion comes at a price; GRAS substances must meet a series of strict criteria specified by Congress.<sup>4</sup>

The statutory definition of GRAS has four key criteria, the third of which is stated in the alternative:

1. There must be general recognition of safety by qualified experts.
2. The experts must be qualified by scientific training and experience to evaluate the substance's safety.
3. The experts must base their determination of safety on scientific procedures or, for substances used in food prior to 1958 only, on scientific procedures or on experience based on common use in food.
4. The determination of general recognition of safety must take full account of the conditions of the substance's intended use.

<sup>2</sup> "Prior-sanctioned" food ingredients, pesticides, and color additives were also excluded from the definition of food additive. 21 U.S.C. Sec. 321(s) (1988).

<sup>3</sup> 21 U.S.C. Sec. 321(s) (1988).

<sup>4</sup> The legislative history of the FAA and the GRAS concept are thoroughly described by Degnan (1991).

Each of these four elements has been examined and elucidated over the years through FDA policy statements and explanations, agency enforcement actions, and the observations and expositions of numerous commentators who have examined the legislative history of the FAA and the subsequent case law.<sup>5</sup>

The FAA created the obvious and significant problem of what should be done about the multitude of food ingredients already consumed in foods as of 1958. Congress provided a transitional period and FDA tried to solve the problem by creating lists of approved food additives and GRAS substances.<sup>6</sup> While cooperating with FDA, FEMA also implemented an innovative, independent approach based on the exclusion for GRAS substances provided in the definition of food additive. FEMA appointed a panel of experts, from outside of the industry, to determine whether each flavor ingredient was GRAS under specified conditions of intended use and therefore safe for addition to food.

The FEMA approach was driven by the characteristics of flavors themselves. Flavors are complex mixtures typically containing various amounts of many individual ingredients which are critical to the flavoring effect but most of which are present in the flavor in small amounts and are present in the finished food in even smaller amounts such as parts per million, parts per billion, or even parts per trillion. Both FDA and FEMA realized that a premarket approval process for each individual flavor ingredient, many of which occur naturally and widely in food at low levels, would not be a wise use of scarce agency resources. This would particularly be true if the approval process was similar to the process used for major food ingredients because it would be highly unlikely that any particular flavor ingredient would be unsafe when consumed as part of food in the intended manner.

The FEMA program began in 1959 with an industry survey to identify flavor ingredients currently in use and to provide estimates of the amounts used by the flavor industry. The first FEMA Expert Panel was appointed

in 1960.<sup>7</sup> Substances that were identified as "in use" by the survey were evaluated for GRAS status by the Panel whose conclusions were then presented to FDA prior to publication.<sup>8</sup> Once the Panel completed the backlog of flavor ingredients in use, they began to evaluate new substances. The first report to include new flavor ingredients was published in 1970 (Hall and Oser, 1970).

A few natural flavors are composed virtually entirely of a single substance, e.g., benzaldehyde in oil of bitter almond. Most, however, are complex and present the difficulties in safety evaluation common to complex mixtures. The Expert Panel has dealt with these natural flavors on the basis of the adequacy of knowledge of their composition, the risks of their biologically active components, and the margins of safety involved in their long-established and common use in food.

The GRAS assessment system employed by the FEMA Expert Panel incorporates state-of-the-art evaluations that have grown and progressed with advancements in science (Gerarde, 1973; Oser and Hall, 1977; Woods and Doull, 1991). A critical part of the FEMA program has been the publication of the Panel's decisions. Not only are the GRAS lists published, but also the scientific information on which the Panel's decisions are based is published in the FEMA Scientific Literature Reviews (SLRs).

The SLRs contain a compilation of data on each GRAS flavor ingredient and an explanation of the Panel's reasons for determining GRAS status. The original SLRs were prepared by FEMA under a contract with FDA and are available for public purchase through the National Technical Information Service (NTIS). Each time a new GRAS list is published, the appropriate SLR volumes are supplemented with relevant information on the new GRAS flavor ingredients and are provided to FDA.

The legislative history of the FAA does not directly address the issue of who can decide whether a substance is GRAS but it is apparent by the construction of the definition of food additive that Congress intended that the private sector have the right to make GRAS determinations. In a 1988 final rule amending the regulations governing the eligibility of substances as GRAS, FDA acknowledged that "persons have the right to make independent GRAS determinations."<sup>9</sup> For over 30 years

<sup>5</sup> See, e.g., Degnan (Note 4); Goodrich, W. (1960). Safe food additives and additives generally recognized as safe, there is a difference. *Food Drug Cosmet. Law J.* 15, 625; Kaplan, A. (1972). Safety and GRAS status or has the GRAS list gone to pot? *Food Drug Cosmet. Law J.* 27, 98; Middlekauff, R. (1975). Food safety review—New concepts for GRAS. *Food Drug Cosmet. Law J.* 30, 288; Lin, L. (1991). Interpretation of GRAS criteria. *Food Drug Cosmet. Law J.* 46, 877-884.

<sup>6</sup> Because of the large number of substances in use, FDA was able to resolve the regulatory status of only some flavor ingredients. The first FEMA GRAS publication was later incorporated into FDA's regulations. This created a substantial overlap of substances that are FEMA GRAS- and FDA-approved food additives or FDA GRAS substances. FDA provides for the use of 856 natural and synthetic flavor ingredients as approved food additives. 21 CFR Secs. 172.510 and 172.515. The agency also provides for the use of 253 GRAS natural flavors, essential oils and extracts (21 CFR Sec. 182.10, 182.20, 482.40, and 182.50), and 21 synthetic flavoring substances. 21 CFR Sec. 182.60. Hundreds of additional flavor ingredients are FEMA GRAS.

<sup>7</sup> The history and operation of the panel was described by Oser and Ford (1991).

<sup>8</sup> The Panel's early conclusions were published in *Food Chemical News* in 1961. In 1965, with the publication of "GRAS 3," FEMA began the tradition of publishing the Panel's conclusions in *Food Technology* so that the information would be published in a journal which is widely read by the food industry. The most recent GRAS list, "GRAS 16," was published in June 1993 (*Food Technol.* 47(6), 104-117).

<sup>9</sup> *Fed. Regist.* 53, 16,544 (10 May 1988). In the proposed rule which resulted in this final rule FDA stated that "persons are free to make their own determinations about whether a substance is GRAS." *Fed. Regist.* 50, 27294 (2 July 1985). In a recent report produced for Rep.

FDA has left many private GRAS determinations unchallenged while challenging others that the agency did not find acceptable. This issue has been explored by Degnan (1991) and others who concluded that private GRAS determinations are permitted.<sup>10</sup>

In its 1992 policy statement on food biotechnology, FDA explicitly acknowledged that the private determination of GRAS status for food ingredients is a valid approach.<sup>11</sup> 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 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 grounds that such foods are or contain an unlawful food additive.

With respect to FEMA, FDA has directly acknowledged the validity of the FEMA GRAS program. FDA recognized the FEMA GRAS publications as "reliable industry GRAS lists" within the context of the agency's bulk labeling regulations for flavors codified at 21 C.F.R. Sec. 101.22(b) (1994). In 1979, FDA stated,

In . . . 1976 . . . the FDA recognized as reliable industry GRAS lists the FEMA GRAS Lists III and 4 through 9, which were published in *Food Technology* . . . FDA also recognized as reliable industry association GRAS lists the FEMA GRAS Lists Nos. 10 and 11 which were published in *Food Technology*. . .<sup>12</sup>

With respect to the FDA/FEMA cooperative effort regarding the safety assessment of flavor ingredients, and the related bulk flavor labeling regulation, FDA described FEMA's participation in the procedure and stated, ". . . reliance upon a reliable published industry association GRAS list in lieu of specific declaration of (flavor) ingredients, may apply to new flavor ingredients if such ingredient is published in a future FEMA GRAS

list and the respective Scientific Literature Review. . . ."<sup>13</sup>

By recognizing the FEMA GRAS lists, FDA has permitted flavor manufacturers to label bulk flavors constituting two or more ingredients by either declaring each ingredient or by stating, "All flavor ingredients contained in this product are approved for use in a regulation of the Food and Drug Administration."<sup>14</sup> While FDA has not completed the safety assessment and regulation of all flavor ingredients under the process begun in the 1960s, it continues to incorporate information provided by FEMA in its flavor database under the procedure established in 1976 for bulk labeling.

#### ELEMENTS OF THE FEMA GRAS ASSESSMENT PROGRAM

The FEMA GRAS program was designed to account for the description of GRAS status in the definition of food additive which states that a substance is excluded from food additive status and therefore exempt from the requirement that FDA grant premarket approval, if it is:

. . . 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, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended uses. . . .<sup>15</sup>

The FEMA GRAS system was designed to follow the four key elements specified for substances generally recognized as safe.

##### 1. General Recognition of Safety

With respect to food additives and GRAS substances, FDA defines safe or safety to mean ". . . that there is a reasonable certainty in the views of competent scientists that the substance is not harmful under the intended conditions of use."<sup>16</sup> The agency also commented on the fact that absolute safety is an impossible concept.

It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered: (1) The probable con-

John Dingell, the General Accounting Office (GAO) concluded that private GRAS determinations do "not have to be submitted to FDA for its review and approval" and cited the FEMA program as an example of qualified experts who can make valid GRAS determinations. *Food Safety and Quality: Innovative Strategies May Be Needed to Regulate New Food Technologies*. GAO/RCED-93-142. GAO. 1993.

<sup>10</sup> See, e.g., Merrill, R., and Hutt, P. (1980). *Food Drug Law*, p. 68; Grisanti, E. (1971). Legal aspects of technical problems and chemical additives. *Food Drug Cosmet. Law J.* **26**, 588-592.

<sup>11</sup> *Fed. Regist.* **57**, 22984, 22989 (29 May 1992). FDA has applied its GRAS affirmation principles to its evaluation of the enzyme chymosin which now can be produced using genetically modified organisms. *Fed. Regist.* **55**, 10932 (23 March 1990—Chymosin from *E. coli*; *Fed. Regist.* **57**, 6476 (25 February 1992—Chymosin from *K. marxianus*); *Fed. Regist.* **58**, 27197 (7 May 1993—Chymosin from *A. niger*).

<sup>12</sup> *Fed. Regist.* **44**, 71460, 71481 (11 Dec. 1979). In this notice FDA announced the GRAS 12 publication and the inclusion of the listed flavor ingredients in its review of flavor ingredients.

<sup>13</sup> *Fed. Regist.* **41**, 4994 (3 Feb. 1976).

<sup>14</sup> 21 C.F.R. Sec. 101.22(g)(2) (1994). FDA has recognized the FEMA GRAS program in other ways. In a 1991 speech to the Scientific Committee for Food of the European Community, A. M. Rulis, Ph.D., FDA's Director of the Office of Premarket Approval, described the long-standing cooperation between FDA and FEMA. Rulis explained that ". . . the Food Additives Amendment did not specifically state that GRAS status should be determined solely by FDA, but rather by experts qualified by training and experience." Rulis noted the significant cooperation between FDA and FEMA and described ways in which FDA "publicly recognized" FEMA GRAS assessments.

<sup>15</sup> 21 U.S.C. Sec. 321(s) (1988).

<sup>16</sup> 21 C.F.R. Sec. 170.3(i) (1994).

sumption of the substance and of a substance formed in or on food because of its use. (2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet. (3) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.<sup>17</sup>

Whether a food ingredient is GRAS depends on general recognition of safety, not on safety per se.<sup>18</sup> GRAS status also depends on whether there is common understanding of a substance's safety. General recognition of safety "requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances . . . added to food."<sup>19</sup> In the preamble to its regulations on the criteria for GRAS status, FDA concluded that a "substance may not be determined to be GRAS when its characteristics are known only to a few experts."<sup>20</sup> FDA also stated that, "general recognition of safety requires not only the general availability of appropriate evidence on the substance but also general agreement on the interpretation of evidence. FDA believes that this general agreement can occur only when similarly qualified experts share an understanding of the concept of safety."<sup>21</sup>

To define general, one court cited Webster's New 20th Century Dictionary, Unabridged, 2d ed., and stated, "There is nothing in the statute to indicate the Congress intended 'generally recognized' in other than its commonly understood meaning . . . extensively, though not universally; most frequently, but not without exceptions. . . ."<sup>22</sup> In *Coli-Trol 80*, the Court concluded that, "what is required is not unanimous recognition but general recognition."<sup>23</sup> However, a few experts who insist the substance is not GRAS can defeat general recognition.<sup>24</sup>

FEMA approached the issue of general recognition of safety on several different levels. First, the Expert Panel has been composed of six to eight members, all of whom have achieved significant status in their fields of expertise. Over the years, the Panel has been composed of members with expertise in toxicology, pharmacology, chemistry, biochemistry and intermediary metabolism, medicine, and statistics (Oser and Ford, 1991). The size and diversity of the Panel lend support to its conclusions of general recognition of safety. Second, all Panel decisions must be unanimous so that there is no disagreement among the Panel as to the GRAS status of a

particular flavor ingredient. Third, all Panel determinations of GRAS status are published so that anyone who disagrees, and thereby contradicts the conclusion of general recognition, is provided the opportunity to do so. The Panel's conclusions are published in periodic GRAS publications in *Food Technology* and the information on which the Panel based its conclusions is published in the SLRs.<sup>25</sup> Most importantly, all of this information is provided to FDA so that the agency has the opportunity to challenge the GRAS status of flavor ingredients as determined by the FEMA Expert Panel.

Advances in the understanding of the mechanisms of toxicity and carcinogenicity have led many to conclude that in certain instances it is possible to establish a safe level of human exposure to a substance which may cause tumors in laboratory animals at the high doses usually employed in such studies. Fortunately, in recent years far more effort has been devoted to the study of the pharmacokinetics and metabolism of substances in test species. Frequently, this has facilitated a critical review of the relevance of high-dose studies to human exposure at far lower levels.

The classification of substances as GRAS that cause tumors in laboratory animals is an important issue. Congress included in the Food Additives Amendment language popularly known as the "Delaney Clause" which prohibits the inclusion in food of food additives "found to induce cancer" in man or animals.<sup>26</sup> It seems clear that if Congress had intended the Delaney Clause to apply to GRAS substances then it would not have fashioned so complete an exemption from the constraints of the definition of food additive. This issue was raised, but not decided, in the color additive *de minimis* case.<sup>27</sup> In comparing the separate Delaney Clauses for color additives and food additives, the Court noted that the GRAS exception may allow the classification as GRAS of carcinogenic substances that carry trivial risk and that are therefore safe for human consumption.<sup>28</sup> The Court noted that this result may appear inconsistent with the absolute prohibition of the food additive Delaney Clause, but this is not inconsistent with the unstated

<sup>17</sup> 21 C.F.R. Sec. 170.3(i) (1994).

<sup>18</sup> *U.S. vs An Article of Food—Food Science Laboratories, Inc.* 678 F. 2d, 735, 740 (7th Cir. 1982); *U.S. vs Article of Food and Drug—Coli-Trol 80*. 518 F. 2d 743, 745 (5th Cir. 1975).

<sup>19</sup> 21 C.F.R. 170.30(a) (1994).

<sup>20</sup> *Fed. Regist.* 41, 53600, (7 Dec. 1976).

<sup>21</sup> *Fed. Regist.* 50, 27294, 27,295 (2 July 1985).

<sup>22</sup> *U.S. vs Seven Cartons—Ferro-Lac*. 293 F. Supp. 660, 663 (S.D. III. 1968).

<sup>23</sup> 518 F. 2d at 746.

<sup>24</sup> *U.S. vs 41 Cases (Naremc)*. 420 F. 2d 1126, 1130 (5th Cir. 1970).

<sup>25</sup> In addition to the original FEMA GRAS publications in *Food Technology*, compilations of FEMA GRAS materials are widely available in various forms in publications such as *Flavor and Fragrance Materials* (1994). Allured Publishing. Carol Stream, IL; *Food Chemicals Codex* (1981). 3rd ed. National Academy Press, Washington, DC; *Fenaroli's Handbook of Flavor Ingredients* (1975). 2nd ed. CRC Press, Cleveland.

<sup>26</sup> 21 U.S.C. 349(c)(3)(A)(1988). For a review of the history of the Delaney Clause and its interpretation see Picut, C.A., and Parker, G.A. (1993). Interpreting the Delaney Clause in the 21st century. *Toxicol. Pathol.* 20, 617-627. Also see the accompanying critique. Flamm, W.G. (1993). Critique. *Toxicol. Pathol.* 20, 628-629.

<sup>27</sup> *Public Citizen vs Young*. 831 F. 2d 1108 (DC Cir. 1987).

<sup>28</sup> The definition of safe or safety does not call for absolute certainty, only "reasonable" certainty. 21 CFR Sec. 170.3(i) (1994). Reasonable certainty clearly may include trivial risks.

conclusion that there is general recognition that the risk is trivial.

Recent advances in the understanding of tumor development have been noted by the FEMA Expert Panel and in several cases have enabled the Panel to conclude that a substance that causes tumors in laboratory animals at high doses is nevertheless GRAS under conditions of intended use in human food because, for any of several reasons, the results from animal studies are not relevant to human safety. For example, *d*-limonene, a common flavor ingredient and natural constituent of more than 70 plant species, including citrus fruits, was determined to have clear evidence of carcinogenicity in male rats in a bioassay sponsored by the National Toxicology Program (NTP). The FEMA Expert Panel evaluated the available data on the mechanism of tumor development and found that the NTP results were irrelevant to human consumption of *d*-limonene and that the substance remained GRAS for use as a flavor ingredient (Burdock *et al.*, 1990).<sup>29</sup> The Expert Panel's conclusion is supported by recent advances in the understanding of renal toxicity and neoplasia in the male rat (USEPA, 1991).

## 2. Among Experts Qualified by Scientific Training and Experience to Evaluate Safety

FDA's regulations and policy statements do not define what an expert is, nor does the case law. Veterinarians, pathologists, food chemists, physicians, and toxicologists have all been recognized as experts in cases involving GRAS status. Courts seem to look at how expert the experts are.<sup>30</sup> When there are questions about which experts to believe, the courts tend to look at the basis for the expert's conclusion such as the scientific procedures or the common use in food.<sup>31</sup>

Experts may testify to general recognition of safety even if they are not qualified to judge the safety of a particular substance. For example, in *41 Cases (Naremc)*, FDA presented as experts several veterinarians who may not have been qualified to evaluate the safety of a chicken feed additive, but the court permitted them to offer opinions on general recognition of safety because they could determine a lack of general recognition by the absence of literature establishing the safety of the substance.<sup>32</sup>

<sup>29</sup> A comprehensive evaluation of the NTP program resulted in a series of recommendations that, if implemented, may lead to more consideration of the relevance of test results. The report stated that NTP "places too much emphasis on testing per se and not enough emphasis on providing the mechanistic insight required for a realistic interpretation of the significance of the testing results with regard to human health. This should be changed." *Fed. Regist.* 57, 31721 (17 July 1992).

<sup>30</sup> See, e.g., *41 Cases (Naremc)*. 420 F. 2d at 1130; *Coli-Trol* 80. 518 F. 2d at 747.

<sup>31</sup> See, e.g., *U.S. vs An Article of Food—Coco Rico*. 752 F. 2d 11,15 (1st Cir. 1985).

<sup>32</sup> 420 F. 2d at 1130.

The issue of who is an expert in legal proceedings remains unsettled. It was hoped that in *Daubert vs Merrell Dow Pharmaceuticals*<sup>33</sup> the Supreme Court would provide guidelines for the admission of scientific evidence in the Federal Courts. However, the Court declined to provide a "definitive checklist or test," preferring to permit the lower courts to act as "gatekeepers." The Court held that the Federal Rules of Evidence provide the standard for admitting expert scientific testimony in a Federal trial. While this case is not directly applicable to the circumstances surrounding the work of the FEMA Expert Panel, an examination of the Panel's scientific analysis techniques and methodology (Oser and Hall, 1977; Woods and Doull, 1991) certainly accounts for the key factors described in *Daubert*.<sup>34</sup>

Over the years, Panel members have been selected for expertise specifically relevant to the safety assessment of flavor ingredients. As previously mentioned, Panel members are, and have been, of significant status in the fields of toxicology, pharmacology, chemistry, biochemistry and intermediary metabolism, medicine, and statistics (Oser and Ford, 1991). The expertise of the FEMA Expert Panel has been unchallenged for more than 30 years.

## 3. Through Scientific Procedures or through Experience Based on Common Use in Foods if Used in Food Prior to 1958

### 3.1 Scientific procedures.

FDA has consistently taken the position that the scientific procedures to determine safety which serve as the basis of expert opinion must meet a strict standard:

General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient. General recognition of safety through scientific procedures shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information.<sup>35</sup>

This is essentially the same test FDA has applied to general recognition of safety and effectiveness for new drugs, a standard approved by the Supreme Court in *Weinberger vs Bentex Pharmaceuticals, Inc.*<sup>36</sup>

<sup>33</sup> 509 U.S. 469 (1993).

<sup>34</sup> While declining to specify an exact test in *Daubert*, the Court described four key factors for consideration: (1) Whether the theory or technique can be tested, (2) peer review and publication, (3) rate of error or reliability, and (4) general acceptance. The Court also commented on the application of the other relevant Federal Rules of Evidence. For comments on *Daubert*, see Mervis, J. (1993). Supreme Court to judges: Start thinking like scientists. *Science* 261, 22; Foster, K. R., Bernstein, D. E., and Huber, P. W. (1993). Science and the toxic tort. *Science* 261, 1509. For additional commentary on the issue of expert scientific testimony in the courts, see Ayala, F., and Black, B. (1993). Science and the courts. *Am. Sci.* 81, 230-239.

<sup>35</sup> 21 C.F.R. 170.30(b) (1994).

<sup>36</sup> 412 U.S. 645 (1973).

FDA says in its regulations that data should “ordinarily” be published, leaving the possibility that in some cases they need not be published such as when knowledge of unpublished data is widespread. In a preamble regarding proposed regulations on GRAS status, FDA stated:

(G)eneral recognition of safety through scientific procedures does require that the scientific evidence . . . has been published in the literature or otherwise widely disseminated throughout the scientific community knowledgeable about the safety of food ingredients. . . . Accordingly, there will be at least some gap between the gathering of the scientific knowledge necessary to provide the toxicological underpinning for general recognition of safety and the dissemination to and assimilation by the scientific community of this material that is necessary for general recognition of safety to exist.<sup>37</sup>

Several courts have held that a complete absence of published literature on a substance precludes a finding of GRAS.<sup>38</sup> As for the quality of the scientific procedures, irrelevant or incomplete toxicity studies cannot support expert opinions,<sup>39</sup> nor can poorly controlled investigations.<sup>40</sup>

Scientific procedures used to support GRAS status need not be limited to the substance’s use in food. It appears that studies on a substance that is an ingredient in both drugs and foods can support expert opinions that the substance is GRAS. In *Dan-Mar*, the Court stated that:

From a scientific standpoint, the safety of a substance is not affected by whether it is labeled as a food or as a drug if it is administered under the same conditions, at the same dosage, and for the same period of time.<sup>41</sup>

However, in a case involving the assertion that evening primrose oil is GRAS, the Court found that data on use as a drug, and unpublished data not subjected to peer review, did not support GRAS status.<sup>42</sup>

**3.2 Common use in food.** The standards for GRAS status when common use in food is the basis of an expert opinion on safety are less strict than for scientific procedures:

General recognition of safety through experience based on common use in food prior to January 1, 1958 may be determined without the quantity or quality of scientific procedures required for the approval of a food additive regulation. General recognition

. . . shall ordinarily be based on generally available data and information.<sup>43</sup>

The reason for the difference lies in the fact that foods which have been widely eaten for many years are presumptively safe; if they were not, some deleterious effects attributable to their use would have become apparent.<sup>44</sup> In addition, there is an implied risk/benefit tradeoff in the law. Congress clearly decided that the consumption of traditional foods is not to be prohibited without persuasive evidence that they cause harm as consumed.

With respect to the use of the ingredient, FDA defines common as “a substantial history of consumption of a substance by a number of consumers. . . .”<sup>45</sup> Mere length of use is not enough to prove common use; a substance which a company had used in its product for 40 years was denied GRAS status because it was used in no other products.<sup>46</sup>

In 1983, the Ninth Circuit, in *Fmali Herb*, struck the FDA’s limitation that the common use must be in the United States. In response to *Fmali Herb*, FDA concluded that a GRAS claim based on common use in a foreign country must be documented and verified by evidence that corroborated the use of the substance, must demonstrate that the information about the foreign use is “widely available in the United States,” and must demonstrate that the substance has been used as a food ingredient and not as a “drug, tonic, or folk remedy.”<sup>47</sup>

The use of a substance as a drug does not appear to satisfy the common use in food standard.<sup>48</sup> However, the court suggested that in some circumstances drug use may be similar enough to food use to warrant consideration in common use in food cases.

We believe that experience based upon common use in food, which is a means of proving to experts the safety of a food additive “under the conditions of intended use” and which serves as an alternative to scientific proof of safety, refers to experience based on common use as a food additive or under conditions producing long-term ingestion and approximating use as a food additive.<sup>49</sup>

The determination of GRAS status of flavor ingredients largely involves an examination of substances found to naturally occur in foods in minute amounts which are in turn used in flavors in low concentrations. The Expert Panel’s approach is a combination of scientific procedures and consideration of common use in food, the two elements of the third criterion for GRAS status stated in the definition of food additive. The Panel has drawn on a variety of sources in the development of its criteria including the FDA’s guidelines for

<sup>37</sup> *Fed. Regist.* 39, 34194 (23 Sept. 1974).

<sup>38</sup> 41 *Cases (Naremco)*. 420 F. 2d at 1129; *U.S. vs Vitality Systems*. Food and Drug Law Reports—1992 (D. OR, 1990).

<sup>39</sup> *Coli-Trol 80*. 518 F. 2d at 747.

<sup>40</sup> *U.S. vs Dan-Mar Enterprises, Inc.* Food, Drug, Cosmetic L. Rep. (CCH), Par. 38215 (N.D. GA, 1978).

<sup>41</sup> Food, Drug, Cosmetic L. Rep. at 38883. See also *U.S. vs Naremco, Inc.* 553 F. 2d 1138, 1143 (8th Cir. 1977) in which the Court suggested the possibility of considering data related to drug use to determine safety under the “common use in food” standard if data reflect “conditions producing long-term ingestion and approximating use as a food additive.”

<sup>42</sup> *U.S. vs Efamol*. 961 F. 2d 808 (9th Cir. 1992; cert. denied).

<sup>43</sup> 21 C.F.R. 170.30(c) (1994).

<sup>44</sup> *Fmali Herb Inc. vs Heckler*. 715 F. 2d 1385, 1389 (9th Cir. 1983).

<sup>45</sup> 21 C.F.R. 170.3(f) (1994).

<sup>46</sup> *Coco Rico*. 752 F. 2d at 15.

<sup>47</sup> *Fed. Regist.* 53, 16544 (10 May 1988).

<sup>48</sup> *Naremco*. 553 F. 2d at 1143.

<sup>49</sup> *Naremco*. 553 F. 2d at 1143.

the safety assessment of food ingredients described in the "Redbook"<sup>50</sup> and other sources.<sup>51</sup>

The Expert Panel applies five specific criteria for determining the GRAS status of a flavor ingredient.

(1) Exposure to the substance in specific foods, the total amount in the diet, and the total poundage; (2) natural occurrence in food; (3) chemical identity (including purity and method of preparation) and specific chemical structure; (4) metabolic and pharmacokinetic characteristics; and (5) animal toxicity. (Woods and Doull, 1991).

The Panel's five criteria exemplify a thorough but balanced approach to food ingredient safety assessment by including the basic elements of chemical identity, exposure, metabolism, and toxicity.

A critical part of the Panel's assessment of GRAS status is the analysis of an individual flavor ingredient within its class of structurally related compounds. In its deliberations, the Panel often draws on toxicologic and metabolic data from structurally related compounds whether or not the related compounds are considered flavor ingredients.

The Panel has also applied structural relationships as a guide to prioritizing its evaluations of GRAS flavor ingredients and in organizing the presentation of data in the FEMA SLRs. The Panel has applied a decision tree approach based largely on exposure and chemical structures to guide the prioritization of GRAS evaluations (Cramer *et al.*, 1978). The Panel has also considered the priority setting system developed jointly by FDA and FEMA (Easterday *et al.*, 1992).

With respect to the FEMA SLRs, the data in the SLRs are grouped by structural class so that a particular SLR includes a discussion of a given substance together with other closely related substances. This facilitates the appropriate use of analogy in determining the safety of an individual flavor ingredient. For example, FEMA SLR A-1 contains data on aliphatic ketones, secondary alcohols, and related esters. Therefore, the reader can easily access data on isopropyl acetate (FEMA No. 2426), isopropyl butyrate (FEMA No. 2935), isopropyl formate (FEMA No. 2944), and other related compounds. In 1993, FEMA initiated a systematic and comprehensive program to update and enhance the utility and availability of the SLRs. The new format will be more user friendly and compatible with computer data-

<sup>50</sup> Food and Drug Administration (1993). Toxicological principles for the safety assessment of direct food additives and color additives used in food—Redbook II. This document is in draft form and comments have been requested by FDA. *Fed. Regist.* **58**, 16536 (29 March 1993). In the new draft FDA once again emphasized that the Redbook consists of guidelines and not mandatory testing requirements and that it does not "preclude the petitioner from demonstrating safety by using other types of data."

<sup>51</sup> *Evaluating the Safety of Food Chemicals* (1970). National Academy Press, Washington, DC. The Expert Panel's evaluation procedures have been described in a number of publications. Gerarde (1973); Oser and Hall (1977); Woods and Doull (1991).

base integration. This project is scheduled for completion in 1998.

Most of the FEMA GRAS flavor ingredients are found in food. Of the 1783 FEMA GRAS substances, approximately 1400 have been identified in nature. The remaining substances have not yet been identified in nature but the chemical structures of most of them suggest that they will probably be identified as natural constituents of food. It is likely that only a few are true xenobiotics. Therefore, in the vast majority of evaluations the Panel determines GRAS status based on scientific procedures and the existing consumption of flavor ingredients as natural constituents of food.

#### 4. Conditions of Intended Use

In the preamble to the agency's proposed regulations on GRAS determinations FDA 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 GRAS food ingredients have proliferated to the point where the GRAS status was brought into serious question.<sup>52</sup>

FDA views conditions of intended use as a limitation and from time to time the agency has tried to prevent GRAS status in one food category from being automatically transferred to another. FDA successfully opposed GRAS status for potassium nitrate in beverages even though it may have been GRAS in meats.<sup>53</sup>

FDA's enforcement actions on evening primrose oil suggest a type of GRAS assertion that the agency will challenge. In *U.S. vs Efamol*, GRAS status for encapsulated evening primrose oil was rejected because there were inadequate supporting data.<sup>54</sup> It appears that FDA's main concern was the intended and actual use of evening primrose oil as a dietary supplement rather than as a food ingredient; dietary supplement use may result in significantly higher exposure than typical food ingredient use, thereby increasing any existing toxic potential.<sup>55</sup> It also appears likely that FDA would challenge private assertions of GRAS status for new macronutrient substitutes. For example, the manufacturer of the fat substitute Simplese chose to file a formal GRAS affirmation petition with FDA rather than face an agency challenge; the petition was granted in 1990.<sup>56</sup>

<sup>52</sup> *Fed. Regist.* **39**, 34194, 34195 (23 Sept. 1974).

<sup>53</sup> *Coco Rico*. 752 F. 2d at 15; see also *U.S. vs Articles of Food—Buffalo Jerky*. 456 F. Supp. 207 (D. NE, 1987).

<sup>54</sup> 961 F. 2d 808 (9th Cir; cert. denied).

<sup>55</sup> Similarly, FDA successfully challenged the GRAS status of methylsulfonylmethane, a DMSO metabolite that was being used as an animal feed supplement; *U.S. vs Vitality Systems*. Food and Drug Law Reports—1992 (D. OR, 1990). In another animal feed supplement case involving gentian violet, a series of enforcement actions went on for more than 10 years culminating in the manufacturer asking a District Court to make a GRAS determination; the Court declined deferring to FDA. *Naremco vs FDA*. Federal Food, Drug, and Cosmetic Act Reporter (W. D. MO, 1990).

<sup>56</sup> *Fed. Regist.* **55**, 6384 (23 Feb. 1990).

FEMA has always considered a thorough evaluation of the conditions of intended use a critical part of GRAS assessments and in fact provided FDA much of the data on uses for the agency's own GRAS assessments of flavor ingredients. The FEMA Expert Panel determines GRAS status for flavor ingredients based in part on information provided by the applicant which states the uses for the substance. For example, the applicant specifies that the substance will be used in flavors which will be added to one or more of a number of food categories.<sup>57</sup> GRAS status for a flavor ingredient applies only to the uses approved by the Panel. Applicants who wish to broaden uses must return to the Panel for a reevaluation and approval.

A significant part of the Panel's analysis of GRAS status is the ultimate consumption of flavor ingredients including both the amount occurring naturally in the food and the amount contained as an added flavor. For each GRAS application, the Panel calculates a possible average daily intake (PADI) and a per capita exposure estimate which, together with the toxicologic and pharmacokinetic data, give the Panel perspective regarding the consumption of the substance as a food constituent. The Panel also utilizes the "consumption ratio" analysis when appropriate. The consumption ratio compares the quantity of a flavor ingredient consumed as a natural constituent of food with the quantity of the flavor ingredient consumed as an added flavor (Stofberg and Kirschman, 1985).

When the GRAS status of flavor ingredients is published, each substance is listed with a series of uses and corresponding use levels which comprise the conditions of intended use for each substance. Historically, FEMA GRAS publications included the average maximum use level for each listed flavor ingredient (see, e.g., Burdock *et al.*, 1990). In an effort to provide additional information, "GRAS 16," and future GRAS publications, will include both average usual and average maximum use levels (Smith and Ford, 1993). The published use levels are not intended to be limits but merely to reflect the range of values considered by the Panel in determining GRAS status (Hall and Oser, 1965). However, a use level significantly above the average maximum published use level may indicate the need for a Panel reassessment of GRAS status.

Therefore, the Panel's analysis of the conditions of intended use of GRAS candidate flavor ingredients consists of two closely related elements. First, the Panel examines the use categories for the material (e.g., baked goods) including whether it is a natural constituent of foods. Second, the Panel evaluates the proposed use levels in light of the total potential exposure to the sub-

stance given its toxicologic and pharmacokinetic characteristics and its known or probable metabolism.

## SUMMARY

The FEMA GRAS assessment system employed by the Expert Panel meets each of the statutory requirements for determining GRAS status and provides for a rigorous and accurate assessment. An important component of the Panel's responsibilities is to apply its expert judgment to the task. The Panel accomplishes this by a thorough evaluation of all available data on flavor ingredients and the available data on structurally related substances. The analysis includes a comprehensive evaluation of the potential exposure to the flavor ingredient through food compared with its toxicologic and pharmacokinetic characteristics. The Panel intentionally operates on a flexible system employing expert judgment at each step and eschews the rote approach of "cookbook toxicology."

The FEMA GRAS assessment program has been developed with a consistent exchange of information and views between FEMA and FDA. The careful development of the FEMA program with the full knowledge of FDA has resulted in a program in which FDA has not yet found it necessary to challenge an assertion of GRAS status for a flavor ingredient.

## CONTINUING GRAS ASSESSMENTS

The FEMA GRAS assessment process is dynamic; as new information becomes available it is brought into the system. The Expert Panel accomplishes this in two ways. First, the Panel employs a comprehensive and systematic review of all GRAS flavor ingredients. Second, the Panel reviews any individual substances for which potentially significant new data are available.

### 1. GRAS Affirmation

In the late 1970s, concurrent with the production of the FEMA SLRs, the Expert Panel reviewed the newly available data on flavor ingredients that were designated FEMA GRAS at that time. This reevaluation, completed in 1985, became known as GRAS affirmation and was undertaken in a systematic and comprehensive manner. The Panel evaluated all available new data on FEMA GRAS substances, accomplishing the task by reviewing flavor ingredients in the structural classes designated by the SLRs. The Panel affirmed GRAS status for the existing GRAS flavor ingredients, with three exceptions,<sup>58</sup> and added a few others.

<sup>58</sup> Three flavor ingredients had their GRAS status revoked: 2-methyl-5-vinyl pyrazine, *o*-vinyl-anisole, and musk ambrette. Over the years, the Panel has revoked GRAS status for 10 flavor ingredients (Oser and Ford, 1991). Also, several hundred flavor ingredients in use at the time of the original FEMA survey were not granted GRAS status because of inadequate data.

<sup>57</sup> There are 34 categories specifically provided for in the FEMA GRAS application including baked goods, confections, beverages, meat sauces and gravies, and meat products.



In 1993, the Panel initiated a second reevaluation of the GRAS status of currently listed flavor ingredients, once again in connection with the FEMA SLRs. As the SLRs are revised and updated under a 5-year project begun in 1993, the Panel will evaluate new data and reaffirm or revoke GRAS status or request other data deemed necessary to make a decision.

## 2. Periodic GRAS Reevaluations

Periodically, the Panel becomes aware of significant new data on flavor ingredients such as a bioassay published by the NTP. In these instances, the Panel evaluates the new information and determines how it affects the GRAS status of the flavor ingredient. Generally, the Panel includes the results of its deliberations as a comment in the periodic GRAS publications. For example, the Panel included a discussion of new data on *d*-limonene in the "GRAS 15" publication (Burdock *et al.*, 1990) and on  $\alpha$ -methylbenzyl alcohol and benzaldehyde in "GRAS 16" (Smith and Ford, 1993). In each of these instances the Expert Panel affirmed GRAS status.

### THE FUTURE OF THE FEMA GRAS ASSESSMENT PROGRAM

The FEMA GRAS assessment program has served the flavor and food industries, consumers, and regulators well for more than 30 years. The program facilitates sound safety assessments of flavor ingredients which are critical parts of our food supply even though they are consumed in minor amounts.

The FEMA Expert Panel continues to confront new issues associated with the GRAS assessment of flavor ingredients including issues arising out of substances produced by new biotechnology processes and safety considerations raised by substances containing natural toxins. The Panel also continues to consider developments in safety assessment techniques such as new

methods to evaluate carcinogenicity, immunotoxicity, and neurotoxicity.

The FEMA GRAS assessment program will continue to integrate new developments in its continuing efforts to improve the program. In this way, the FEMA program can remain a model GRAS assessment program.

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