Food and Chemical Toxicology 138 (2020) 111236

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

The GRAS provision - The FEMA GRAS program and the safety and regulation of flavors in the United States

John B. Hallagan*, Richard L. Hall, Joanna Drake

The Flavor and Extract Manufacturers Association of the United States, 1101 17th Street, N.W., Suite 700, Washington, D.C, 20036, USA

ARTICLE INFO

Dedication: This report is dedicated to the memory of Richard L. Hall, Ph.D. who passed away in August 2019 as this report was undergoing final revisions.

Keywords:
FEMA GRAS
GRAS
Flavor safety
Flavors

ABSTRACT

With the Food Additives Amendment of 1958 the U.S. Congress established the pre-market approval requirement for food additives unless such food ingredients were "generally recognized as safe" (GRAS). Beginning in 2010 with the publication of an audit by the U.S. Government Accountability Office, the GRAS provision has received much attention from regulators and policy-makers, the media, and non-governmental organizations. This report provides an overview and update of the policies, procedures, and scope of the GRAS program for flavor ingredients sponsored by the Flavor and Extract Manufacturers Association of the United States (FEMA), and its alignment with the requirements for GRAS conclusions established by Congress and FDA.

1. Introduction

The U.S. food supply is among the safest in the world, if not the safest. A long-standing regulatory program for food ingredients mandated by the U.S. Congress in the Federal Food, Drug, and Cosmetic Act and implemented and managed by the Food and Drug Administration (FDA) assures that food ingredients added to our food are safe.

A significant amount of attention has been focused in recent years on the ingredients of foods that in the U.S. are regulated as food additives and substances "generally recognized as safe" ("GRAS"). Public concern about the GRAS concept has existed for some time. This concern is reflected in several reviews of the GRAS concept by a federal government agency, the Government Accountability Office, and consumer-oriented non-governmental organizations. These reviews identified concerns related to GRAS conclusions such as a lack of transparency on procedures, the potential for conflict of interest issues due to industry sponsorship of GRAS expert panels, an absence of mandated re-evaluation after an initial GRAS conclusion is made that would account for increases in potential exposure or the availability of new, relevant safety data, and a perceived lack of scientific rigor (*e.g.* GAO, 2010; Neltner et al., 2011). For example, partially hydrogenated oils were considered GRAS by FDA for many years but a more timely re-evaluation of GRAS status likely would have meant that the available adverse human health effect information would have negated GRAS status sooner. FDA started the process of removing GRAS status for these materials in 2013 stating that "… the GRAS status of … a particular substance is time dependent … [E]xpert opinion … may change so that there is no longer consensus that the specific use is safe" (FDA, 2013). Concerns have also been raised about the status of caffeine as an FDA-listed (21 CFR 182.1180) GRAS substance with the agency taking action to protect consumers from significant over-exposures to caffeine in dietary supplement products (FDA, 2018d).

Americans are living longer, healthier lives as demonstrated by consistent increases in life expectancy since 1900. Today, American women can, on average, expect to live for 81 years and men for 76 years (Xu et al., 2020), and mortality rates from cancer have declined consistently since the early 1990s (Siegel et al., 2019). However, many consumers are choosing to reduce their consumption of highly processed packaged foods that are manufactured with a variety of food additives and GRAS substances in the belief that foods containing such substances are less healthy than foods manufactured with fewer, or none, of these substances.

With the exception of illness associated with extreme overconsumption of a few food ingredients (*e.g.* bromine toxicity associated with the extreme overconsumption of beverages containing brominated vegetable oil – Bendig et al., 2012; caffeine toxicity – FDA, 2018d) there are very few instances of approved food additives or GRAS substances causing acute or chronic illness under their conditions of intended use. Unfounded concerns over food additives and GRAS substances may divert attention from food safety issues that are proven to be of

* Corresponding author.
E-mail addresses: Hondobear@aol.com, jbhallagan@femaflavor.org (J.B. Hallagan).

https://doi.org/10.1016/j.fct.2020.111236
Received 21 November 2019; Received in revised form 25 February 2020; Accepted 28 February 2020
Available online 02 March 2020
0278-6915/

significant public health concern, most prominently the microbial contamination of a variety of commonly consumed foods.

This is the third in a series of reports (Hallagan and Hall, 1995a, 2009) that describes how the FEMA GRAS program addresses the scientific, legal and regulatory requirements for GRAS conclusions for flavor ingredients and assures their safety.

2. The GRAS provision

The 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act mandated the premarket approval of all food ingredients as "food additives" unless the ingredient is,

> (G)enerally 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. 21 U.S.C. Section 321(s).

There are two aspects of the GRAS provision that exclude GRAS substances from the statutory definition of "food additive." GRAS conclusions may be based on the safe and common use in food prior to 1958 to account for the known safety of the many uses of food ingredients already in place when the Food Additives Amendments were enacted. The second aspect is the conclusion of GRAS status through scientific procedures. It is now rare for the common use in food aspect of the GRAS exemption to be applied. After initial efforts were completed to determine the scope of food ingredients in use in 1958 through a survey conducted by the National Academy of Sciences (NAS, 1977) attention was focused on the scientific procedures approach within the GRAS provision.

FDA has long recognized the statutory right for private entities to make their own conclusions that food ingredients are generally recognized as safe. In the preamble to their final rule codifying regulations for its voluntary GRAS notification program, the agency stated:

> Although we have premarket review authority over food additives, a food manufacturer can intentionally add a substance to human food or animal food without our premarket review or approval if the substance is generally recognized as safe under the conditions of its intended use (GRAS) … It is on the basis of the GRAS provision within the food additive definition that many substances (such as vinegar, vegetable oil, baking powder, and many spices, flavors, gums and preservatives) are lawfully marketed today … (FDA, 2016a).

There are four current pathways to obtain regulatory authority to use flavor ingredients in the U.S.: (1) FDA food additive status; (2) FDA voluntary GRAS notification; (3) private GRAS determination; and (4) FEMA GRAS status (Hallagan and Hall, 2009). A "legacy" pathway is codified FDA GRAS status in which several hundred flavor ingredients, and a variety of other food ingredients, were listed in the Code of Federal Regulations at 21 CFR Parts 182 and 184 largely in the 1960s and 1970s (Hanlon et al., 2017). These FDA-listed flavor ingredients also have FEMA GRAS status. By far the most common current pathway is an evaluation by the FEMA Expert Panel to determine FEMA GRAS status.

Under FDA policy GRAS status applies only to the designated uses of substances and not to the substances themselves. This key concept of the designated conditions of intended use places a significant limitation on the application of the GRAS provision. FDA has described its policy several times and stated that food ingredients determined to be GRAS for one use should not be used for other uses not determined to be GRAS. As FDA stated in promulgating its initial GRAS affirmation regulations in 1974:

> It has too often been 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 GRAS status was brought into serious question … Any use of the (GRAS) ingredient under conditions other than those explicitly set out in (a GRAS) regulation (*e.g.* a use in a different category of food, or for a different functional purpose, or at a higher level) will automatically require a food additive regulation prior to such use. Thus, these limitations have the same effect as a limitation in a food additive regulation. (FDA, 1974).

FDA reiterated its policy in the preamble to its 1997 proposal to implement its voluntary GRAS notification program, and confirmed it in its 2016 final rule (FDA, 2016a). The 1997 preamble described the information that is required for a private GRAS determination to be recognized by FDA:

> (FDA) requires that the GRAS exemption claim include the applicable conditions of use that are supported by data and information … including the foods in which the notified substance is to be used, levels of use in such foods, and the purpose for which the notified substance is used (FDA, 1997).

Therefore, it is clear under FDA policy, that a substance whose use as a flavor ingredient is GRAS is not GRAS for other uses in food, such as sweetening, if under different conditions of use it provides such an effect (*e.g* a higher concentration in food).

3. The FDA voluntary GRAS notification program

Because of real and perceived inefficiencies in FDA's GRAS affirmation program, most prominently the long period of time it took for the agency to promulgate a final regulation, the agency proposed and instituted a new voluntary GRAS notification program in 1997 (FDA, 1997; Hanlon et al., 2017). FDA began operating this program in 1997 in the absence of final implementing regulations which later became the subject of currently ongoing litigation over the validity of the agency's actions (*Center for Food Safety v. Azar* (Case 1:17-cv-03833-VSB S.D.N.Y. 2019).

In 2010, the federal Government Accountability Office (GAO) published its report, "FDA Should Strengthen Its Oversight of Food Ingredients Determined to Be Generally Recognized as Safe" marking the beginning of several years of extensive review and evaluation of the GRAS provision (GAO, 2010). While there were few, if any, suggestions that the application of the GRAS provision had resulted in adverse public health outcomes, a number of critics asserted that the application of the GRAS provision was not an appropriate regulatory scheme because it was not adequately transparent and had potential for the presence of conflicts of interest among experts making GRAS assessments.

The GAO report included several recommendations to improve the FDA's voluntary GRAS notification program.

- Develop a strategy to require any company that conducts a GRAS determination to provide FDA with basic information – as defined by the agency to allow for adequate oversight – about this determination, such as the substance's identity and intended uses, and to incorporate such information into relevant agency databases and its public website;
- Develop a strategy to minimize the potential for conflicts of interest in companies' GRAS determinations, including taking steps such as issuing guidance for companies on conflict of interest and requiring information in GRAS notices regarding expert panelists' independence;
- Develop a strategy to monitor the appropriateness of companies' GRAS determinations through random audits or some other means, including issuing guidance on how to document GRAS

determinations;

- Develop a strategy to finalize the rule that governs the voluntary notification program, including taking into account the experience of the program to date, incorporating input from a new public comment period, and reporting to Congress and the public the agency's timeline for making it final;
- Develop a strategy to conduct reconsiderations of the safety of GRAS substances in a more systematic manner, including taking steps such as allocating sufficient resources to respond to citizen petitions in a timely manner, developing criteria for circumstances under which the agency will consider the safety of a GRAS substance, and considering how to collect information from companies on their reconsiderations; and
- Develop a strategy to help ensure the safety of engineered nanomaterials that companies market as GRAS substances without the agency's knowledge … (GAO, 2010).

In 2012, the non-governmental organization the Center for Food Safety sued FDA asserting that the agency had violated the Administrative Procedures Act by conducting the voluntary GRAS notification program without finalizing the 1997 proposal (See *Center for Food Safety v. Sebelius*. Case No. 1:14-cv-267 (D.D.C. Feb. 20, 2014)). In August 2016, to comply with the settlement negotiated in the *Center for Food Safety* case, FDA published its final regulations implementing the GRAS notification program (FDA, 2016a). The final regulations differed little from the 1997 proposal but helpful guidance was provided by the agency in the preamble to the final regulations and in a series of policy documents (FDA, 2017a; FDA, 2017b) that addressed a number of the issues raised in the GAO audit. The final regulations are currently being challenged by several non-governmental organizations based on allegations that FDA's program violates the Federal Food, Drug, and Cosmetic Act and the Administrative Procedures Act (*Center for Food Safety v. Azar*. Case 1:17-cv-03833-VSB. S.D.N.Y. 2019).

The FDA's voluntary GRAS notification program has resulted in the identification of more than 800 food ingredients whose uses are considered GRAS by their sponsors without objection by FDA. An inventory of these substances is available on FDA's website (www.fda.gov). Flavor ingredients have rarely been submitted to the FDA notification program because of the long-standing success of the FEMA GRAS program and the corresponding economic value of FEMA GRAS status as recognized by the food industry.

In the context of its voluntary GRAS notification program, FDA issued additional guidance in 2017 on best practices for convening a panel of experts to assess the GRAS status of food ingredients (FDA, 2017a; FDA, 2017b). FDA made a series of "non-binding" recommendations in its guidance on convening a GRAS panel that are helpful in conducting GRAS assessments that are likely to be acceptable to the agency. The recommendations address the following points:

1. Appropriate and balanced expertise in a GRAS panel.
2. Assessment and management of procedural issues associated with the organization and deliberation of a GRAS panel.
3. Assessment and management of conflict of interest and appearance issues of potential GRAS panel members.
4. Information provided to a GRAS panel.
5. Documenting the deliberations and conclusions of a GRAS panel.
6. Considerations when a GRAS notice is or is not submitted to FDA.
7. Honoraria provided to members of a GRAS panel.

With respect to the FDA's monitoring and enforcement of GRAS determinations, the agency often focuses on the designated conditions of intended use. FDA often notes in its "no objection" letters to parties asserting GRAS status that the substance is GRAS only for the specified use or technical effect in food while generally not commenting on the two other aspects of the conditions of intended use - food categories and use levels. The agency conducts some monitoring of the use of GRAS substances and has issued warning letters when the use and marketing of products containing GRAS substances indicates that such use is inconsistent with GRAS status (Hanlon et al., 2017).

4. Flavor added to foods

Flavors added to foods are most often mixtures of individual substances known generically as "flavor ingredients." Flavor ingredients can be "flavoring substances" or "flavorings" (substances that impart or modify flavor) or "flavor adjuvants" (substances that facilitate the function of the flavoring substances in the mixture). These flavor mixtures can be described as "compounded flavors" (Hallagan and Hall, 2009) and may consist of as many as 100 or more flavor ingredients. Flavoring substances in the compounded flavor may include chemically-defined individual flavoring substances such as vanillin, and natural flavoring complexes such as botanical extracts (*e.g.* vanilla extract) and essential oils (*e.g.* orange and other citrus oils).

FDA has designated substances used to formulate compounded flavors as "flavoring agents and adjuvants," defined by FDA as "substances added to impart or help impart a taste or aroma to food." (21 CFR 170.3(o) (12)). In relation to the terminology used in the FEMA GRAS program, substances designated by FDA as "flavoring agents" are considered flavoring substances by FEMA – substances that impart or modify flavor. Substances considered flavoring adjuvants by FDA (also described as "non-flavor ingredients" for labeling purposes by FDA) and FEMA do not impart or modify flavor but do "help impart a taste or aroma to food" by facilitating the function of compounded flavors in foods to which they are added.

Some food ingredients can serve multiple functions when added to foods. However, if a GRAS conclusion is the basis for regulatory authority to use that substance then it is only the designated technical effect – the specific function and use – that is GRAS. Some FEMA GRAS flavor ingredients (*i.e.* flavoring substances and flavor adjuvants) can provide different technical effects in food depending on their use levels such as flavorings with modifying properties (FMPs), flavoring substances that do not impart flavor themselves but modify, or "help impart" flavor when used in conjunction with flavoring substances that impart flavor in a compounded flavor. Some FMPs may provide a flavor modifying effect at low levels but a sweetening or other effect at higher levels. Critically, it is only the flavor modification technical effect that is provided with regulatory authority to use (as an FMP) through its FEMA GRAS status. FMPs used in food under conditions of intended use outside of those described for FEMA GRAS status are not "FEMA GRAS."

Therefore, the designated technical effect of a substance – its designated use - serves as a limitation on the regulatory authority to use the substance in the U.S. Consistent with FDA policy, the designated technical effect is one of the three elements of the conditions of intended use for FEMA GRAS determinations with the other two being the designated food categories in which the substance may be used, and the designated use levels within those food categories. Together these three elements of the conditions of intended use as required by Section 201(s) of the Federal Food, Drug and Cosmetic Act (FFDCA) and long-standing FDA policy comprise the key parameters for the use of flavor ingredients determined to be FEMA GRAS. It is important to note that while the designated technical effect for a FEMA GRAS flavor ingredient and the designated food categories are limitations on FEMA GRAS status, the use levels identified for FEMA GRAS flavor ingredients are limitations only to the extent that an increase in the use levels in the designated food categories results in a significant increase in exposure when consumed in food (Smith and Ford, 1993).

5. Elements of FEMA GRAS assessments and conclusions – new developments

In 1960, shortly after the passage of the Food Additives Amendment, FEMA established what would become the longest-

running and most extensive food industry sponsored GRAS assessment program (Hallagan and Hall, 1995a, 2009). For more than fifty years the FEMA GRAS program has been the primary route to market for flavors in the U.S. More than 3,000 individual flavor ingredients have FEMA GRAS status and therefore may be marketed in the U.S. for addition to human foods and beverages.

As described in our previous reports (Hallagan and Hall 1995a, 2009), there are four elements of the statutory requirements of FFDCA Section 201(s) for GRAS conclusions made through scientific procedures.

- There must be general recognition of safety by qualified experts.
- The experts must be qualified by scientific training and experience to evaluate the substance's safety.
- The experts must base their conclusion of safety on scientific procedures.
- The conclusion of general recognition of safety must take account the substance's conditions of intended use.

Regarding the GAO audit of the GRAS concept and FDA's voluntary GRAS notification program, while the FEMA GRAS program was not a focus of the audit, the GAO did include comments on the FEMA program in its report based on extensive information provided by FEMA. GAO stated,

> Actions taken by the Flavor and Extract Manufacturers Association better ensure the independence of scientific assessments of the association's GRAS determinations and obtain information about these determinations. This association conducts GRAS determinations exclusively for its approximately 70 member companies that manufacture these substances. Once a member company submits a flavor or extract – known as a flavoring substance – to the association's GRAS process, the company is not supposed to market it until the association determines the substance is GRAS. … The Flavor and Extract Manufacturers Association voluntarily informs FDA of its GRAS determinations including the name of the substance, its properties, and the basis of the determination. … In addition, the association has published journal articles on the workings of its expert panel. It also announces its GRAS determinations in a food industry trade magazine and makes these publications available on the association's website for a fee … the association's GRAS process achieves a level of public disclosure and agency notification similar to FDA's voluntary GRAS notification program. (GAO, 2010).

The GAO audit report included a specific and significant criticism of private GRAS conclusions when they are made without informing FDA. Informing FDA of private GRAS conclusions made outside of the agency's voluntary GRAS notification program would be helpful according to the GAO albeit at some cost to the agency. The GAO stated,

> We believe that developing strategies and collecting information (on private GRAS determinations) would cost-effectively contribute to improving the safety of the food supply. For example, FDA has acknowledged the usefulness and cost-effectiveness of the GRAS determination information provided voluntarily by the Flavor and Extract Manufacturers Association. Receiving similar information from other companies on GRAS determinations made outside of the voluntary notification program would likely provide similar benefits. (GAO, 2010)

The GAO further expressed concern that FDA is not generally aware of any re-evaluations of GRAS conclusions made by private entities. However, GAO recognized that the FEMA GRAS program actively engaged in periodic re-evaluations of the available safety data and its GRAS determinations. Regarding the FEMA GRAS program, GAO stated,

> FDA is aware of some reconsiderations conducted by companies because the Flavor and Extract Manufacturers Association periodically reconsiders the thousands of substances it has determined to be GRAS and publishes the results of these reviews. … The association's expert panel periodically conducts comprehensive and systematic reviews of all GRAS flavoring substances that its members manufacture and reviews any individual substances for which potentially significant new data become available. … In addition to these comprehensive reviews, the panel periodically becomes aware of significant new data on prior GRAS decisions during its review of the available scientific data related to flavoring substances. In these cases, the panel re-evaluates the safety of the flavoring substance and may conclude that the substance is no longer GRAS. In some instances the expert panel requests that additional studies be performed by industry members. Over the last four decades, these review processes have led to numerous studies to address a variety of safety assessment issues that arose during the reviews. Most of these studies have been published. The review processes also resulted in 11 substances being removed from the association's list of GRAS flavoring substances. (GAO, 2010).

The GAO audit and report served as the impetus for other groups to begin their own reviews of the application of the GRAS provision. Several non-governmental organizations (NGOs) initiated programs focused on both the FDA notification program and on what has been commonly referred to as “private” GRAS conclusions – GRAS assessments sponsored by industry. Two NGOs, the Pew Charitable Trusts, through its Food Additives Project, and the Natural Resources Defense Council (NRDC), published reports asserting that there are significant flaws in U.S. food ingredient regulation such as “data gaps” in the information supporting “private” GRAS conclusions, lack of transparency in such GRAS conclusions, and potential conflicts of interest among experts asserting private GRAS conclusions (Maffini et al., 2011; Neltner et al., 2011, 2013a, 2013b; Pew, 2013; Neltner and Maffini, 2014).

A review of the elements of FEMA GRAS assessments demonstrates that the design and conduct of the FEMA GRAS program anticipated many of the criticisms identified by the GAO and several NGOs, and has addressed them with well-defined and articulated polices that have been available to the public and regulators since the inception of the program.

6. General recognition of safety

6.1. Information serving as the basis for GRAS conclusions

FDA policy is that the safety of GRAS uses of substances must meet the same requirements for data supporting safety as a substance regulated as a food additive. FDA stated, “A substance cannot be classified as GRAS under its conditions of intended use if the available data and information do not satisfy the safety standard for a food additive under the FD&C Act.” (FDA, 2016a). Therefore, uses of GRAS food ingredients must meet the safety standard of a “reasonable certainty of no harm” in FDA's food additive regulations at 21 CFR 170.3(i).

The FEMA Expert Panel evaluates flavor ingredients for GRAS status through “scientific procedures” as described in FFDCA Section 201(s). FDA states,

> Scientific procedures include the application of scientific data (including as appropriate, data from human, animal, analytical, or other scientific studies), information, and methods, whether published or unpublished, as well as the application of scientific principles, appropriate to establish the safety of a substance under the conditions of its intended use. 21 CFR Section 170.3(h).

The FEMA Expert Panel applies its published criteria for the assessment of flavoring substances that are candidates for FEMA GRAS status (Smith et al., 2005; Cohen et al., 2018a). The Expert Panel

reviews all available information relevant to its GRAS conclusion to assure the safety of the candidate flavoring substance under its conditions of intended use whether the data are published or unpublished. In doing so, the FEMA Expert Panel complies with the FDA regulations governing GRAS assessments. Specifically, the Expert Panel's review complies with 21 CFR Section 170.30(b) which states that GRAS assessments,

> (S)hall be based upon the application of generally available and accepted scientific data, information or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods.

FDA recognized the importance of information serving as the basis for GRAS conclusions being publicly available to meet the requirement for "general recognition." FDA stated, "Regardless of whether the data and information are published or unpublished … a GRAS conclusion must be based on data and information that are generally available and accepted, and as such are publicly available." (FDA, 2016a). The FEMA GRAS program was designed to make use of all available information relevant to performing a rigorous GRAS assessment. As acknowledged by FDA in its regulations, GRAS assessments should be conducted with the understanding that unpublished information may be valuable especially when the use of the substance being evaluated is new or the substance itself is novel, and information relevant to a GRAS assessment may not yet be published. In 1974 in the preamble to its proposed GRAS regulations, 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 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. (FDA, 1974).

FEMA encourages sponsors of applications for FEMA GRAS status to publish their supporting information. To address instances when, for a variety of reasons, information used in a GRAS assessment are not published by the sponsor the FEMA Expert Panel requires that all sponsors agree that the results of their unpublished studies may be made publicly available by FEMA, share them with FDA, and distribute them to whoever requests them resulting in the widespread dissemination of information. One often overlooked difficulty related to publishing scientific studies in general is that many peer-reviewed scientific journals prefer to publish studies or review articles that report adverse effects – data showing that the test substance does not cause deleterious effects in the test animals or the test system are generally of less interest. This is especially the case for genotoxicity assays, of which hundreds are conducted by various industries on many types of substances each year. While the results of these assays may be reported to regulatory agencies they are often never published in the peer-reviewed literature.

In the preamble to its 1997 proposed rule on substances that are considered generally recognized as safe, FDA provided guidance on information that can be used to meet the two parts of a GRAS conclusion - the "technical element" (the safety of a substance) and the "common knowledge element" (the general recognition of safety). FDA stated,

> A determination that a particular use of a substance is GRAS requires both technical evidence of safety and a basis to conclude that this technical evidence of safety is generally known and accepted. … Thus, a GRAS substance is distinguished from a food additive on the basis of the common knowledge about the safety of the substance for its intended use rather than on the basis of what the substance is or the types of data and information that are necessary to establish its safety. … FDA uses the term "technical element" when discussing technical evidence of safety and "common knowledge element" when discussing general knowledge and acceptance of safety. (FDA, 1997).

The FEMA GRAS program has complied with the technical element of GRAS assessments by employing state-of-the-art scientific procedures that have been clearly described over the years in a series of publications in the peer-reviewed scientific literature (Gerarde, 1973; Oser and Hall, 1977; Woods and Doull, 1991; Hallagan and Hall, 1995a, 2009; Smith et al., 2005; Cohen et al., 2018a, 2019). One important aspect of the Expert Panel's assessments of the safety of flavor ingredients has long been its review of individual flavor ingredients within the context of a larger group of structurally-related substances. In other words, data from structurally-related substances can be used to determine the safety and GRAS status of candidate GRAS substances using the established approach of "chemical read across" (FDA, 2018e; Lester et al., 2018; Myatt et al., 2018). FDA addressed this issue in its final rule on its voluntary GRAS notification program:

> One comment asks us to recognize that published literature does not need to address a specific substance but could involve publications on a class of substances or a related substance to support a conclusion that the use of a substance is GRAS through scientific procedures. We agree that published information for a specific substance is not always necessary to support a conclusion that the use of a substance is GRAS through scientific procedures. For example, there may be situations where the safety of the use of the substance in food can be demonstrated by relevant published information on a closely structurally related compound. (FDA, 2016a).

Because new data are constantly being generated, FDA has long emphasized the importance of continued reviews of existing GRAS substances. As an example, in its proposed rule regarding partially hydrogenated oils, FDA stated,

> Importantly, the GRAS status of a specific use of a particular substance is time-dependent. That is, as new scientific data and information develop about a substance … evolves, expert opinion regarding the safety of a substance for a particular use may change so that there is no longer consensus that the specific use is safe. (FDA, 2013).

The FEMA Expert Panel reviews FEMA GRAS substances on a cyclical basis to assure that its GRAS conclusions have accounted for advances in science and safety assessment. The FEMA Expert Panel has completed two comprehensive reviews of all FEMA GRAS substances and has initiated its third.

With respect to the common knowledge element of GRAS conclusions, FDA stated in its 1997 proposal,

> The common knowledge element of the GRAS standard includes two facets: (1) The data and information relied on to establish the technical element must be generally available; and (2) there must be a basis to conclude that there is consensus among qualified experts about the safety of the substance for its intended use. … The usual mechanism to establish that scientific information is generally available is to show that the information is published in a peer-reviewed scientific journal. However, mechanisms to establish the basis for concluding that there is expert consensus about the safety of a substance are more varied. In some cases, publication in a peer-reviewed scientific journal of data (such as toxicity studies) on a test substance has been used to establish expert consensus in addition to general availability. In other cases, such publication of data and information in the primary scientific literature has been supplemented by: (1) publication of data and information in the secondary

scientific literature, such as scientific review articles, textbooks, and compendia; (2) documentation of the opinion of an "expert panel" that is specifically convened for this purpose … (FDA, 1997).

In its 1997 proposal, FDA proposed to revise two sections of its regulations relevant to the technical and common knowledge elements, 21 CFR Section 170.3(h), the definition of scientific procedures, and 21 CFR Section 170.30(b) on the common knowledge element. In 2010, FDA reopened the comment period on its 1997 proposal. Regarding the common knowledge element, FDA explained,

> In the 1997 proposed rule, we proposed to revise Section 170.30 to broaden the description of the common knowledge element to clarify the types of technical evidence of safety that would form the basis of a GRAS determination, and to clarify the role of publication in satisfying the common knowledge element. Specifically, we proposed revising Section 170.30(b) from "… ordinarily be based upon published studies and other data and information" to "based upon generally available and accepted scientific data, information, methods or principles, which ordinarily are published and may be corroborated by unpublished scientific data, information, or methods." (FDA, 2010).

Regarding the definition of "scientific procedures," FDA explained its proposal as follows:

> We also proposed a companion change to the definition of scientific procedures … from "Scientific procedures include those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance." To "Scientific procedures include scientific data (such as human, animal, analytical, or other scientific studies), information, methods and principles, whether published or unpublished, appropriate to establish the safety of a substance. (FDA, 2010).

None of the comments received by FDA in response to the 1997 proposal, as summarized by the agency in its 2010 notice, objected to the use of published and unpublished scientific studies and other information as the basis for GRAS conclusions. (FDA, 2010). FDA provided additional guidance in the report, "*Guidance for Industry, Considerations Regarding Substances Added to Foods, Including Beverages and Dietary Supplements*" (FDA, 2014). FDA stated as a "nonbinding recommendation" that,

> For a particular use of a substance to be GRAS, there must be both evidence of safety and a basis to conclude that this evidence is generally known and accepted by qualified experts. In other words, the GRAS standard first requires that the scientific evidence about the substance establishes that the intended use of the substance is safe; … In addition, under the second part of the GRAS standard, the scientific evidence to establish the safety of the substance for its intended use must be generally available, and there must be a basis to conclude that consensus exists among qualified exerts about the safety of the substance for its intended use (see 21 CFR 170.30(a)-(c)).

FDA's regulations and policy statements focus on the general availability of information used in GRAS assessments and the actions taken to assure that general knowledge of GRAS conclusions is available to the scientific community knowledgeable about the safety of food ingredients and to the public. The FEMA GRAS program complies with the common knowledge element of GRAS conclusions in a number of ways.

- The FEMA Expert Panel ordinarily uses published information corroborated by unpublished information in its GRAS assessments. The Expert Panel uses all available information, whether published or unpublished.
- The Expert Panel makes its decisions on GRAS status available shortly after they are completed by publishing them on the public portion of the FEMA website.
- The identity of all FEMA GRAS flavor ingredients is published, along with the corresponding conditions of intended use, in the food industry journal, *Food Technology,* which is widely-read by the scientific community knowledgeable about the safety of food ingredients. This information is also shared directly with FDA.
- The scientific bases for FEMA GRAS conclusions are summarized in the "Key Findings" supplementary sections for FEMA GRAS reports published in *Food Technology* (*e.g.* Cohen et al., 2018b). The Expert Panel also regularly publishes review articles in the peer-reviewed scientific literature assuring broad dissemination of information (*e.g.* Cohen et al., 2019). This information is also shared directly with FDA.
- As described on the public portion of the FEMA website, anyone may request information related to the technical element of a FEMA GRAS conclusion and receive it for only the cost of duplication.
- The FEMA Expert Panel is specifically convened solely for the purpose of evaluating the GRAS status of flavor ingredients. The FEMA GRAS publications in *Food Technology* therefore document the opinion of an expert panel that is convened specifically for the purpose of assessing the safety and GRAS status of flavor ingredients. The FEMA Expert Panel is convened and operated consistent with the FDA's guidance on GRAS panels (FDA, 2017b).
- The FEMA Expert Panel is typically composed of six to eight members of various scientific disciplines relevant to the safety evaluation of flavor ingredients and their decisions on GRAS status must be unanimous. This provides a high degree of confidence that decisions made by the Panel are consistent with current scientific concepts and that the decisions would be generally recognized as scientifically appropriate and as a consensus among qualified experts. The composition of the FEMA Expert Panel reflects the "appropriate and balanced expertise" recommended by FDA (FDA, 2017b).

6.2. The FEMA GRAS program is transparent

Concerns have been expressed that some GRAS conclusions determined by private entities are not adequately transparent – meaning that in some instances the identity of food ingredients subject to private GRAS assessments and the scientific basis for them are not available for public evaluation.

Since 1965 (Hall and Oser, 1965), the identities of all flavor ingredients determined to be FEMA GRAS are published regularly in the widely-read journal *Food Technology* and all of these publications are available to the public on the FEMA website (www.femaflavor.org). The identity of the flavor ingredients most recently determined to be FEMA GRAS are published on the public portion of the FEMA website (www.femaflavor.org) prior to their publication in *Food Technology* together with the key findings supporting GRAS status. In addition, more than two hundred and fifty individual publications describing the FEMA GRAS program and the safety of flavor ingredients (www.femaflavor.org/GRAS).

In the preamble to the final rule on its voluntary GRAS notification program, FDA responded to a request that FDA "require companies to maintain active and accurate registrations for GRAS substances in a public database (FDA, 2016a)." FDA declined this request. FEMA, on its own initiative, developed such a database for FEMA GRAS flavor ingredients. Since 2016, a searchable compilation of all FEMA GRAS flavor ingredients has been available to the public on the FEMA website in the FEMA Flavor Ingredient Library (www.femaflavor.org).

The scientific bases for the Expert Panel's GRAS conclusions, including detailed summaries of the supporting scientific information, are published in widely-read, peer reviewed, scientific journals such as *Food and Chemical Toxicology*. In addition, extensive summaries of the information supporting the safety of more than 2,000 FEMA GRAS substances are also published by the Joint FAO/WHO Expert

Committee on Food Additives (JECFA), an independent international scientific advisory body managed through the United Nations (See www.who.int/foodsafety/chem/jecfa/en/index.html). These reviews (*e.g.* JECFA, 2009) are based in part on the scientific information contained within the original GRAS assessments of flavor ingredients and the cyclical affirmations of GRAS status conducted and published by the FEMA Expert Panel. The information used in JECFA's safety assessments is published by JECFA in publicly available monographs on structurally-related groups of flavor ingredients.

All GRAS conclusions made by the FEMA Expert Panel are provided to FDA along with the scientific information supporting the conclusions and FDA has long recognized these GRAS conclusions as appropriate evidence of GRAS status. At one time FDA explicitly acknowledged GRAS conclusions made by the FEMA Expert Panel in *Federal Register* notices stating that FEMA GRAS substances were "approved for inclusion in the FDA GRAS review process" and therefore were eligible for the application of its bulk flavor labeling policy (FDA, 1976; Hallagan and Hall, 1995a; Hallagan and Hall, 2009).

In June 2018, FDA announced a new publicly available, searchable database, the "Substances Added to Food" inventory. The new database replaced the agency's previous database, the "Everything Added to Food in the U.S." (EAFUS) inventory. The FDA stated, "The new searchable inventory contains approximately 4,000 substances, and includes information on food additives, color additives, Generally Recognized as Safe (GRAS) and prior-sanctioned substances." (FDA, 2018b). FDA's new inventory contains listings for the identities of FEMA GRAS flavor ingredients through the "GRAS 25" publication (Smith et al., 2011) with the agency intending to bring the inventory current with respect to FEMA GRAS substances in the future.

6.3. The application of the Delaney Clause to flavoring substances regulated by FDA as food additives

The Delaney Clause was enacted as part of the Food Additives Amendment of 1958 to the Federal Food, Drug, and Cosmetic Act (Pub. L.85–929 Sec.1. 6 Sept. 1958) and states "that no (food) additive shall be deemed safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal." (21 U.S.C. Sec. 348(c)(3) (A)). The Delaney Clause does not modify the robust safety standard which already exists in the statute but rather attempts to advance a policy objective to eliminate risks associated with the ingestion of carcinogens through hazard identification rather than risk assessment. In the 1950s, when the Delaney Clause was debated and enacted, the prevailing scientific consensus was that exposure to even one molecule of a carcinogenic food additive presented a significant human health risk and therefore a complete prohibition of exposure to such substances was necessary to protect public health. At that time, it was assumed that carcinogens, including those present in food, caused tumors in test animals solely through a linear dose-response, direct-acting mechanism with no threshold.

Our understanding of the mechanisms of carcinogenesis have advanced significantly since 1958 and it is now clear that the Delaney Clause represents antiquated science and that carcinogens do not all act consistent with the model of carcinogenesis upon which the Delaney Clause was based (Bevan and Harrison, 2017). In addition, it now also appears that high-dose rodent feeding studies do not accurately predict carcinogenic potential in humans and may lead to conclusions in hazard identification schemes that substances cause cancer when in reality they are highly unlikely to (Boobis et al., 2016; Goodman, 2018).

Despite significant advances in understanding carcinogenesis, the Delaney Clause has not been revised since its enactment in 1958, and if read strictly its application can lead to policy outcomes that are not in accord with current scientific safety evaluation principles. A careful reading of the Delaney Clause shows that Congress afforded FDA flexibility in its application of the Delaney Clause. Even within the scope of its literal application, the Delaney Clause is not self-executing. For example, the agency may take into account within its process of considering a finding of carcinogenicity whether there exist "appropriate tests" for the "evaluation of safety" of the substance. (FFDCA Section 348(c)(3) (A)). The legislative history for the Food Additives Amendment clearly shows that Congress contemplated that the FDA would exercise scientific judgment in applying the Delaney Clause. In Congressional hearings on the Delaney Clause as applied to color additives, Health, Education and Welfare Secretary Arthur Flemming stated:

> The opposition to the inclusion of an anticancer clause arises largely out of a misunderstanding of how this provision works. It allows the Department and its scientific people full discretion and judgment in deciding whether a substance has been shown to cause cancer … (Color Additives: Hearings Before the House Committee on Interstate and Foreign Commerce. 86th Congr. 501. 1960).

The Delaney Clause does not dictate how FDA must come to a conclusion on whether a food additive induces cancer. Congress enacted the Delaney Clause with the intent that FDA, the expert on food additive safety, should utilize its expertise and judgement when evaluating the carcinogenic potential and safety of food additives, and determine the appropriate types of information that are required for the agency to fulfill its obligation to assure the safety of food additives. The Delaney Clause exists within the broader statutory construct requiring FDA to evaluate the available and relevant scientific data on a food additive. The FD&C Act specifically requires that "no such (food additive) regulation shall issue if a fair evaluation of the data before the Secretary establishes the safe use of the (food) additive. (21 U.S.C. Sec. 348(c)(1) (A). Therefore, the statute requires FDA to take affirmative action to evaluate all available data to make the agency's own safety determination. Food law experts who have reviewed this issue have observed that with respect to the conclusion that a food additive induces cancer leading to a "Delaney finding" by the FDA, "Scientific judgment has played, and apparently was intended to play, an important role in the policy's application." (Merrill, 1978).

A small number of naturally occurring flavoring substances have been asserted to be carcinogens based on some positive endpoints in rodent lifetime toxicity/carcinogenicity feeding studies when large amounts of these substances were administered. A coalition of NGOs, citing the Delaney Clause, submitted a food additive petition to FDA to delete the existing FDA food additive approvals at 21 CFR 172.515 for seven synthetic flavoring food additives (CSPI et al., 2015). The seven flavoring food additives are benzophenone, ethyl acrylate, methyl eugenol, *B*-myrcene, pulegone, pyridine, and styrene. None of the seven flavoring substances has a significant reported volume of use in the U.S. (Harman and Murray, 2018). All seven occur naturally in a variety of foods. Of the seven, for example, *B*-myrcene is naturally occurring in citrus fruits and other foods, and pulegone is present in natural mint oils used in gum, candy and other foods. Spices and essential oils in which these two substances are naturally occurring constituents are permitted by FDA for use in foods (21 CFR 182.10; 182.20) and the NGO petition does not address these uses. The seven flavoring food additives can also be produced through processing widely considered to result in "synthetic" substances.

In October 2018, the FDA responded to the NGO petition by granting the petition for six of the substances (benzophenone, ethyl acrylate, methyl eugenol, *B*-myrcene, pulegone, and pyridine) noting that the seventh substance, styrene, was being delisted because it is no longer used as a flavoring substance (FDA, 2016c; FDA, 2018c). In doing so, FDA stated,

> We are taking this action (on the six flavoring substances) because, despite FDA's scientific analysis that these substances do not pose a risk to public health under the conditions of their intended use, the petitioners provided data demonstrating that these additives induce

cancer in laboratory animals, and, as a result of this finding in animals, FDA cannot as a matter of law maintain the listing of these synthetic flavoring food substances in the food additive regulations (FDA, 2018c).

FDA explained that it had based its decision "as a matter of law" on the "extraordinarily rigid" Delaney Clause of the Federal Food, Drug, and Cosmetic Act. The FDA further explained,

> We have evaluated the data and information submitted by the petitioners, as well as other relevant carcinogenicity data and information, and have determined the remaining six synthetic flavoring substances (*i.e.* other than styrene) that are the subject of FAP 5A4810 are unlikely to pose a potential or significant carcinogenic risk for humans at the levels that these synthetic flavoring substances are used in foods, and that the use of these food additives is safe for human consumption. In other words, FDA has a reasonable certainty that the substances do no harm under the intended conditions of use (the standard for approving food additives). (FDA, 2018c).

In its decision on the NGO petition, FDA made a clear demarcation in how it was compelled to apply the Delaney Clause in this specific instance. The agency was not applying Delaney regarding the agency's scientific discretion as allowed by Congress. In fact, FDA performed a rigorous safety assessment and concluded that the six synthetic flavoring substances were safe for their intended use. FDA did apply Delaney strictly regarding the agency's legal discretion hence the agency applying Delaney in this instance only "as a matter of law."

In its final rule on the NGO petition, FDA affirmed the safety of the flavoring substances at issue stating that the agency "has a reasonable certainty that the substances do no harm under the intended conditions of use" (FDA, 2018c). FDA stated,

> (N)one of the data in our evaluations of the six synthetic flavoring substances supports a finding that they are human carcinogens when consumed at the levels of intended use. (FDA, 2018c).

FDA stated in its final rule that its action to delist the flavoring substances is limited to their synthetic versions.

> In making this determination, we reiterate the point, first made in our 1964 proposed rulemaking, that all of the synthetic flavoring substances that are the subject of the petition have a natural counterpart in food or in natural substances used to flavor foods. … FDA's revocation of the listings providing for the use of these synthetic flavoring substances and adjuvants does not affect the legal status of foods containing natural counterparts or non-synthetic flavoring substances extracted from food, and there is nothing in the data FDA has reviewed in responding to the pending food additive petition that causes FDA concern about the safety of foods that contain natural counterparts or extracts from such foods. (FDA, 2018c).

In the final rule, FDA limited the reach of the Delaney Clause and distinguished between the antiquated hazard-only identification approach of Delaney and a scientifically current risk-based approach. FDA explained the original purpose of the Delaney Clause at the time it was enacted in 1958.

> The Delaney Clause limits FDA's discretion to determine the safety of food additives in that it prevents FDA from finding a food additive to be safe if it has been found to induce cancer when ingested by humans or animals, regardless of the probability, or risk, of cancer associated with exposure to the additive or of the extent to which the experimental conditions of the animal study or carcinogenic mode of action provide insight into the health effects of human consumption and use of the additive in question … Congress intended for the Delaney Clause to be "extraordinarily rigid." (FDA, 2018c).

It has long been recognized that the Delaney Clause "recognizes no distinctions based on carcinogenic potency and, at least in theory, it applies equally to additives used in large amounts to those present at barely detectable levels. It thus takes no account of the actual risk a carcinogenic additive might pose." (Merrill, 1997). This point is especially relevant to flavoring substances that are most often present in food through added flavors in ppm or even ppb levels. Consistent with these concepts, FDA commented on the data it reviewed in making its decision on the NGO petition distinguishing between simple hazard identification and the far more relevant matter of human risk. FDA stated,

> FDA acknowledges that the NTP studies (the primary data cited by petitioners) are designed for hazard identification and not for assessing the human carcinogenicity risk of chemicals under specific conditions of use. (FDA, 2018c).

FDA distinguished the rigid interpretation of the Delaney Clause from its practical application to the most relevant issue – does the scientific information available on a given food additive support the conclusion that there is a reasonable certainty that no harm will result from the human ingestion of the substance? With respect to the carcinogenic potential of the six flavoring substances, FDA stated, "(N)one of the data in our evaluations of the six synthetic flavoring substances supports a finding that they are human carcinogens when consumed at the levels of intended use." (FDA, 2018c).

While applying the Delaney Clause "as a matter of law," FDA concluded that the six substances are safe for human consumption. FDA stated,

> We have evaluated the data and information submitted by the petitioners, as well as other relevant carcinogenicity data and information, and have determined the remaining six synthetic flavoring substances (*i.e.* other than styrene) that are the subject of FAP 5A4810 are unlikely to pose a potential or significant carcinogenic risk for humans at the levels that these synthetic flavoring substances are used in foods, and that the use of these food additives is safe for human consumption. In other words, FDA has a reasonable certainty that the substances do no harm under the intended conditions of use (the standard for approving food additives). (FDA, 2018c).

Of the seven synthetic flavoring food additives that were the subject of the NGO petition, five are considered to be "generally recognized as safe" (GRAS) by the FEMA Expert Panel (benzophenone, ethyl acrylate, *B*-myrcene, pulegone, and pyridine). Prior to FDA's action on the petition, the FEMA Expert Panel concluded that two of the seven (methyl eugenol and styrene) were no longer FEMA GRAS – methyl eugenol because the available scientific information was not adequate to maintain GRAS status and styrene because it was no longer used as a flavoring substance (Cohen et al., 2015, 2018b). For the other five synthetic flavoring food additives, the FEMA Expert Panel "reviewed the FDA's final rule and determined that no change is necessary in the FEMA GRAS status of benzophenone, ethyl acrylate, *B*-myrcene, pulegone, and pyridine" (Cohen et al., 2020). The Expert Panel's conclusion is consistent with FDA's finding that these substances are safe.

GRAS substances are subject to the same statutory safety standard as food additives (a reasonable certainty of no harm) but are specifically exempted from the definition of food additives (FFDCA Section 201(s)). FDA recognized this distinction in its final rule for its voluntary GRAS notification program:

> In creating the premarket approval requirement for food additives in the 1958 amendment, Congress excluded a substance that is GRAS under the conditions of intended use from the definition of food additive. The creation of this GRAS provision reflected Congress' determination that many substances intentionally added to food for a specific use do not need premarket review by FDA to ensure their

> safety, either because their safety has been established by a long history of safe use in food, or because their safety has been established by information that is generally available to and accepted by qualified experts regarding the conditions of intended use of a substance in food. (FDA, 2016a)

The application of the Delaney Clause to GRAS substances has not yet been directly settled in the courts but recent assertions by FDA and the Department of Justice (DOJ) in ongoing litigation over the FDA's GRAS notification program indicate that it does not. In a memorandum supporting a motion for summary judgement in *Center for Food Safety* et al. *v. Azar* et al. (Case 1:17-cv-03833-VSB S.D.N.Y., memorandum filed 17 June 2019), FDA and DOJ assert that the uses of a substance that are GRAS are excluded from regulation as food additives and therefore the Delaney Clause does not apply to such uses. FDA and DOJ stated,

> Plaintiffs assume that the Delaney Clause governs the determination of whether a substance is GRAS or a food additive. This assumption cannot be squared with the plain text of the clause, which prohibits FDA from approving "food additives" that can cause cancer. A substance is, by definition, not a "food additive" if it is GRAS.

In January 2020, FDA confirmed the effective date for the final rule on the seven synthetic flavoring food additives and responded to an objection to the final rule (FDA, 2020b). FDA clarified several procedural issues, and one important substantive issue – the exclusion of GRAS substances from the consideration by FDA as food additives under the FFDCA. FDA stated,

> A substance is generally recognized as safe (GRAS) if there is general recognition, among qualified experts, to be safe under the conditions of its intended use. A substance that is GRAS under the conditions of its intended use is excluded from the statutory definition of food additive under section 201(s) of the FD&C Act (21 U.S.C. 321(s)).

The FDA's decision on the NGO petition has reinvigorated the long-standing debate on the scientific relevance, public health benefits, and reach of the application of the Delaney Clause. A recent series of publications calls for significant changes in how we evaluate substances for carcinogenic potential and how such substances are regulated (Wolf et al., 2019; Doe et al., 2019). It is time for a thorough debate on the need for statutory reform that would reflect the significant advances in understanding of the mechanisms of carcinogenesis and their relevance to human health since the institution of the Delaney Clause more than sixty years ago (Armstrong and Dunaif, 2019).

7. Experts must be qualified by scientific training and experience to evaluate safety

7.1. The current FEMA expert panel

The current members of the FEMA Expert Panel are: Samuel M. Cohen, M.D., Ph.D. (University of Nebraska, Expert Panel Chair); Gerhard Eisenbrand, Ph.D. (University of Kaiserslautern, retired); Shoji Fukushima, M.D., Ph.D. (Japan Bioassay Research Center, retired); Nigel J. Gooderham, Ph.D. (Imperial College London); Fred Guenrich, Ph.D. (Vanderbilt University); Stephen S. Hecht, Ph.D. (University of Minnesota); Ivonne M.C.M. Rietjens, Ph.D. (Wageningen University, Netherlands) and Thomas Rosol, D.V.M. (Ohio University). Current Expert Panel members are well-recognized experts in toxicology, pathology, metabolism, pharmacology, and pharmacokinetics with more than 250 years of collective relevant experience. The Expert Panel's composition reflects the "appropriate and balanced expertise" recommended by FDA (FDA, 2017b). The academic credentials of Expert Panel members and each member's extensive publications in their fields of expertise clearly establish that FEMA Expert Panel members are experts "qualified by scientific training and experience to evaluate the safety of flavor ingredients." Expert Panel members have direct and extensive experience in the safety assessment of flavor ingredients.

7.2. Procedures to address potential conflicts of interest

In order to assure that there is confidence in GRAS conclusions, it must be clear that the experts making the conclusions are free from potential conflicts of interest and are not subject to bias in their decision-making (FDA, 2017b). A common criticism of GRAS conclusions made by experts sponsored by industry is that such experts have inherent conflicts of interest by virtue of their associations with industry and compensation by industry for their services (Neltner et al., 2013b).

A number of measures are in place to assure that FEMA Expert Panel decisions on GRAS status are fully objective and based solely on the merits of the available information and are not subject to bias (Marnett et al., 2013).

- When evaluating GRAS applications, Expert Panel members do not know the identity of the company responsible for the application. The identity of applicant-companies is maintained as confidential information by the FEMA staff even after the use of the substance is evaluated and granted GRAS status.
- FEMA Expert Panel members do not prepare GRAS applications. Applications for FEMA GRAS assessments are prepared by the FEMA member seeking the GRAS assessment for the substance at issue.
- Companies submitting GRAS applications are not allowed to contact Expert Panel members in any way nor are they allowed to attend meetings during which their applications are being considered.
- The Expert Panel is self-appointed – members are not appointed by FEMA. When a member retires from the Panel, the remaining Expert Panel members consider the necessary qualifications of possible successors and make the appointment of a replacement.
- The identities of the members of the Expert Panel are known to the public through their regular publications in *Food Technology, Food and Chemical Toxicology,* and other publicly available journals, and posting on the public portion of the FEMA website (www.femaflavor.org).
- FEMA Expert Panel members conduct their reviews of GRAS applications during in-person meetings, usually three times per year and receive a honorarium from FEMA for their service whether or not they conclude that any substances are GRAS.
- FEMA Expert Panel members are not allowed to have consulting relationships with FEMA member companies regarding anything to do with flavors in the context of the FEMA GRAS Program.
- FEMA Expert Panel members provide a declaration of their consulting and business relationships prior to each Expert Panel meeting for review and action, if necessary, by the Panel's Legal Advisor. Action may include mandated recusal at meetings.
- FEMA staff members support the Expert Panel at the direction of the Panel in several ways including the preparation of data packages and other support functions, and are not allowed to have independent consulting or business relationships with FEMA member companies regarding anything to do with flavors in the context of the FEMA GRAS program.
- When the first FEMA Expert Panel began operations in 1960 it included the name of FEMA in its title ("FEMA Expert Panel") to be fully transparent about its association with FEMA and the flavor industry.

8. Safety based on scientific procedures

For more than fifty-five years, the FEMA Expert Panel has applied thorough and state-of-the-art scientific procedures in its GRAS assessments to comply with the "technical element" for GRAS conclusions as required by FDA. As previously noted, FDA has explicitly acknowledged GRAS conclusions made by the FEMA Expert Panel by the inclusion of

FEMA GRAS flavor ingredients in the agency's new Substances Added to Food inventory (FDA, 2018b). Furthermore, FDA has never objected to the measures adopted by the Panel for compliance with the "technical element" for GRAS determinations made through scientific procedures.

The procedures employed by FDA and the FEMA Expert Panel to determine safety are remarkably similar as evident in the agency's description of its safety evaluations for the flavoring substances at issue in the NGO petition where FDA came to the same conclusion as the FEMA Expert Panel that the available data demonstrated that the flavoring substances are safe under their intended conditions of use (FDA, 2018c). FDA, the FEMA Expert Panel, and other expert bodies all rely on the same general set of widely accepted principles of safety assessment (Munro et al., 1998; Magnuson et al., 2013) including consideration of the "Margins of Exposure," the interpretation and relevance of genotoxicity data, and estimates of dietary exposure (Smith et al., 2005; Cohen et al., 2018a; FDA, 2018c; Smith et al., 2018; Gooderham et al., 2020). When appropriate data are available, the FEMA Expert Panel has begun applying mathematical modeling methods of dose-response data for studies to allow for the estimation of a benchmark dose (Cohen et al., 2020; Rietjens et al., 2020).

The Expert Panel has consistently reviewed and updated its procedures to assure that it employs the best available approaches in its GRAS assessments. The Expert Panel has published these procedures to assure transparency and that any gaps in its GRAS conclusions may be identified and called to the Panel's attention (Gerarde, 1973; Oser and Hall, 1977; Woods and Doull, 1991; Smith et al., 2005; Cohen et al., 2018a; Gooderham et al., 2020). The Expert Panel has long employed the practice of evaluating the safety of flavor ingredients within structurally-related groups thereby employing all available safety assessment information that may be helpful in their GRAS assessments. As FDA noted:

> We agree that published information for a specific substance is not always necessary to support a conclusion that the use of a substance is GRAS through scientific procedures. For example, there may be situations where the safety of the use of the substance in food can be demonstrated by relevant published information on a closely structurally related compound. (FDA, 2016a).

8.1. Policy on the review of changes in methods of production

While there is no distinction for safety assessment purposes between the synthetically produced forms of food ingredients and their naturally-derived counterparts, production methods should be considered in such safety assessments (FDA, 2012). Flavor ingredients may be produced in a variety of ways and the FEMA Expert Panel's assessments include a review of the method of production for the ingredients, including changes that may be implemented after a flavor ingredient is determined to be FEMA GRAS (Cohen et al., 2015).

It is long-standing FEMA policy that significant changes in the use or production of FEMA GRAS flavoring substances requires that their GRAS status be reevaluated by the Expert Panel. The Expert Panel states its policy in GRAS determination letters provided to successful applicants:

> *Significant* changes in use levels within an approved category, or use in new food categories, require a re-evaluation of this material by the Expert Panel. *Re-evaluation may also be required if there is a significant change in the composition or production method of the product in commerce*. The Expert Panel reserves the right to re-evaluate the GRAS status of this substance if new relevant data becomes available or if there is a significant increase in the annual volume of use of this substance. (Emphases added).

The Expert Panel's policy is consistent with guidance issued by the Food and Drug Administration (FDA, 2012) that indicates that methods of production for new food ingredients and new methods of production for food ingredients already in commerce should be reviewed to assure that they do not result in potential safety concerns.

In the 1990s significant exploration of new methods of producing flavor ingredients began. Some of these involved techniques of genetic modification and subsequently a process for performing a safety assessment for flavoring substances produced by these new methods was published (Hallagan and Hall, 1995b). The FEMA Expert Panel first explained its process for evaluating flavoring substances produced through biotechnology production methods in the "GRAS 17" publication (Smith et al., 1996). As noted by Smith et al. (1996), the issues evaluated by the Expert Panel in such a safety assessment are consistent with FDA policy (*e.g.* FDA, 2019) focusing on the identity of the substance and its existing regulatory status, *i.e.* whether it is currently permitted for addition to food which would indicate a previous safety inquiry to comply with premarket approval requirements. However, this safety assessment process was seldom applied by the FEMA Expert Panel because the production of flavoring substances using biotechnology has only recently become economically and practically viable.

Newer biotechnology production methods are more efficient and are being employed for a few targeted flavor ingredients that are economically viable such as vanillin and nootkatone (Fritz, 2013; Shetty, 2013). Consistent with the Expert Panel's long-standing policy of applying the best available science, the Panel revisited the issues associated with newer biotechnology techniques (*e.g.* "synthetic biology" methods) and updated their policies on FEMA GRAS reviews of uses of substances produced using such methods (Cohen et al., 2015). The Expert Panel's policies are consistent with FDA's policies for the safety review of such substances (FDA, 2019).

The recent development and use of "gene editing" techniques such as CRISPR may lead to development and marketing of flavoring substances derived from plants modified using these techniques. These gene editing techniques differ significantly from other methods of genetic modification in that they do not involve the insertion of genetic material from other species but rather involve the "editing" of the target species' inherent genome. For example, if certain citrus fruits were modified to edit out a specific gene or genes related to ripening that would be advantageous for the production of citrus essential oils then these large volume flavor ingredients might be produced more efficiently in greater quantities and higher quality.

The U.S. Department of Agriculture (USDA) recently issued correspondence relevant to the use of gene editing technologies in the production of some food crops (USDA, 2018a; USDA, 2018b; USDA, 2019) distinguishing gene editing techniques from genetic modification techniques involving the insertion of exogenous genetic material and concluded that several plant varieties produced in this manner need not be regulated by USDA. The USDA opinions may have implications for flavoring substances produced from such plants in terms of safety assessment and labeling as "natural" or "synthetic."

8.2. Intake estimates for flavor ingredients

Intake estimates are a critical component of the safety assessment and GRAS conclusions of flavor ingredients (Hallagan and Hall, 2009). One criticism of GRAS conclusions is that it is difficult to reliably estimate the potential human intake for GRAS food ingredients, a perceived problem exacerbated by the asserted lack of knowledge of the identity of GRAS substances present in the U.S. food supply (Neltner et al., 2011).

FEMA has addressed this issue for existing FEMA GRAS flavor ingredients and for new GRAS flavor ingredients. For existing FEMA GRAS flavor ingredients, FEMA has for many years conducted periodic surveys of the amounts of FEMA GRAS flavor ingredients that "disappear" into the U.S. food supply on an annual basis. These data are used to facilitate the calculation of a conservative estimate of human intake (Hall and Ford, 1999; Hallagan and Hall, 2009). The most recent

survey was published in 2018 reporting annual data from 2015 (Harman and Murray, 2018). These survey data can be used to calculate a reliable and conservative method of human dietary exposure. FDA acknowledged the value of the FEMA surveys in its final rule on the NGO petition.

> We also estimated dietary exposure for the six synthetic flavoring substances using information from the 2015 Poundage and Technical Effects Survey from the Flavor and Extract Manufacturers Association (FEMA) collected from its member companies … To estimate dietary exposure to the synthetic flavoring substances, we used a "per capita times ten" approach that conservatively assumes 10 percent of the population consumes 100 percent of the available flavoring substance. (FDA, 2018c).

For new GRAS flavor ingredients, FEMA requires that applicants for GRAS status include an estimate of annual volume of use for the candidate flavor ingredient. For flavor ingredients not yet in use, there is no poundage survey information available upon which to initially estimate human intake. In the absence of such data, the Expert Panel requires the company applying for GRAS status to provide anticipated annual poundage that the company expects to sell into the U.S. food supply during the first year. Survey information and experience demonstrate that for the vast majority of newly GRAS flavor ingredients, the annual anticipated poundage reported on the GRAS application is a significant over-estimation (Waddell et al., 2007).

8.3. The role of genotoxicity assays in the GRAS assessment of flavor ingredients

The significance and role of genetic toxicity hazard identification is a recurring topic in many discussions on the safety assessment of foods and food ingredients (Kirkland et al., 2005; Kirkland et al., 2007; EFSA, 2011). Data from genotoxicity assays are generally considered relevant in understanding the mode of action of food ingredients being evaluated for carcinogenic potential. Flavor ingredients generally do not raise concern for genotoxic potential based on their structure, and the vast majority of flavor ingredients that have been subjected to genetic toxicity testing are negative in standard *in vitro* and *in vivo* assays that assess mutagenic, clastogenic, and aneugenic potential.

The FEMA Expert Panel has consistently evaluated the results and relevance of genotoxicity assays on flavor ingredients within its GRAS assessments (Smith et al., 2005, 2009). The Expert Panel considers genetic toxicity testing data within the larger context of all information, including the biochemical fate of flavor ingredients, and animal toxicity and carcinogenicity study data. The Expert Panel has recently completed a publication on the consideration is of genetic toxicity testing data within its GRAS assessments. This publication reflects advances in the standards for genotoxicity testing and changes in emphasis in the relevance of certain test assays (Gooderham et al., 2020).

FDA evaluated the genotoxic potential of the synthetic flavoring food additives that were the subjects of the NGO petition. FDA concluded that five of the substances (benzophenone, ethyl acrylate, *B*-myrcene, pulegone and pyridine) did not demonstrate genotoxic potential in relevant studies. The conclusions that these substances are not genotoxic support the agency's conclusion that they are not a carcinogenic risk to humans when added to food as flavoring substances. FDA noted that one exception among the subject flavoring substances was the genotoxicity data on methyl eugenol, a substance that the FEMA Expert Panel had determined was no longer FEMA GRAS in 2015 (Cohen et al., 2015). FDA stated,

> (W)ith the exception of the data concerning methyl eugenol, the data from animal studies demonstrated that the modes of action (MOA) of carcinogenicity are not acting through mechanisms of genotoxic alterations and are not relevant to humans. (FDA, 2018c).

9. Under the conditions of intended use in food

The FEMA Expert Panel conducts GRAS assessments of flavor ingredients only under their conditions of intended use in human food. FFDCA Section 201(f) defines "food" as, "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used as components of any such article." Although the statutory definition of "food" covers more than human food, the FEMA Expert Panel conducts GRAS assessments only for articles used as components of human food, drinks, and chewing gum.

The conditions of intended use of a food ingredient are a key element of a GRAS determination. Because it is the use of the substance that is GRAS, and not the substance itself, the conditions under which a substance is determined to be GRAS are critical for compliance with the statutory requirements described in FFDCA Section 201(s). The conditions of intended use for the GRAS status of a food ingredient has three components:

- The designated technical effect in the food;
- The use in specified food categories and;
- The use levels corresponding to the specified food categories.

In applying the three components of the conditions of intended use to substances that are candidates for FEMA GRAS status, first, the substance must be a flavor ingredient in its technical effect. There are two general classes of flavor ingredients:

1. Flavoring substances – substances that impart or modify flavor;
2. Flavor adjuvants – including emulsifiers, preservatives or solvents that allow the flavoring substances to function in the finished food.

Second, food categories in which the substance is to be used must be identified. A FEMA GRAS flavor ingredient is GRAS only for use in the food categories that are specified. Third, in terms of the specified use levels, these are provided to give guidance on the range of use levels for which the substance is GRAS. Significant deviation from the maximum end of the range that results in either a technical effect other than that specified, or a significant increase in exposure would mean that the substance is not GRAS for the specified use. The FEMA Expert Panel has had a long-standing policy that changes in the conditions of intended use must be submitted to the Expert Panel for evaluation as a condition of maintaining FEMA GRAS status.

A compounded flavor may consist of flavoring substances that impart or modify flavor (*i.e.* taste perception), and other non-flavoring substances (*i.e.* flavor adjuvants) such as solvents, emulsifiers, carriers, and preservatives. Flavoring substances and adjuvants are both candidates for FEMA GRAS status provided that their conditions of intended use are solely for formulating compounded flavors. 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).

FEMA GRAS assessments are conducted by the Expert Panel only on the individual flavor ingredients and not on the compounded flavor – the flavor mixture that is added to food. While there are approximately 3,000 FEMA GRAS flavor ingredients, there are a myriad of compounded flavors that are regularly added to foods. There is no indication that individual flavor ingredients when present in compounded flavors have any different toxicological properties than when they are

consumed individually. Furthermore, it would be impracticable to evaluate each of the many thousands of compounded flavor formulations.

In applying FDA policy on conditions of intended use, the FEMA Expert Panel has been clear that its GRAS conclusions are solely for substances under their conditions of intended use as flavor ingredients (Waddell et al., 2007; Hallagan and Hall, 2009). Other uses of FEMA GRAS flavor ingredients, such as use for a sweetening effect, must have "regulatory authority to use" other than FEMA GRAS status to be legally added to food in the U.S. Such other regulatory authority may include food additive status as determined by FDA, submission to the FDA's voluntary GRAS notification program and receipt of a "no objection" letter from FDA, or an independent GRAS determination that meets the statutory requirements of the GRAS provision at FFDCA Section 201(s), and that complies with FDA's regulations and policies on GRAS conclusions.

9.1. Flavorings with modifying properties

An active area of flavor industry research and development is the identification of flavoring substances that "modify" the existing flavor of foods through the inclusion of these substances in the compounded flavors added to foods. Such flavoring substances, known as flavorings with modifying properties (FMPs), include substances of natural origin such as *Stevia* derivatives that produce a flavor modification effect in foods at levels well-below which they provide a sweetening effect. Other FMPs are novel structures that are specific for certain taste receptors that can modify the human perception of sweetness, sour, savory and salty, and that have no perceptible flavor themselves.

Properly addressing the conditions of intended use for FMPs is particularly important. A number of FEMA GRAS FMPs such as thaumatin, neohesperidine dihydrochalcone, and various *Stevia* derivatives provide sweetening effects at use levels significantly above the use levels specified as the conditions of intended use for FEMA GRAS status. The sweetening effect provided by these substances at higher use levels is not within the bounds of the FEMA Expert Panel's consideration of FEMA GRAS status. Therefore, before these substances may be added to food for their sweetening effects regulatory authority to use them as sweeteners (*e.g.* food additive status or a GRAS determination for sweetening use) must be established. Establishing appropriate regulatory authority to use FMPs has important implications for the proper labeling of flavors and the foods to which they are added (Hallagan and Drake, 2018).

To facilitate the proper identification of the technical effect in food of FMPs and other flavoring substances, FEMA developed guidance for flavor product developers on how to conduct sensory testing (Harman and Hallagan, 2013). This guidance provides a standard series of sensory tests that can be used to support an application for GRAS status to be evaluated by the FEMA Expert Panel.

9.2. The use of flavors in "Vaping" products

"Electronic nicotine delivery systems" (ENDS) and other products allowing consumers to "vape", or inhale, a variety of materials are widely used. These products, which include "electronic cigarettes" ("e-cigarettes"), involve a delivery vehicle through which the user inhales vapor from a mixture of constituents that may include nicotine, compounded flavors, and other materials including cannabis derivatives. It is important to note that the GRAS provision in FFDCA Section 201(s) applies only to food as defined in Section 201(f) of the Act, and that the FEMA Expert Panel evaluates flavor ingredients only for use in human food. FEMA GRAS status for the use of flavor ingredients in food does not provide assurance that the flavor ingredients are safe for use in vaping products, nor does it provide regulatory authority to use the flavor ingredient in such products (FEMA, 2020).

FDA published its final regulations to deem e-cigarettes as tobacco products subject to the regulatory authority of the 2009 Family Smoking Prevention and Tobacco Control Act amendments to the FFDCA thereby bringing them under regulation by FDA (FDA, 2016b). FDA has identified flavors used in "e-liquids" as a likely target of regulation and has solicited information related to the use of flavors in such products in an Advanced Notice of Proposed Rulemaking (FDA, 2018a). In January 2020, FDA announced guidance in the form of enforcement priorities that would begin the process of restricting the sale of flavored vaping products while advancing the agency's requirements for premarket authorization of such products (FDA, 2020a).

10. Changes in FEMA GRAS status for use as flavor ingredients

A number of substances once considered GRAS for use as flavor ingredients have, upon additional review, been determined to no longer meet the criteria for FEMA GRAS status for such use. These substances have been re-evaluated for one or more reasons including review during one of the periodic, cyclical affirmation reviews conducted by the Expert Panel, or review of an individual flavor ingredient because new, relevant safety information has become available. The most common reason for removing flavor ingredients from the FEMA GRAS list has been that the existing safety data no longer allow for a conclusion of "general recognition" of safety. In some instances this means that existing data do not meet current scientific standards, and in other instances it may mean that newly available information calls into question the conclusion of general recognition of safety. In a few instances, substances have been removed from the FEMA GRAS list because they are no longer used as flavor ingredients. While some substances have been re-evaluated based on a significant increase in use identified through FEMA's periodic annual poundage surveys, the low use levels of flavor ingredients in food means that even with increases in volumes of use there is an adequate margin of exposure to assure safety and none have been removed for concerns related to increases in exposure.

Over the years, the uses of the following substances used as flavor ingredients have been determined to no longer meet the criteria for FEMA GRAS status: acetamide, 3-acetyl-2,5-dimethylthiophene, calamus, calamus oil, ethyl nitrite, ethylene oxide, 2-hexyl-4-acetotetrahydrofuran, methyl eugenol, 4-methylquinoline, 2-methyl-5-vinylpyrazine, musk ambrette, 3-nonanon-1-yl acetate, quinoline, styrene, and *o*-vinylanisole. Based on the review of new information, the uses of two substances as flavor ingredients, 2-hexyl-4-acetotetrahydrofuran and 2-methyl-5-vinylpyrazine, were once again determined to be GRAS after they were removed from the FEMA GRAS list a number of years ago (Smith et al., 2011).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors are or were affiliated with the Flavor and Extract Manufacturers Association of the United States (FEMA). Author Hallagan is currently the FEMA Senior Advisor. Author Drake is the General Counsel for FEMA. Author Hall had no role with FEMA for approximately the last 20 years of his life but served in several capacities prior to that including Senior Science Advisor to FEMA. FEMA provided financial support for the preparation of this manuscript.

Acknowledgements

All authors are or were affiliated with the Flavor and Extract Manufacturers Association of the United States (FEMA). FEMA provided financial support for the preparation of this report. Author Hallagan is currently the FEMA Senior Advisor. Author Drake is the General Counsel for FEMA. Author Hall had no role with FEMA for approximately the past 20 years but served in several capacities prior to that including Senior Science Advisor to FEMA.

References

Doe, J.E., Boobis, A.R., Dellarco, V., Fenner-Crisp, P.A., Moretto, A., Pastoor, T.P., Schoeny, R.S., Seed, J.G., Wolf, D.C., 2019. Chemical carcinogenicity revisited 2: current knowledge of carcinogenesis shows that categorization as a carcinogen or non-carcinogen is not scientifically credible. Regul. Toxicol. Pharmacol. 103, 124.

Food and Drug Administration (FDA), 2020a. Enforcement priorities for electronic nicotine delivery systems (ENDS) and other deemed products on the market without premarket authorization. Guidance for Industry. www.fda.gov/tobacco-products/products-guidance-regulations/rules-regulations-and-guidance.

Armstrong, S., Dunaif, G.E., February/March 2019. Food Additive Reforms: Time to Repeal the Delaney Clause. Food and Drug Law Institute Update Magazine.

Bendig, P., Maier, L., Vetter, W., 2012. Brominated vegetable oil in soft drinks – an underrated source of human organobromine intake. Food Chem. 133, 678.

Bevan, R.J., Harrison, P.T.C., 2017. Threshold and non-threshold chemical carcinogens: a survey of the present regulatory landscape. Regul. Toxicol. Pharmacol. 88, 291.

Boobis, A.R., Cohen, S.M., Dellarco, V.L., Doe, J.E., Fenner-Crisp, P.A., Moretto, A., Pastoor, T.P., Schoeny, R.S., Seed, J.G., Wolf, D.C., 2016. Classification schemes for carcinogenicity based on hazard-identification have become outmoded and serve neither science nor society. Regul. Toxicol. Pharmacol. 82, 158.

Cohen, S.M., Fukushima, S., Gooderham, N.J., Hecht, S.S., Marnett, L.J., Rietjens, I.M.C.M., Smith, R.L., Bastaki, M., McGowan, M.M., Harman, C., Taylor, S.V., 2015. GRAS flavoring substances 27. Food Technol. 69 (8), 40.

Cohen, S.M., Eisenbrand, G., Fukushima, S., Gooderham, N.J., Guengerich, F.P., Hecht, S.S., Rietjens, I.M.C.M., Davidsen, J.M., Harman, C.L., Taylor, S.V., 2018a. Updated procedure for the safety evaluation of natural flavor complexes used as ingredients in food. Food Chem. Toxicol. 113, 171.

Cohen, S.M., Eisenbrand, G., Fukushima, S., Gooderham, N.J., Guenrich, F., Hecht, S.S., Rietjens, I.M.C.M., Harman, C., Taylor, S.V., 2018b. GRAS flavoring substances 28. Food Technol. 72 (7), 63.

Cohen, S.M., Eisenbrand, G., Fukushima, S., Gooderham, N.J., Guengerich, F.P., Hecht, S.S., Rietjens, I.M.C.M., Bastaki, M., Davidsen, J.M., Harman, C.L., McGowen, M., Taylor, S.V., 2019. FEMA GRAS assessment of natural flavor complexes: *citrus*-derived flavoring substances. Food Chem. Toxicol. 124, 192.

Cohen, S.M., Eisenbrand, G., Fukushima, S., Gooderham, N.J., Guengerich, F.P., Hecht, S.S., Rietjens, I.M.C.M., Rosol, T., Harman, C.L., Taylor, S.V., 2020. GRAS 29 Flavoring Substances. Food Technology (in press).

Center for Science in the Public Interest (CSPI), Natural Resources Defense Counsel, Center for Food Safety, Consumer's Union,Improving Kids' Environment, Center for Environmental health, Environmental Working Group, James Huff Food Additive Petition FAP 5A4810, 30 July 2015. Also see 81. Fed. Reg. 42, 4 January 2016.

European Food Safety Authority (EFSA), 2011. Scientific opinion on genotoxicity testing strategies applicable to food and safety assessment. EFSA J 9 (9), 2379.

Food and Drug Administration (FDA), 23 September 1974. General recognition of safety and prior sanctions for food ingredients. Fed. Regist. 39, 34194.

Food and Drug Administration (FDA), 3 February 1976. Extension of effective date for labeling of certain flavor ingredients. Fed. Regist. 41, 4954.

Food and Drug Administration (FDA), 17 April 1997. Substances generally recognized as safe. Fed. Regist. 62, 18938.

Food and Drug Administration (FDA), 28 December 2010. Substances generally recognized as safe; reopening of the comment period. Fed. Regist. 75, 81536.

Food and Drug Administration (FDA), 2012. Guidance for Industry - Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives.

Food and Drug Administration (FDA), 8 November 2013. Tentative determination regarding partially hydrogenated oils; Request for comments and for scientific data and information. Fed. Regist. 78, 67169.

Food and Drug Administration (FDA), January 2014. Guidance for Industry – Considerations Regarding Substances Added to Foods, Including Beverages and Dietary Supplements. Food and Drug Administration. Center for Food Safety and Applied Nutrition.

Food and Drug Administration (FDA), 17 August 2016a. Substances generally recognized as safe. Fed. Regist. 81, 54960.

Food and Drug Administration (FDA), 10 May 2016b. Deeming tobacco products to be subject to the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the sale and distribution of tobacco products and required warning statements for tobacco products. Fed. Regist. 81, 28974.

Food and Drug Administration (FDA), 15 June 2016c. Styrene information and research center; filing of a food additive petition. Fed. Regist. 81, 38984.

Food and Drug Administration (FDA), 16 November 2017a. Best practices for convening a generally recognized as safe panel: draft guidance for industry; availability. Fed. Regist. 82, 53433.

Food and Drug Administration (FDA), November 2017b. Best Practices for Convening a Generally Recognized as Safe Panel: Draft Guidance for Industry. Center for Food Safety and Applied Nutrition; Center for Veterinary Medicine.

Food and Drug Administration (FDA), 21 March 2018a. Advance notice of proposed rulemaking; regulation of flavors in tobacco products. Fed. Regist. 83, 12294.

Food and Drug Administration (FDA), 2018b. Center for food safety and applied nutrition – constituent update. FDA updates the everything added to food in the U.S. Inventory. www.fda.gov Published 26 June.

Food and Drug Administration (FDA), 9 October 2018c. Food additive regulations; synthetic flavoring agents and adjuvants. Fed. Regist. 83, 50490.

Food and Drug Administration (FDA), 2018d. FDA takes step to protect consumers against dietary supplements containing dangerously high levels of extremely concentrated or pure caffeine. www.fda.gov Published 12 April.

Food and Drug Administration (FDA), 2018e. FDA's Predictive Toxicology Roadmap. U.S. Food and Drug Administration. Silver Spring, Maryland.

Food and Drug Administration (FDA), 2019. Biotechnology guidance documents and regulatory information. www.fda.gov/food/guidance-documents.

Food and Drug Administration (FDA), 31 January 2020b. Food additive regulations; synthetic flavoring agents and adjuvants; confirmation of effective date. Fed. Regist. 85 5555.

Flavor and Extract Manufacturers Association of the United States (FEMA), 2020. Safety assessment and regulatory authority to use flavors – focus on vaping products. www.femaflavor.org.

Fritz, C., 2013. Biotechnology ushers in a new era of innovation for perfumers and flavorists. Perfum. Flavor. 38 (11), 18.

Government Accountability Office (GAO), 2010. Report to Congressional Requesters: Food Safety - FDA Should Strengthen its Oversight of Food Ingredients Determined to Be Generally Recognized as Safe IGRAS). United States Government Accountability Office GAO-10-246.

Gerarde, H., 1973. Survey update: determining the safety for flavor chemicals in food. Food Prod. Dev. 7, 82.

Gooderham, N.J., Cohen, S.M., Eisenbrand, G., Fukushima, S., Guengerich, F.P., Hecht, S.S., Rietjens, I.M.C.M., Rosol, T.J., Bastaki, M., Linman, M.J., Taylor, S.V., 2020. The Safety Evaluation of Food Flavoring Substances: the Role of Genotoxicity Studies. Critical Reviews in Toxicology. (in press).

Goodman, J.I., 2018. Goodbye to the bioassay. Toxicol. Res. 7, 558.

Hall, R.L., Ford, R.A., 1999. Comparison of two methods to assess the intake of flavouring substances. Food Addit. Contam. 16, 481.

Hall, R.L., Oser, B.L., 1965. 3. GRAS substances. Food Technol. 19 (2) Supp.

Hallagan, J.B., Drake, J., Harman, C.L., 2018. FEMA GRAS and U.S. regulatory authority: U.S. flavor and food labeling implications. Perfum. Flavor. 43 (11), 54.

Hallagan, J.B., Hall, R.L., 1995a. FEMA GRAS – a GRAS assessment program for flavor ingredients. Regul. Toxicol. Pharmacol. 21, 422.

Hallagan, J.B., Hall, R.L., 1995b. Safety assessment of flavor ingredients produced by genetically modified organisms. In: Engel, Takeoda, Teranishi (Eds.), Genetically Modified Foods-Safety Aspects. American Chemical Society, Washington, D.C..

Hallagan, J.B., Hall, R.L., 2009. Under the conditions of intended use – new developments in the FEMA GRAS program and the safety assessment of flavor ingredients. Food Chem. Toxicol. 47, 267.

Hanlon, P.R., Frestedt, J., Magurany, K., 2017. GRAS from the ground up: review of the interim pilot program for GRAS notification. Food Chem. Toxicol. 105, 140.

Harman, C.L., Hallagan, J.B., 2013. Sensory testing for flavorings with modifying properties. Food Technol. 11, 44.

Harman, C.L., Murray, I., 2018. 2015 FEMA Poundage and Technical Effects Survey. The Flavor and Extract Manufacturers Association of the United States. Washington.

JECFA, 2009. Safety Evaluation of Certain Food Additives. WHO Food Additive Series:60. International Programme on Chemical Safety. World Health Organization.

Kirkland, D., Aardema, M., Henderson, L., Muller, L., 2005. Evaluation of the ability of a battery of three *in vitro* genotoxicity tests to discriminate rodent carcinogens and non-carcinogens.I. Sensitivity, specificity, and relative predictivity. Mutat. Res. 584, 1.

Kirkland, D., Aardema, M., Banduhn, N., Carmichael, P., Fautz, R., Meunier, J., Pfuhler, S., 2007. *In vitro* approaches to develop weight of evidence and mode of action discussions with positive *in vitro* genotoxicty results. Mutagenesis 22 (3), 161.

Lester, C., Reis, A., Laufersweiler, M., Wu, S., Blackburn, K., 2018. Structure activity relationship (SAR) toxicological assessments: the role of expert judgment. Regul. Toxicol. Pharmacol. 92, 390.

Maffini, M.V., Alger, H.M., Bongard, E.D., Neltner, T.G., 2011. Enhancing FDA's evaluation of science to ensure chemicals added to human food are safe" workshop proceedings. Compr. Rev. Food Sci. Food Saf. 10, 321.

Magnuson, B., Munro, I., Abbot, P., Baldwin, N., Lopez-Garcia, R., Ly, K., McGirr, L., Roberts, A., Socolovsky, S., 2013. Review of the regulation and safety assessment of food substances in various countries and jurisdictions. Food Addit. Contam. 30, 1147.

Marnett, L.J., Cohen, S.M., Fukushima, S., Gooderham, N.J., Hecht, S.S., Rietjens, I.M.C.M., Smith, R.L., Adams, T.B., Hallagan, J.B., Harman, C., McGowan, M.M., Taylor, S.V., 2013. GRAS flavoring substances 26. Food Technol. 67 (8), 38.

Merrill, R.A., 1978. Regulation of carcinogens in food: a legislator's guide to the food safety provisions of the Federal Food, Drug and Cosmetic Act. 77. Mich. Law Rev. 171.

Merrill, R.A., 1997. Food safety regulation – reforming the Delaney clause. Annu. Rev. Publ. Health 18, 313.

Munro, I.C., Shubik, P., Hall, R.L., 1998. Principles for the safety evaluation of flavoring substances. Food Chem. Toxicol. 36, 529.

Myatt, G.J., Ahlberg, E., Akahori, Y., 2018. And many more. *In silico* toxicology protocols. Regul. Toxicol. Pharmacol. 96, 1.

National Academy of Sciences (NAS), 1977. Survey of Industry on the Use of Food Additives. Doc. PB-80-113418. National Technical Information Service.

Neltner, T.G., Maffini, M., 2014. NRDC Report - Generally Recognized as Secret: Chemicals Added to Foods in the United States. Natural Resources Defense Council.

Neltner, T.G., Kulkarni, N.R., Alger, H.M., Maffini, M.V., Bongard, E.D., Fortin, N.D., Olson, E.D., 2011. Navigating the U.S. food additive regulatory program. Compr. Rev. Food Sci. Food Saf. 10, 342.

Neltner, T.G., Alger, H.M., Leonard, J.E., Maffini, M.V., 2013a. Data gaps in toxicity testing of chemicals allowed in food in the United States. Reprod. Toxicol.

Neltner, T.G., Alger, H.M., O"Reilly J, .T., Krimsky, S., Bero, L.A., Maffini, M.A., 2013b. Conflicts of interest in food additives determined to be generally recognized as safe – out of balance. JAMA Intern. Med.

Oser, B.L., Hall, R.L., 1977. Criteria employed by the Expert panel of FEMA for the GRAS

evaluation of flavoring substances. Food Chem. Toxicol. 15, 457.
Pew Charitable Trusts (Pew), 2013. Fixing the Oversight of Chemicals Added to Our Food: Findings and Recommendations of Pew's Assessment of the U.S. Food Additives Program. The Pew Charitable Trusts Food Additives Project.
Rietjens, I.M.C.M., Cohen, S.M., Eisenbrand, G., Fukushima, S., Gooderham, N.J., Guengerich, F.P., Hecht, S.S., Rosol, T., Davidson, J.M., Harman, C.L., Murray, I.M., Taylor, S.V., 2020. FEMA GRAS assessment of natural flavor complexes: *cinnamomum* and *Myroxylon*-derived flavoring ingredients. Food Chem. Toxicol (in press).
Shetty, R., 2013. Cultured ingredients arrive. Perfum. Flavor. 38 (11), 34.
Siegel, R.L., Miller, K.D., Jemal, A., 2019. Cancer statistics, 2019. *CA*. Canc. J. Clin. 69 (1), 7.
Smith, R.L., Ford, R.A., 1993. GRAS flavoring substances 16. Food Technol. 47 (6), 104.
Smith, R.L., Newberne, P., Adams, T.B., Ford, R.A., 1996. Hallagan J.B. And the FEMA expert panel. GRAS flavoring substances 17. Food Technol. 50 (10), 72.
Smith, R.L., Cohen, S.M., Doull, J., Feron, V.J., Goodman, J.I., Marnett, L.J., Munro, I.C., Portoghese, P.S., Waddell, W.J., Wagner, B.M., Adams, T.B., 2005. Criteria for the safety evaluation of flavoring substances. Food Chem. Toxicol. 43, 1141.
Smith, R.L., Waddell, W.J., Cohen, S.M., Feron, V.J., Marnett, L.J., Portoghese, P.S., Rietjens, I.M.C.M., Adams, T.B., Gavin, C.L., McGowen, M.M., Taylor, S.V., Williams, M.C., 2009. GRAS flavoring substances 24. Food Technol. 63 (6), 46.
Smith, R.L., Waddell, W.J., Cohen, S.M., Fukushima, S., Gooderham, N.J., Hecht, S.S., Marnett, L.J., Portoghese, P.S., Rietjens, I.M.C.M., Adams, T.B., Gavin, C.L., McGowen, M.M., Taylor, S.V., 2011. GRAS flavoring substances 25. Food Technol. 65 (7), 44.
Smith, R.L., Cohen, S.M., Fukushima, S., Gooderham, N.J., Hecht, S.S., Guengerich, F.P., Rietjens, I.M.C.M., Bastaki, M., Harman, C.L., McGowen, M., Taylor, S.V., 2018. The safety evaluation of food flavoring substances: the role of metabolic studies. Toxicol. Res. https://doi.org/10.1039/c7tx00254h. Online access.
United States Department of Agriculture (USDA), 14 May 2018a. Letter from M.J. Firko to H.J. Klee regarding request for regulatory status of a genome edited tomato variety.
United States Department of Agriculture (USDA), 12 July 2018b. Letter from M.J. Firko to P. Schnable Regarding Confirmation of Regulatory Status of Null Segregant Maize Lines.
United States Department of Agriculture (USDA), 8 February 2019. Letter from M.J. Firko to S. Boddupalli Regarding Confirmation of the Regulatory Status of Genome Edited *Lactuca sativa* (Lettuce).
Waddell, W.J., Cohen, S.M., Feron, V.J., Marnett, L.J., Portoghese, P.S., Rietjens, I.M.C.M., Smith, R.L., Adams, T.B., Gavin, C.L., McGowen, M.M., Williams, M.C., 2007. GRAS flavoring substances 23. Food Technol. 61 (8), 22.
Wolf, D.C., Cohen, S.M., Boobis, A.R., Dellarco, V., Fenner-Crisp, P.A., Moretto, A., Pastoor, T.P., Schoeny, R.S., Seed, J.G., Doe, J.E., 2019. Chemical carcinogenicity revisited 1: a unified theory of carcinogenicity based on contemporary knowledge. Regul. Toxicol. Pharmacol. 103, 86.
Woods, L., Doull, J., 1991. GRAS evaluation of flavoring substances by the Expert Panel of FEMA. Regul. Toxicol. Pharmacol. 14, 48.
Xu, J., Murphy, S.L., Kochanek, J.D., Arias, E., January 2020. Mortality in the United States 2018. NCHS Data Brief No. 355. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics.