

## GRAS use of Flavor Substances: Risk Management

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### Abstract:

Under sections 201(s) of the Federal Food Drug and Cosmetic Act, any substance intentionally added to food is a food additive and is subject to approval by the FDA unless it is generally recognized as safe (GRAS) by qualified experts as having been adequately shown to be safe under the conditions of its intended use. The GRAS process supports the use of over 10,000 substances in human food in the United States (Neltner, et al., 2011, p. 342). Of those approximately 10,000 substances, about 2700 are flavor substances (Neltner, et al., 2011, p. 355). Flavor substances include more than 2400 single chemicals, 300 natural flavor complexes and flavor adjuvants such as antioxidants, emulsifiers, solvents, and flavor modifiers (Hallagan & Hall, 2009, p. 268). Risk assessment is the first step in determining the GRAS status of a flavor substance, however risk management and control is also required. Steps are needed to manage and assure flavor substances are used in accordance with food additive regulations so as to prevent possible adulteration of the food supply (DHHS, 2015, para. 7). Training, accurate exposure data and toxicity data are controls that can assure flavor substances are used as intended. The proposed “FDA Food Safety Modernization Act” (FSMA) rules for human food mandates written preventive controls for food manufacturing facilities and may address the potential gaps that can result because of misuse of flavor substances. Because it is difficult to assess the permissible use of GRAS

substances in food, clear guidance and training material must also be available.

CONTENTS:

I. Background

II. Introduction to FEMA GRAS™

III. Potential gaps in FEMA GRAS™ program

A. GRAS use of flavor substances

B. Training on the GRAS use of flavor substances

1. Current approaches to training

2. Baseline assessment of training-certified flavor chemists

a. Materials and methods

b. Demographic data on returned surveys

c. Demographic data on food categories

d. Training

e. Discussion

C. Exposure data

1. Food consumption surveys

2. Sharing of exposure data

3. Intake from non-food sources

4. When to reassess exposure data

5. Quantitative analysis of concentration in food supply

D. Gaps in toxicity data

IV. Future with FSMA

A. Food industry role

B. Certified flavor chemist role

C. FEMA's role

D. FDA role

V. Conclusion

## I. BACKGROUND

In 1958, concern over health threats from cancer and demand for information on food additives led to the Food Additives Amendment to the Food, Drug and Cosmetic Act (proposed 21 CFR 170.36 (c)(1)(iii)). This amendment houses the additive exemption for GRAS substances. GRAS ingredients do not need pre-market approval by FDA like food additives do, but still require a strong consensus among all qualified experts that the substances meet the same safety standards as FDA approved food additives (21 U.S.C. §321(s)).

Recently the GRAS exemption has caused some controversy. Reasons for this controversy include the fact that GRAS notification is voluntary, there is no systematic way to reassess the safety of GRAS substances and there is conflict of interest with qualified experts being employed by additive manufacturers. These controversies were brought to the public's attention in the 2010 Government Accountability Office (GAO) report, "FDA Should Strengthen Its Oversight of Food Ingredients Determined to Be Generally Recognized as Safe" (GAO-10-246).

## II. INTRODUCTION: FEMA GRAS™

This same GAO report applauds the Flavor and Extract Manufacturers Association (FEMA) GRAS™ risk assessment process. FEMA is an association with more than 140 members, which include flavor manufacturers, flavor users, flavor ingredient suppliers

and others interested in assuring the supply of safe flavoring materials (FEMA, 2013-2014, p. 17). These members manufacturer or market more than 95 percent of all flavors sold in the United States (Cox, 2013, para. 2). Since 1960, FEMA has utilized an expert panel of eight academic experts to determine GRAS status of flavor substance (as cited in Adams & Smith, 2004,p. 210). FEMA voluntarily informs FDA of its GRAS determinations, including the name of the substance, its properties, and the basis of the determination. To build transparency, FEMA GRAS™ determinations are made publically available in a trade magazine, *Food Technology*. In addition, FEMA requests that all expert panelists complete a financial conflict of interest form (GAO-10-246, 2010, p. 17-18). All safety decisions made by the expert panel must be unanimous (Smith et al., 2005 p. 1143). As of January 11, 2011 there have been 2702 flavor substances that have been affirmed FEMA GRAS™ (Neltner, et al., 2011 p. 355).

Educational workshops and webinars are provided by FEMA for a fee on their website and the webinar FEMA GRAS™ is currently available. Information on workplace safety and the current GRAS publication are provided free of charge. Meetings and educational events are accessible for paying FEMA members, however, occasionally FEMA will open meetings and events for non-members to attend.

When reviewing scientific data related to flavors, the FEMA Expert Panel also identifies new data that may affect prior FEMA GRAS™ decisions. In some cases, the panel will choose to reevaluate the safety of a GRAS flavor ingredient and conclude that the substance is no longer GRAS. This process has led to the deGRASing of flavor

substances (Smith, 2005, p. 1146). Use level is key when assessing whether a substance is safe for consumption as a food. Section 201(s) for the FFDCFA (Federal Food Drug and Cosmetic Act) states that a substance that may be generally recognized as safe must be shown to be safe “under the conditions of intended use”. Therefore, it is not the flavor substance itself that is considered GRAS, but the actual use. As part of the statute requirements, increases in use levels or proposed new uses should be evaluated to ensure continued GRAS status (21 U.S.C. §321(s)).

FEMA monitors increase in use of flavor substances by conducting flavor ingredient poundage surveys. Poundage data from the most recent survey to the past survey identify trends in the use of flavor ingredients. These surveys tend to occur every five years. If there are significant increases, the data is reviewed to determine if it means a significant increase in exposure. Poundage data is also used to calculate flavor intake via the maximized survey-derived daily intake (MSDI) method. The MSDI method relies on estimates of flavor ingredients sold to food manufacturers each year and indicates when new uses of flavor substances need to be evaluated to maintain FEMA GRAS™ status. In the publication “GRAS flavoring substances 24,” the expert panel reviewed and reported new use levels for six flavor substances (Smith, 2009 p. 105).

### III. POTENTIAL GAPS:

#### A. GRAS use of flavor substance:

GRAS uses of flavor substances are considered safe only if there is reasonable certainty that the substance is not harmful under the intended conditions of use (21 U.S.C.

§321(s)). Flavorings are often used at very low concentrations such as 0.001-0.1% in food (Smith, 2005 p. 1142). Flavor substances are considered self-limiting; because when used too high, they are not palatable. In some instances, flavor substances are added to food in accordance with Good Manufacturing Practices (GMP). Good Manufacturing Practices require that the quantity of the flavor substance in a food not exceed the amount reasonably required to accomplish the intended technical effect in food (21CFR184.1(b)). In other instances, flavor substances were evaluated to be safe within limited conditions of use and not merely GMP (21CFR184.1A(b)(1)).

Although most flavor substances are used at extremely low levels in food, there are some exceptions. In the publication “GRAS flavoring substances 24” (Smith, 2009 p. 82, 92, 105), the following substances had higher than standard maximum use in certain food categories:

<b>Substance</b>	<b>FEMA #</b>	<b>Maximum use</b>	<b>Food item</b>
Choline Chloride	4500	2500ppm (0.25%)	Baked goods
Citral	2302	10000 ppm (1%)	Chewing gum
N-Ethyl-2,2-diisppropyl butanamide	4557	6000 ppm (0.6%)	Chewing gum

Some foods; such as chewing gums, baked goods, alcoholic beverages and energy drinks require high levels of flavors. Flavor substances used at significant levels in food categories should be closely monitored for use level to assure compliance.

For example, FEMA has acknowledged that the expert panel pays careful attention to flavoring substances that provide cooling sensation (amides) because they can taste

better at higher levels and do not have clear self-limiting properties (Hallagan & Hall, 2009, p. 275). These amide flavoring substances that provide cooling sensation, are referred to as cooling agents. For example, Ethyl-2-isopropyl-5-methyl cyclohexane FEMA 3455 is a cooling agent and FEMA reports use of 1200 ppm in chewing gum (Burdock, 2009 p.598).

Certain sub-populations that over consume specific food categories may be at risk from GRAS flavor ingredients. For example, in 2012, David Egilman and John Schilling reported consumer cases of bronchiolitis obliteran potentially due to high exposure to butter flavored microwave popcorn (BFMP) and suggested that BFMP and specifically diacetyl, FEMA #2379, and diacetyl-containing flavorings can pose a significant respiratory risk to consumers. These consumers were eating at least 2 bags of popcorn per day and were exposed to potentially harmful diacetyl vapors. Another reported overconsumption includes a 10-year-old boy who developed hypertension and posterior reversible encephalopathy syndrome from daily consumption of licorice treats with glycyrrhizic acid, FEMA#2528. (Tassinari, 2015).

Besides the chance that certain subpopulations may ingest substances in high amounts, food or beverage manufacturers may not use flavor substances as within permissible limitations. For example in 2009, as a result of consumer injury and death the FDA issued warning letters to alcoholic beverage companies using caffeine in alcoholic beverages. In these letters, the FDA stated that they have not made a determination regarding the GRAS status of use of caffeine in alcoholic beverages. FDA went on to

warn, “If FDA determines that the use of caffeine in your alcoholic beverages is not GRAS or subject to a prior sanction, FDA will take appropriate action to ensure that these products are removed from the marketplace. It is your continuing responsibility to ensure that the foods you market are in compliance with all applicable legal and regulatory requirements”. The “FDA Food Additive Status List” reports caffeine GRAS at levels of 0.02% in cola beverages and there is no GRAS use for use in alcoholic beverages. (<http://www.fda.gov/food/ingredientpackaginglabeling/foodadditivesingredients/ucm091048.htm#ftnC>). One alcoholic beverage manufacturer that received a warning letter used the GRAS Notification process to advise FDA that caffeine is GRAS as a flavoring agent in alcoholic beverages at 200 ppm (0.02%), but later instructed FDA to cease to evaluation of their notice (<http://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=347>) .

FDA has continued to monitor and evaluate the use of caffeine in foods and beverages outside of the use in cola. In 2013, FDA announced that it “is taking a fresh look totality of new and easy sources of caffeine may have on health, particularly vulnerable population such as children and youth and, if necessary, take appropriate action”. This statement was in regards to the launch of a new caffeinated gum in April 2013. In May of the same year, FDA followed up with a statement that applauded “Wrigley’s decision “to pause production, sales and marketing of Alert Energy Caffeine gum”(FDA, 2013). Alert gum was touted as containing 40 mg of caffeine per piece (Shute, 2013).

Even though FEMA is monitoring use of GRAS flavor substances for risk assessment purposes, FEMA's technical committee passes risk management and the preventive controls on the intended use of flavor substances to the food manufacturer. In the FEMA technical committee guidance, "Proposal for HACCP for the Flavor Industry" (Bednarczyk, A., 1998) stated, "although many HACCP protocols take into account the intended use of the products, our protocols will evaluate our processes only to point of distribution to the customers (food manufacturers), since the customers end use is often unknown. We feel it is more appropriate for our customers to include our materials as a raw material in our customers own HACCP protocols"(p.10). FEMA's technical committee suggested that a flavor manufacturer's proposed HACCP plan "be limited to microbiological contamination" (p.21) since chemical hazards "pose no significant health risk to the general population because of the typical use level of our finished products" (p.21). Studies on animals for carcinogenicity in humans support this stance. In 2002, William Waddell, reported that certain "flavoring agents have a clear threshold for carcinogenicity in animals and it is well above the levels currently approved for use in foods" (p.275). He suggests that because of these results, "these animal studies should be viewed as providing evidence for the safety of these compounds at current levels of human exposure"(p.275). However, previous incidences of overuse of misuse of flavor substances by consumers and food manufacturers verify that there is indeed risk and it needs to be managed to assure a safe food supply.

FEMA's science committee acknowledged the need to update the 1998 HACCP guide when they published a revised HACCP guide in July 2014. This guide included an

overview on proposed Hazard Analysis and Risk Based Preventive Controls (HARPC), which are a provision of FSMA and an explanation of the differences between Hazard Analysis Critical Control Points (HACCP) and HARPC. This guide points out that records required for HARPC should include intended use of flavor, however this guidance does not suggest that these records are the responsibility of the flavor manufacturer. In fact, a footnote to this record keeping requirement indicates that “flavor manufacturers may not know customer company end use or details of customer processes...it may not be appropriate for the HARPC system to require maintenance of records on customer company intended use” (FEMA Science Committee, 2014 p. 7). The FEMA Science Committee has not issued final guidance on how the GRAS use of flavor substances will be monitored and controlled so that intended use (trade secrets) are kept confidential.

Assuring use level in a specific food category within GRAS determination parameters is an essential preventive control. Also, assuring that FEMA GRAS™ substances are used as flavorings and not for any other “technical effects such as antioxidant, sequestrant, or humectant” is also important for compliance. FEMA GRAS™ substances can be used for other purposes besides flavor and controls to assure that they are used strictly for flavor development should be instilled. For example, FEMA GRAS™ substances from “GRAS Flavoring Substances 22 and 26” that may have another function in a food or beverage item:

<b>Substance</b>	<b>FEMA #</b>	<b>Max. Use</b>	<b>Food item</b>	<b>Use beside flavor</b>
Tomato Lycopene	4110	20 ppm	Beverage	Dietary supplement

Steviol glycoside extract, Rebaudioside A 60%	4771	200 ppm	Chewing gum	Sweetener
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Finally, consideration that a FEMA GRAS™ flavor substance should meet the specifications of the flavor material originally approved as GRAS is also an important consideration in preventing misuse. Unfortunately, the specification of the originally approved FEMA GRAS™ substance is often difficult to determine and rarely designated in the CFR. This lack of designation is convenient for the producer who wants to fit their material under the “umbrella of a chemical name” but causes difficulties for the users who are trying to determine if the substance is compliant (Matulka & Burdock, 2009 p.71). For example, an essential oil that is comprised of 90 percent terpenes is considered FEMA GRAS™. Subsequent rectification of this essential oil yields a terpene free oil and changes the composition, yet the producer may categorize the terpene free oil under the same FEMA GRAS™ number as the original unrectified essential oil.

B. Training on GRAS use of flavor substances

1. Current approaches to training:

Training is one method to control the use of a flavor substance in a food product. In the comments on proposed FSMA, FEMA notifies FDA that they “support food industry coalitions and working group activities like the Food Safety Preventive Controls Alliance (FSPCA).” FSPCA is an alliance of industry, academia and government that supports safe food production by developing curriculum, training and outreach programs to assist food manufacturing (Cox, 2013 pp.1-2).

Preventive controls are often part of the product design process. For example, developers can minimize the use of allergens during the development phase of a new product. Similar to allergen preventive controls, critical points in flavor and product development can be control steps to reduce risk to the consumer. A development team with “at least one member trained in food safety and specifically hazard analysis and critical control points (HACCP)” (Stier, R. 2010 p.43) can assure that flavor substances are used as intended and GRAS use parameters are communicated to the food product developer. Proper training can ensure that flavor substances are used as intended and that use is communicated to the food product developer.

Many of the flavor developers in the flavor industry are certified members of the Society of Flavor Chemists (SFC). According to the 2012 SFC by-laws, a certified member “must exhibit a working knowledge of ... raw materials, laboratory procedures, production processes, legal/regulatory consideration and the economics involved in the creation, production and utilization of flavors”. In order for flavor chemists to become certified, they receive training from a mentor and study the “syllabus” published by the Society of Flavor Chemists. The syllabus includes the following regulatory and safety topics: CFR, FEMA, Foods Chemical Codex (FCC), International Organization of the Flavor Industry (IOFI), JEFCA, Consumption Ratio, Food Allergen Research and Resource Program (FARRP), Expert Panel, United State Pharmacopoeia (USP) and GMP. Certification is granted once a candidate demonstrates that he or she has a working knowledge of the material on the syllabus. Based on these expectations, SFC members should have a good understanding of the potential hazards that may be associated with misuse of GRAS

flavor substances.

2. Baseline assessment of certified flavor chemist training program:

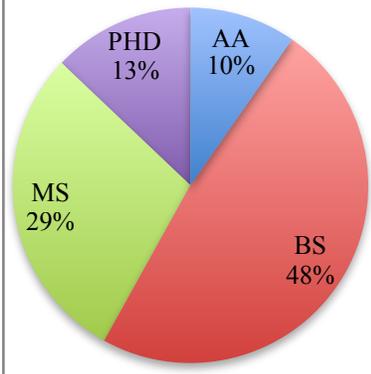
a. Materials and methods:

To develop a baseline assessment of training SFC members received on the use of GRAS substances, this researcher sent a brief survey to current membership that had an email account available (292 members). Questions on this survey included years of experience, size of employer, food category that they service, educational background and if formal training on the safe use of GRAS flavor substances was received. The researcher received 31 returned surveys from non-retired workers (11 percent return response). Response rate was low and potentially a source of error.

b. Demographical data on returned surveys:

The majority of respondents (80 percent) report having eleven or more years experience in flavor development work. Of those respondents, 48 percent had a Bachelor of Science degree and the majority worked for an employer with 100 or more employees.

### Highest degree obtained- Surveyed flavor chemists



Field of study was primarily reported as chemistry or Food Science (70 percent).

Biology, Biochemistry, Molecular Biology, Nutrition & Dietetics, Horticulture Science and Environmental Science were the other reported fields of study.

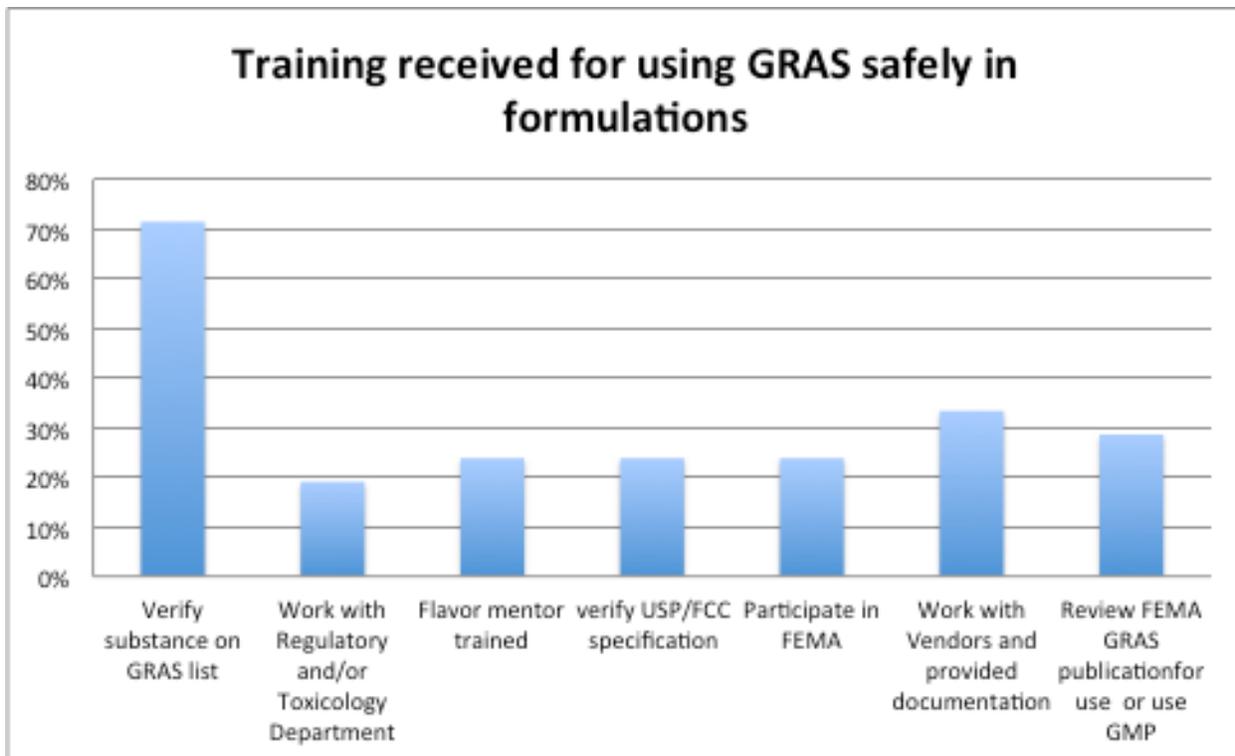
#### c. Demographic data on food categories

Fifty percent or more of respondents developed flavors for the following food categories: confections, beverage, alcoholic beverage, dairy products, soups/sauces, seasonings or baked goods. Eighty eight percent of respondents indicated that they work directly with food, feed or beverage manufacturers.

#### d. Responses on training received:

Seventy-seven percent of respondents indicate they received training in using substances safely in flavor formulations and described the sort of training they received. In order to categorize and report responses, the investigator interpreted descriptions.

The majority responded that were trained to check GRAS status, which was interpreted to mean to verify that flavor substance is on a FEMA GRAS™ list and not necessarily verify conditions of use. Comments such as “if you start GRAS, you stay GRAS” with no reference to intended use, led the investigator to make this determination. In contrast, two respondents were active in the FEMA GRAS™ program. One was responsible for writing GRAS applications on new flavor compounds and understood the GRAS process from the decision tree analysis for identifying potential risk of a new compound to the toxicology studies (including dose) that would be required to obtain approval by the expert panel. Another respondent had served on the FEMA science committee and FCC panel and stated that analysis work to verify flavoring item conformed to FEMA-GRAS™ and FCC specifications was part of their training program on the safe use of GRAS substances. It is possible that these flavor chemists who received specialized training on the GRAS process and participated in the GRAS process were more likely to respond to this survey. A few respondents also mentioned training to check EPA status, California Proposition 65 list, and the EFSA status before using a flavor substance in formulation.



e. Discussion

The results of this assessment indicate that the majority of certified flavor chemists that responded believe they have received training on using GRAS substances safely in flavor formulations. However, this training may not be adequate to control misuse of flavor substances. Only about 30 percent of respondents indicated that they review use information or original GRAS publication on flavor substance use. Of those that review use information, 50 percent also work with their regulatory or toxicology department on the safety of flavor substances. Thirty-three percent of respondents indicate they work with vendors and review their paperwork in order to assure the safe use of flavor substances. This is helpful when determining if flavor substance meets specifications, however, it is not always possible to find acceptable use level on vendor paper work. For example, FEMA GRAS™ 3455, Ethyl-2- isopropyl-5- methyl

cyclohexane carboxamide is an amide cooling agent that may not become unpalatable at high levels. GRAS status limits its maximum use level of 0.6% in chewing gum. Vigon is a supplier for this item. On Vigon's website, one can find:

- Product specification
- MSDS (Material Safety Data Sheet)
- Kosher certificate
- Food Grade Certificate
- Allergen Statement
- GMO statement
- Irradiation and sewage sludge statement
- Heavy metals and pesticides statement
- Dietary preferences (vegan status)
- Animal testing status
- Proposition 65 statement
- EU declaration

There is no mention of maximum use limitation of this flavor substance on the vendor website or paperwork, but the MSDS recommends use is "according to legal FEMA GRAS/FDA guidelines." Amides are a group of cooling compounds that the FEMA expert panel is giving extra attention to, because they do not have clear self-limiting properties (Hallagan & Hall, 2009 p.275). Flavor chemists are trained to verify that there is indeed a FEMA GRAS™ number for the substance that they are using, but they may not be trained to consistently verify that this substance is used as intended.

Approximately 25 percent of flavor chemists that responded to the survey indicated that they have been trained to review the purity or composition of a flavor substance before using in formulation. Resources among others include analytical equipment, Gas Chromatography/Mass Spectrometer, Food Chemical Codex and United States Pharmacopoeia. Surveyed flavor chemists indicated that they often check several lists

before making a complete assessment of a flavor substance. These lists include: EPA, EU, Proposition 65, vendor paper work, GRAS publications, and FCC.USP. The multitude of lists and documents that a flavor chemist must check and verify indicate it is not an easy task for flavor chemists to assess the specification and permissible use of GRAS use of flavor substances.

### C. Exposure data:

In determining exposure to a flavor additive, it is important to know the concentration used in food and the consumer intake of food that contains the additive (FDA, 2006). Determining exposure is a complex process, but essential for determining risk adequately. Scientists need to understand not only the acute dose exposure, but also the chronic lifetime daily exposure.

#### 1. Food consumption surveys:

In FDA “Guidance for Industry: Estimating Dietary Intake of Substances in Food” published in 2006, source food consumption surveys that are referenced include the Continuing Survey of Food Intake by Individuals (CSFII), National Health and Nutrition Examination Survey (NHANES), the Integrated CSFII/NHANES and the MRCA 14 day food frequency survey. The US Department of Agriculture conducts the CSFII survey, the Center for Disease Control and Prevention (CDC) conducts the NHANES survey and a marketing group conducted the MRCA study between the years of 1982-1987. The FDA and the EPA primarily rely on the Integrated CSFII/NHANES survey data to make dietary exposure assessments (Alger, H., Maffini, M., Kulkarni, N., Bongard, E, & Neltner, T., 2013, p.94). The CFFII/NHANES survey is based on 2-day consumption

data and assumes that respondents would eat the reported food every 1 to 2 days for the rest of their life. Of course, the American diet tends to vary extensively, so there are limitations to this data. Also, the CFFII/NHANES consists of only an approximately 10,000 responses that are intended to represent the nation. CFFII/NHANES data does not address regional or seasonal differences in food consumption. Experts have indicated that although the NHANES data is the best consumption data currently available, this “data needs strengthening” and could benefit from additional data sources, so it would be reflective of a larger number of the US population and subpopulation (Alger et al., 2011, pp. 101-102).

## 2. Sharing of exposure data

Experts from academia, government and industry all agree that interagency collaboration between FDA, USDA and EPA will improve dietary consumption data (Alger et al., 2011, pp. 101-102). A 2104 program review of the Center for Food Safety and Applied Nutrition (CFSAN), agreed that there is limited sharing of data from other Federal agencies and outside sources. Suggestions for improvement include a “CFSAN liaison contact position that could establish relationships with other Centers, HHS agencies, Federal agencies/department groups to explore what data are available and to facilitate access” (DHHS, 2006, p. 14). On March 16, 2015, EPA and FDA improved sharing capabilities by signing a memorandum of understanding (MOU) or an agreement to share data on toxic substances and pesticides under the jurisdiction of both agencies, such as food safety, veterinary medicine and cosmetics (Campbell, 2015). This MOU is a good step for sharing data on chemicals that have both uses as flavor additives and pesticides. For example, Benzaldehyde FEMA 2127 is also listed on EPA’s

Integrated Risk Information System (CASRN#100-52-7).

Government agencies should also collaborate with industry and internationally for consumption data. In 1984, the flavor industry and the International Organization of the Flavor Industry (IOFI) realized that there was a need to measure the amount of flavor substances a consumer was exposed to as naturally present in food. “Chemicals that are consumed as natural components of foods probably number between hundreds of thousands” (Stofberg & Kirschman, 1985, p. 857). There was a recognized weakness in the safety assessment of flavor substances. Claiming that a flavor material is “self-limiting by the virtue of sensory impact is not an adequate argument” (Stofberg & Kirschman, 1985, p. 858) for the safety of flavor substance exposure dose. Industry and IOFI determined that a method to compare the average quantitative intake of an additive flavor substance and the intake of a flavor substance as a component of a traditional food needed to be implemented. This method is called the Consumption Ration (CR) and it is used by industry to prioritize safety evaluations of flavor substances. IOFI has sponsored a continuing research project in the Netherlands that has resulted in the continually updated database called “Volatile Compounds in Foods.” This database reviews quantitative data on flavor substances naturally found in food and encourages researchers to contribute to this database.

### 3. Intake from non-food sources:

As mention previously, FEMA GRAS™ substances can have non-food uses. The CFSAN chemical safety program review recommends that lists of various data sources and databases of chemical safety review be in one location on the CFSAN intranet website.

Accessibility to chemical safety information will help interagency exposure data collaboration on these shared substances. This review also found that collaboration could be increased if agency scientists received increased funding to attend scientific meetings. Collaboration and communication is essential, because flavor additives have other uses, such as pesticides, dietary supplements (i.e. Lycopene FEMA#4110) and cosmetics (i.e. Sodium lauryl sulfate FEMA #4437). Long term, FEMA GRAS™ substances have opportunity for new uses, such as their use as bioactive compounds that promote health and wellness (Martinez-Mayorga, 2013). A plan for long-term consistent collaboration is needed.

4. When to reassess exposure data:

Experts agree that there is room for improvement in the FDA's current procedure for reassessing dietary exposure to food and flavor substances. Because of the large number of food and flavor additives, it is not practical for the FDA to conduct systematic reviews for exposure. Some items that experts believe that should prompt regulatory reassessment include (Alger et al., 2013 p. 104-105):

- When there are significant changes in food consumption trends, such as the Greek yogurt trend
- When new toxicity data is available
- When there is an increase in public awareness
- When a substance is a sole source food (such as infant formula)
- When a subpopulation is identified as being of concern

The FDA has pointed out to manufacturers that once a substance has entered the marketplace and is consumed by the public, manufacturers must ensure the continued

safety of the substance for the intended use. Unfortunately, this re-assessment is not a regulatory requirement and the FDA does not have a systematic method to conduct post-market assessment. FEMA reassesses the toxicological properties of GRAS flavor substances, so there is some review and in some instances GRAS status has been revoked for flavor substances previously determined to be GRAS.

A priority concern for FDA with reassessing safety is the consideration of susceptible populations. Susceptible populations can include the elderly, the young, pregnant or lactating mothers, those that regularly consume alcohol or smoke, those with disease risk factors, those with exposure to multiple chemical hazards or those with compromised immune systems. CFSAN realizes that in administering the Food Drug and Cosmetic Act, they must ensure that chemical assessments and resulting risk management decisions protect all affected human populations. This issue was brought to the attention of CFSAN in a 2013 report from the National Research Council. The NRC report recommended, “consideration should be given to whether dose response should focus on the population as a whole or involve separate assessments for susceptible groups” (The National Academies, 2013). The US Office of Foods and Veterinary Medicine is reviewing its chemical safety program to ensure consistent safety and risk assessment procedures (Fitzpatrick, 2014).

##### 5. Quantitative analysis of concentration in food supply

FDA monitors levels of a wide range of substances (such as pesticides) in foods through the Total Diet Study (TDS), which collects and analyzes a wide range of foods that

represent the average American diet. The TDS includes 280 foods that are collected and analyzed four times per year to monitor pesticide residues and nutrient elements. The TDS assessment does not include analysis for GRAS substances or food additives and it is not designed to for this purpose. FDA does conduct post market assessments of food additives, but this is on a case-by-case basis (Alger et al., 2013 p.106-107).

Therefore, FDA relies on industry data to support concentration of flavor additives and GRAS substances in food. Key data for intake assessments is determined by poundage and technical effect surveys that FEMA conducts. Information that can be obtained from these surveys includes where flavor substance is used, how it is used, at what level, the trends of use and the estimated amount of substance in food supply. FEMA has conducted, validated and published these surveys regularly: 1995, 2005 and 2010. Data is reported electronically and there is a standard operating procedure for collection and review of data. The most recent survey was part of a global IOFI survey that brought together data from FEMA (US), JFFMA (Japan) and EFFA (EU). The number of companies responding to FEMA poundage surveys has declined, partially due to consolidation of flavor companies, but also due to a decrease in food and beverage company participation. Broad industry participation is necessary in order to continually update additive usage data in the United States. To this end, industry cooperation is imperative in the success of determining exposure data (Vollmuth, 2014).

#### D. Gaps in toxicity data:

The FDA's mission is to protect public health by assuring the safety of our nation's food supply and to help the public get the accurate, science-based information they need to use foods to maintain and improve their health (FDA, 2014). The FDA has limited resources and must prioritize yet is criticized because it lacks the authority and resources to collect the information it needs to assure public safety and safe use of GRAS substances (Neltner, T., Alger, H., Leonard, J., Maffini, M., 2013). There are more than 10,000 chemicals that are allowed to be added, directly or indirectly, to human food in the United States. Of those chemicals, less than 38 percent have published feeding studies. The specific number of flavor substances without oral toxicity studies are 511 out of 2950, and the number of flavor substances without a LD50 study are 866 out of 2950. Reasons for the gaps in testing data is that "FDA and FEMA rely on threshold of exposure for flavor below which no feeding studies were expected" and that "once a manufacturer determines a chemical is safe to add to food, industry has little incentive to conduct additional studies"(Neltner, T., et al.,2013, p. 9).

Feeding studies may not be used to fill the gaps in toxicity studies. FDA is partnering with other regulatory agencies in developing and implementing Tox 21 to fill the gaps. Tox 21 uses computational toxicology to fill gaps in toxicology data by identifying chemicals with potential hazards based on chemical structure modeling.

Tox 21 is a program used by the National Toxicology Program (NIEHS/NTP), NIH Chemical Genomics Center (NHGRI/NCGC), the FDA and the EPA that uses *in vitro* testing and robotic equipment to run large numbers of chemicals across a wide range of concentration and cell types to rapidly screen them for toxicity (<http://www.epa.gov/>

ncct/Tox21/ ). Tox 21 will help prioritize which chemicals need more extensive toxicological testing and will create a database of toxicology data that is available for FDA.

#### IV. FUTURE with FSMA:

The FDA Food Safety Modernization Act (FSMA) will be the most sweeping reform of our food safety laws in more than 70 years. It shifts the focus on food safety to prevention rather than reaction. The food industry, SFC, FEMA and the FDA all play a role in the prevention of food safety hazards potentially linked to use of flavor substances in food.

##### A. Food Industry role:

Food manufacturers in the Grocery Manufacturers of America (GMA) are taking initiatives to assure the safety of food additives and implement outreach efforts to the consumer to inform them of “the steps being taken by industry to increase the integrity of procedures to assess ingredient safety” (GMA, 2014). It is expected that food manufacturers will continue to increase their focus on food safety and recognize that a flavor is a substance that must be used in a consumer food product per the GRAS notification or it may be considered an unapproved food additive (Federal Register, 2013, p.3734). Proposed FSMA defines “significant hazard” to mean that “a known or reasonably foreseeable hazard for which a person knowledgeable about the safe manufacturing, processing, packing or holding of food would, based on the outcome of hazard analysis, establish controls to significantly minimize or prevent the hazard in a

food and components to manage those controls (such as monitoring, corrections, or corrective actions, verification and records) as appropriate to the food, the facility and the nature of the control” (Federal Register, 2014, p.58542). Industry experts have speculated that “the application of the word “unapproved” to “food and color additives” in the (FSMA) statute suggests that facilities now must have a written documentation confirming that all substances added to food are allowed by the food additive regulatory program” (Neltner et al.,2011, p.357). Based on studies indicating that consumer and food industry overconsumption and misuse can cause health damage, written controls are necessary. In the case of licorice flavor, consumer overconsumption may be a health hazard and FDA has issued an advisory to consumers on licorice consumption hazards. In this instance, a control step of a warning label might be the appropriate to mitigate this hazard. In order for a food manufacturer to be compliant with FSMA, a written plan to control the hazard of potential food flavor overconsumption is necessary.

Because it is difficult to understand the regulatory limitations for using flavor substances in food, manufacturers will need to work closely with suppliers to determine significant hazards and implement controls. Proposed FSMA requires records to be gathered that support supplier approval and verification. Food manufacturers may want to work closely with reputable flavor suppliers to determine flavor use limits (Federal Register, 2013, p.3765). In “Controlling organic chemical hazards in food manufacturing: A HACCP approach”, it is recommend that “Food processors...maintain adequate additive lists and be able to demonstrate that all additives used in the manufacture of a given foodstuff are suitable for their intended use” (Ropkins & Beck,

2002 p.262). Working relationships with flavor suppliers to establish controls will be essential.

B. Certified flavor chemist role:

Eighty- eight percent of certified flavor chemists that responded to the training survey indicated that they work directly with food, beverage or feed manufacturers. Therefore, a certified flavor chemist could play an integral role in communicating use of flavor substance and can be a requirement in a written flavor supplier approval and verification control plan. Verifying flavor chemists have adequate training on use of FEMA GRAS™ substances could be an important step in a flavor supplier approval plan. However, the current syllabus and training program for flavor chemists needs to be updated to include knowledge of the FEMA GRAS™ process; specifically that GRAS status depends on use of substance and that the substance must fit the specifications originally determined to be GRAS. The most common training flavor chemists received on the safe use of GRAS flavor substances is to verify that the material is on the FEMA GRAS™ list. It is important to note that the majority of certified flavor chemists responding the survey did not clearly indicate that it was the use of a substance, not the substance itself that is considered GRAS.

While it is possible the majority of flavor chemists may be complacent towards checking specification of flavor substance and GRAS publication, it was indicated in the survey findings there are some flavor chemists that are doing this. Risk with use of flavor substances used in food is low because it is known that approximately 50 percent of

flavor substances (simple acids, aldehydes, alcohols, and esters) are rapidly metabolized and excreted by the body (Watson, 2002, p.209). Regardless, in order for a flavor substance to be considered an approved additive under the Food Drugs and Cosmetic Act Additive Amendment, it must be used within the parameters of safety determination. It should not be debated if exceeding the Acceptable Daily Intake (ADI) is a human health risk; since the substance is considered an unapproved food additive if it exceeds the use parameters of GRAS approval. Complacency puts a consumer at risk.

Working with a supplier that employs a certified flavor chemist can be a supplier verification requirement that food manufacturers use to meet FSMA demands. In order to assure the flavor chemist is trained adequately to address safety concerns during the formulation process, the Society of Flavor Chemists must add further training requirements to provide assurance that the certified member understands and is keeping their knowledge current on food safety legislation.

Although FEMA GRAS<sup>TM</sup> number is easy to locate, it is a difficult task to assess the specification and permissible use of GRAS flavor substances. There are several resources that flavor chemists cited in the survey.

- 1) The Good Scents Company Information system: A web based database developed by a creative perfumer. There is no fee for the information or guarantee. For an item like butan-2-one, the Good Scents Company provides some of the following: structure, synonyms, CAS#, FEMA#, COE, Molecular weight, JECFA, FLAVIS, FDA regulation for direct food additive and FDA regulation for indirect additive.

- 2) *Allured Flavor and Fragrance Materials Buyers Guide*: A global directory of ingredients used in flavor and fragrance creation; FEMA#, CAS#, Natural and Artificial designation, Botanical names, suppliers and company information are available for both purchasing and researcher.
- 3) *Fenaroli 's Handbook of Flavor Ingredients*: Lists alphabetically flavor substances by name with synonyms, structure, description and annual consumption data. Also provided are CAS#, FEMA#, CoE#, JECFA#, specification, synthesis and natural occurrence. FEMA reported uses are listed by food category with usual and maximum use data.
- 4) FEMA GRAS™ supplier documentation: Documentation to support the safe use of flavor substances in food. Often Specification, MSDS, Food Grade certificate, Allergen statement, Heavy Metals analysis, Proposition 65 and EU declaration are available from vendor. Maximum use level listed per food category is often not available.
- 5) EU list of flavouring substances: A positive list of approximately 2500 flavourings substances that are approved for use in the European Union. The list contains approved flavourings and European Union restrictions on use in specific food categories.

A central list with all applicable safety information, like the EU positive list of flavouring substances, would aid a flavor chemist in determining the permissible use of a FEMA GRAS™ flavor substance quickly and efficiently.

### C. FEMA's role:

FEMA's science committee will need to determine the best guidance for flavor manufacturers, so they can be compliant with the "FDA Food Modernization Act" (FSMA) and control the hazards of misuse of FEMA GRAS™ substances in food. "It is likely that food manufacturers will not have the necessary experience of knowledge to identify these hazards" (Ropkin, 2002 p. 268). The flavor producer is more likely to understand and identify the potential hazards of a flavor substance and they should caution a food or beverage manufacturers when there is potential for misuse. The validity of the FEMA GRAS™ program's risk assessment could be compromised if risk management and control of flavor substance use is not effective.

FEMA should continue efforts to train manufacturers and users of flavor substances on the safe use of GRAS flavor substances and verify that their outreach is effective.

Currently, FEMA outreach focus has been on communicating the FEMA GRAS™ program to food manufactures (Mermelstein, 2015), which is essentially the premarket safety assessment process. However, "a manufacturer must fulfill certain post market responsibilities" (Neltner et al., 2011 p. 356) and continued outreach and clear education to end user on the parameters for the basis of safety determination are warranted as risk management steps.

Because post market assessment is critical to ensure consumer safety, outreach on the importance of FEMA flavor poundage surveys to stake holders is critical. Voluntary participation in these surveys helps assess the concentration of flavor additives used in food and therefore broad industry participation is important. These surveys are essentially a control step in assuring the safe use of flavor substances in food. Currently

there is no regulatory requirement for postmarket assessment, but depending upon how FDA chooses to enforce and clarify FSMA requirements, participating in post market safety assessments could be a regulatory requirement.

There are limitations with epidemiology for assessing chemical risk, so toxicological risk assessment is the primary way to determine the probability, type and magnitude of human health effects from exposure to food chemicals (Winter & Francis, 1997 pp. 85-86). Since risk assessment is the primary method to assure a food chemical is safe, exposure data is critical.

#### D. FDA's role:

A challenge that the FDA struggles with is that food toxicology is severely underfunded and “drug safety receives more funding than food safety, yet people eat food everyday” (Alger, H., et al., 2011, p. 98). The federal government mandate for food manufacturers to develop written food preventive controls for human food should also mandate that funding not only be set aside for implementation of the rule, but for toxicology studies that are preventive. Funding for drugs to cure disease is essential, but increasing funding for preventive care is essential as well. Detailed and regular exposure surveys are necessary to validate toxicological safety assessments of FEMA GRAS™ substances.

FDA is making critical decisions needed to ensure the safety of the nations' food supply for all consumers. They have signed a MOU with the EPA to share data on toxic

substances under the jurisdiction of both agencies and this will help subject matter experts determine if there are unforeseen hazards with chemicals that are used in various consumer products. FDA has also acknowledged that a priority concern is the consideration of susceptible populations and that they must ensure that chemical assessments and resulting risk management decisions protect all affected human populations.

FSMA is anticipated to have further requirements from FDA that will assure the safety of the US food supply. Not only will FDA need to enforce the FSMA regulation, “successful implementation requires a modernization of how FDA does its food safety work” (DHHS, 2015). The FDA has indicated they need funding to strengthen their technical expertise and capacity to support investigators and industry in implementing the new preventive standards. The development of a “positive flavor substance list” with use restriction per food category, specifications and broad use in consumer products will aid both industry and FDA investigators in implementation of FSMA standards. Currently, there is a broad set of lists and no central list with regulatory guidance on permissible use of the over 2700 flavor substances.

It is unclear if the proposed FSMA rule adequately addresses non-pathogenic hazards and submitted FSMA comments have addressed this concern (Neltner, 2013 p.2). The introduction to FSMA regulations focuses entirely on disease from pathogens, “each year, about 48 million Americans (1 in 6) get sick, 128,000 are hospitalized, and 3,000 die from food borne diseases” (Federal Register, 2013 p.3650). This statement seems to

support the assessment that the focus of FSMA is on biological hazards. However, section 103 of the “FDA Food Safety and Modernization Act” clearly refers to chemical hazards and unapproved food additives; “ a facility shall identify and evaluate all known or reasonably foreseeable hazards ...including biological, chemical, physical, and radiological hazards natural toxins, pesticides, drug residues, decomposition, parasites, allergens, and unapproved food and color additives”. One reason the FSMA introductory statement focuses on food borne diseases is because there are epidemiology tools that can link food with illness from pathogens, but there are “limitations on the use of epidemiology to predict risks from human exposure to chemicals in the diet”(Winters & Francis, 1997, p.85). The FDA should assure FSMA legislation is enforced adequately to address all hazards.

#### V. CONCLUSION:

The FEMA GRAS™ risk assessment process does not have the gaps that the US GRAS risk assessment process has been identified as having: lack of transparency, conflict of interest and no post market reassessment process. However, based on the baseline flavor chemist training survey, there is strong indication there are significant training gaps in the risk management process of FEMA GRAS™ substances. With the implementation of “FDA Food Safety Modernization Act”, written preventive controls will have further requirements on food facilities for the control and management of FEMA GRAS™ flavor substances. Written assurances that FEMA GRAS™ flavor substances are not misused should be required, supply sources should be monitored for safe practices and use trends should be monitored to assure that consumer is not at risk.

Furthermore, because it is very difficult for the user to know and understand permissible conditions of use, FDA and FEMA should offer guidance to food and flavor manufacturers on the permissible use of FEMA GRAS™ substances. A central list of the approximately 2700 flavor substances with clear definitions on the safe parameters of use is needed. Not only should flavor and food manufacturers receive training on how to safely use flavor substances, but regulators should also be trained on the identification of possible risk with misuse of FEMA GRAS™ substances. These control steps are needed to assure the risk assessment of FEMA GRAS™ is accurate and compliant with statutes.

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