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Hidden Ingredients

What are 'flavors' and 'spices,' and are they safe?

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2025 Revision

This report was originally published in April 2024. Since then, CSPI continued to investigate flavor safety and regulatory issues, and we identified additional flavors that are banned or restricted in the European Union due to safety concerns. We are publishing this revised report to detail our analysis of those flavors, which helps highlight the need for policy change (see Chapter 2, Section B). This version also includes minor editorial changes for clarity, specificity, and accuracy.

Executive Summary

The way a food tastes and smells is important when it comes to choosing what we eat. Food companies engineer foods to ensure they taste and smell appealing by adding flavors and spices. These can be natural substances or chemicals synthesized in a laboratory. They can be a single ingredient—like vanilla extract, dried basil, or a specific chemical—or blends of many ingredients formulated and developed by professional flavorists.

One thing all spices and flavors have in common is that food companies do not actually have to tell consumers which of these substances they have added to a food.

Almost all other food ingredients must be identified specifically by name in the ingredient list found on food packages. But federal regulations allow the food industry to use the vague catchall terms "artificial flavor," "natural flavor," and "spices" instead of identifying each individual flavor substance by name. This report explores the problems that arise when companies hide ingredients from consumers and regulators under these vague terms.

Flavor is a $14 billion global industry with powerhouse trade groups that play outsized roles in dictating which substances are used in our foods. Many factors contribute to the particularly complex problem of flavor:

- **The GRAS loophole and industry influence and control:** Food and flavor companies leverage a legal loophole that allows anyone, including companies themselves or industry-paid experts, to declare that a substance is "generally recognized as safe," or GRAS, and in effect, bypass U.S. Food and Drug Administration (FDA) approval for new food chemicals (we call this the "GRAS loophole"). Worse yet, food companies do not even have to notify the FDA of their GRAS determinations before or after adding the substances to our foods (we call this pathway within the GRAS loophole "secret GRAS"; see Figure 3). The GRAS loophole is widely exploited by the flavor industry, resulting in thousands of flavor substances currently in use that have never been formally deemed safe and approved by the FDA. Because companies can hide these substances behind the terms "natural flavor," "artificial flavor," or "spices," not even the FDA knows which substances have been added to our foods. The only entities who can attest to the safety of those substances are the companies selling them, which is a clear and troubling conflict of interest. Flavor and food companies closely guard their flavor blends as "trade secrets" to prevent competitors from making copycats of their popular foods. In practice, flavor and food companies are the primary entities deciding whether flavor chemicals are safe, not the FDA.
- **Thousands of flavors in hundreds of thousands of foods:** There are thousands of individual substances currently in use as flavors, and one food can contain more than 100 individual flavor substances. Over half of the packaged foods in the U.S.—which is hundreds of thousands of products—contain either added flavor (natural or artificial) and/or spice.
- **Imprecise food labeling:** The exact same chemical can appear on food ingredient labels as a natural flavor or artificial flavor depending on what it is made from. For example, vanillin can come from vanilla extract—in which case it can be labeled as "natural flavor" or by the name "vanillin"—or it can be synthesized in a lab, in which case it can be listed in the ingredient label as "artificial flavor" or by name. Furthermore, the FDA allows natural flavors to be derived

from any natural substance but does not require companies to name that substance. Because of this, in some products listing "natural beef flavor" as an ingredient, there may be no beef or beef-derived ingredient at all. That "natural beef flavor" may be derived from plants, where "beef" describes the taste and not the source material. This situation likely causes tremendous consumer confusion.

- **Dueling regulatory agencies:** Regulatory jurisdiction over food labeling, like regulation of the underlying foods themselves, is split between two federal agencies, the FDA and the U.S. Department of Agriculture (USDA). The two agencies have different definitions and disclosure requirements for flavors, producing unnecessary confusion around what the terms mean.

The food industry is capable of disclosing flavors but chooses not to.

While there are many factors to consider when improving regulation for flavors, shifts in disclosure practices are possible. The personal care products industry is a prime example. As with foods, personal care products—like lipstick, shampoo, and toothpaste—are regulated by the FDA and are currently permitted to use the vague terms "flavor" and "fragrance" in their ingredient lists. Some major personal care product brands have recently begun voluntarily disclosing the composition of their flavor and fragrance ingredients to consumers. Following this trend, California passed a law in 2020 that requires greater flavor and fragrance disclosure in personal care products. The food industry is similarly capable of voluntarily providing full disclosure, yet we have not seen similar trends or commitments in the food industry.

The FDA is failing to monitor flavor safety.

Federal law obligates the FDA to declare any food or color additive shown to cause cancer in humans or animals as unsafe. The FDA has failed to uphold this responsibility. Despite evidence emerging years-to-decades earlier, the FDA failed to ban seven carcinogenic flavors until 2018. It was only after the Center for Science in the Public Interest (CSPI) and our partners sued the agency to force them to respond to our coalition's 2016 petition that the agency finally enacted the ban. The FDA's inaction on these seven substances raises questions and concerns about the FDA's efforts to monitor the safety of the thousands of other flavors in our food supply.

It may surprise some to learn, however, that the seven substances banned by the FDA in 2018 are still present in foods as added flavors. How is that possible? The FDA only banned the synthetic (lab-made) forms of these chemicals. But each of these seven substances occur in natural products, like herbs, and so can still be added to foods if they come from natural sources. Importantly, the mere presence of these substances in food does not mean that they pose a major risk to consumers. However, some of these substances belong to a class of chemicals for which no safe dose can be established, meaning any reduction in exposure would be beneficial. In the European Union (E.U.), limits have been set on the amounts of certain naturally occurring harmful flavors in foods. The E.U. has also banned a number of other flavors that are still allowed in the U.S. There is no equivalent to the GRAS loophole in Europe, making E.U. flavor regulations more protective overall than the FDA's (although not necessarily perfect).

Consumers should have the information they need to protect themselves.

Current ingredient labelling laws deprive consumers of the information they need to protect themselves from food allergens or identify products aligned with their ethical beliefs (such as those following a vegan diet). Federal law requires allergen labeling for only nine "major allergens," but at least 59 foods can cause life-threatening allergic reactions. By our assessment, each of these substances can legally be hidden behind the terms "spice" or "natural flavor." There also appears to be a diverse array of animal-derived substances available for purchase, or otherwise greenlit by the FDA or industry, that could also be obscured by the term "natural flavor."

It is quite clear: Consumers need ingredient disclosures to make fully informed decisions about the foods and beverages they buy, serve, and consume. Unfortunately, current federal flavor laws make it impossible for consumers to access that information.

RECOMMENDATIONS FOR ACTION

Federal policymakers, state and local policymakers, and industry can each take steps to address safety and transparency concerns around flavors. Our recommendations include:

Federal policymakers should:

- Mandate full disclosure of flavors and spices (or as a first step, require those using "natural flavor" to specify source materials).
- Close the GRAS loophole (or as a first step, end secret GRAS) and increase funds and resources available to the FDA to regulate food chemical safety.
- Set maximum levels for toxic substances that occur naturally in spices and natural flavors.
- Improve post-market monitoring of food chemicals and develop a comprehensive food chemical database.
- Align ingredient disclosure requirements and terminology between FDA- and USDA-regulated foods.

State and local policymakers should:

- Collect and publish information currently kept secret by industry.
- Ban dangerous chemicals.
- Mandate full disclosure of flavors and spices.

The food and flavor industries should:

- Implement full flavor and spice disclosure.
- Stop exploiting the GRAS loophole (or as a first step, stop using the secret GRAS pathway).

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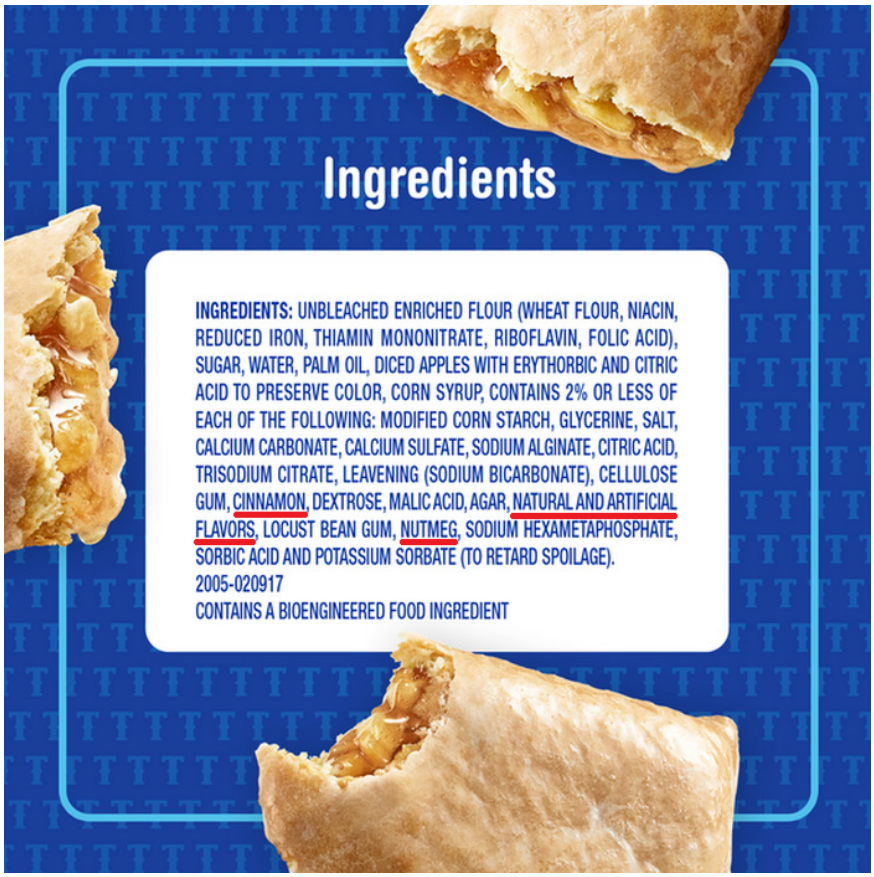
Chapter 1. What Is Flavor?

Flavor encompasses the collective sensations we experience when eating foods, including our perceptions of a food's taste and smell.[1] A food's flavor is determined by its chemical composition. This is true of raw whole foods (like a Granny Smith apple), homecooked foods (like homemade apple pie), and packaged processed foods (like a green apple-flavored candy). In raw whole foods, the flavor chemicals are produced naturally as the plant, animal, or fungus grows and produces an edible fruit, vegetable, grain, mushroom, herb, spice, or animal product. Flavor compounds are also produced during cooking and other types of food processing (like fermentation). Home cooks and food manufacturers alike add additional flavor substances on top of those occurring naturally in the food's raw ingredients or produced during cooking.

For instance, whether making an apple pie at home or mass-producing a packaged apple pie to be sold at grocery stores, bakers are likely to add ground spices like cinnamon and nutmeg to the pie filling to complement the flavors of the cooked apples and sugar.

Indeed, a Tastykake glazed apple pie product lists both cinnamon and nutmeg on the ingredient label. In addition, it also lists "natural and artificial flavors" among the ingredients[i] (Figure 1).

Figure 1. Tastykake Glazed Apple Pie ingredient list with flavors and spices underlined.



What are these "natural and artificial flavors"?

Substances used for flavoring can be naturally derived or produced artificially, and they can be single chemicals or mixtures of many different chemicals. In this report, we use the term "flavor substances" to refer to this entire diverse group collectively.

[i] From: https://www.instacart.com/products/149149-tastykake-glazed-apple-pie-4-5-oz.

Tastykake could have added vanilla extract—a natural flavor—to the filling or the glaze. Or artificial butter flavor could have been used to increase the buttery flavor in the crust. But because the ingredients only list "natural and artificial flavors," consumers are left guessing about the actual ingredients in their food.

How is this possible? Since 1938, packaged foods have been required to include a list of ingredients on their labels, thanks to the Federal Food, Drug, and Cosmetic Act.[2] But not all ingredients must be disclosed under this law, which allows manufacturers to use vague catchall terms for some ingredients, including flavors, spices, and some colors. Rather than listing each individual substance used to flavor or scent their products, industry can simply list "artificial flavors," "natural flavors," or "spices" in the ingredient list.[ii] These vague ingredient terms prevent regulators and public health advocates from monitoring the use and safety of ingredients. Lack of clear information also limits consumers' ability to make informed decisions. Consumers need transparency to identify flavor ingredients derived from allergens or ingredients that pose religious or ethical concerns (such as pork, shellfish, or other animal products).

The lack of transparency undermines confidence in the safety of flavor, undercuts consumer choice, and creates opportunities for corporate conflicts of interest to prevail over public health protection. We need full flavor disclosure, such that consumers, regulators, and watchdogs alike have access to the full list of individual substances intentionally added to any food on the market.

A. THE BASICS OF FLAVOR

Although the concept of a single flavor like "vanilla" may seem simple, the chemical composition of flavors is quite complex.

Natural substances, like vanilla beans, that are used to create natural flavors contain a multitude of aromatic and flavorful chemicals. As a result, the flavorful derivatives of these natural substances, like vanilla extract, also contain mixtures of chemicals. The primary chemical responsible for the flavor of vanilla bean and extract is called vanillin, but the chemicals piperonal, eugenol, glucovanillin, vanillic acid, anisic acid, and anisaldehyde also contribute to the characteristic flavor and aroma of vanilla beans.[3]

There is an entire industry of flavor formulators who create and sell flavor substances. To add to the inherent complexity of the naturally occurring mixtures of chemicals in natural extracts, essential oils, and other natural flavor substances, flavor companies create their own unique flavor mixtures. These blends, called compounds or compound flavors, can include natural or synthetic substances and are often proprietary, with the ingredients known only by the flavor companies and the food companies that use them.[3] Commercial compound flavors may comprise more than 100 ingredients, including individual chemicals, like vanillin, or natural flavor substances, like vanilla extract, according to the flavor industry.[4] The flavor industry currently has thousands of substances to choose from to create these compound flavors (see Chapter 1, Section B.iii).

Rather than buying and mixing many individual chemicals or substances to create desired flavor profiles, food companies can simply purchase compound flavors from flavor companies to achieve a specific flavor profile. This is comparable to home cooks choosing to use McCormick's "apple pie spice" (which comprises cinnamon, allspice, and nutmeg) in their apple pie instead of individually adding each of the three spices in various quantities[iii] (Figure 2). The benefit of these premixed blends for the end user is simplicity. McCormick's premixed product promises to be "perfectly blended for sweet, aromatic flavor," essentially saving cooks the effort of having to find the optimal mix of the three spices to deliver the ideal flavor. Similarly, food manufacturers can purchase compound flavors from flavor companies to deliver a flavor profile to their products without having to go through the flavor formulation process themselves.

[ii] This report is focused on how flavors and spices are listed in the ingredients list. Different regulations apply when flavor terms are used on the front label of a food and in marketing. Unless otherwise specified, when describing labeling, we are referring to ingredient labeling specifically.
[iii] From: https://www.amazon.com/McCormick-Apple-Pie-Spice-1-12/dp/B0005XNEXW/.

Figure 2. McCormick apple pie spice.

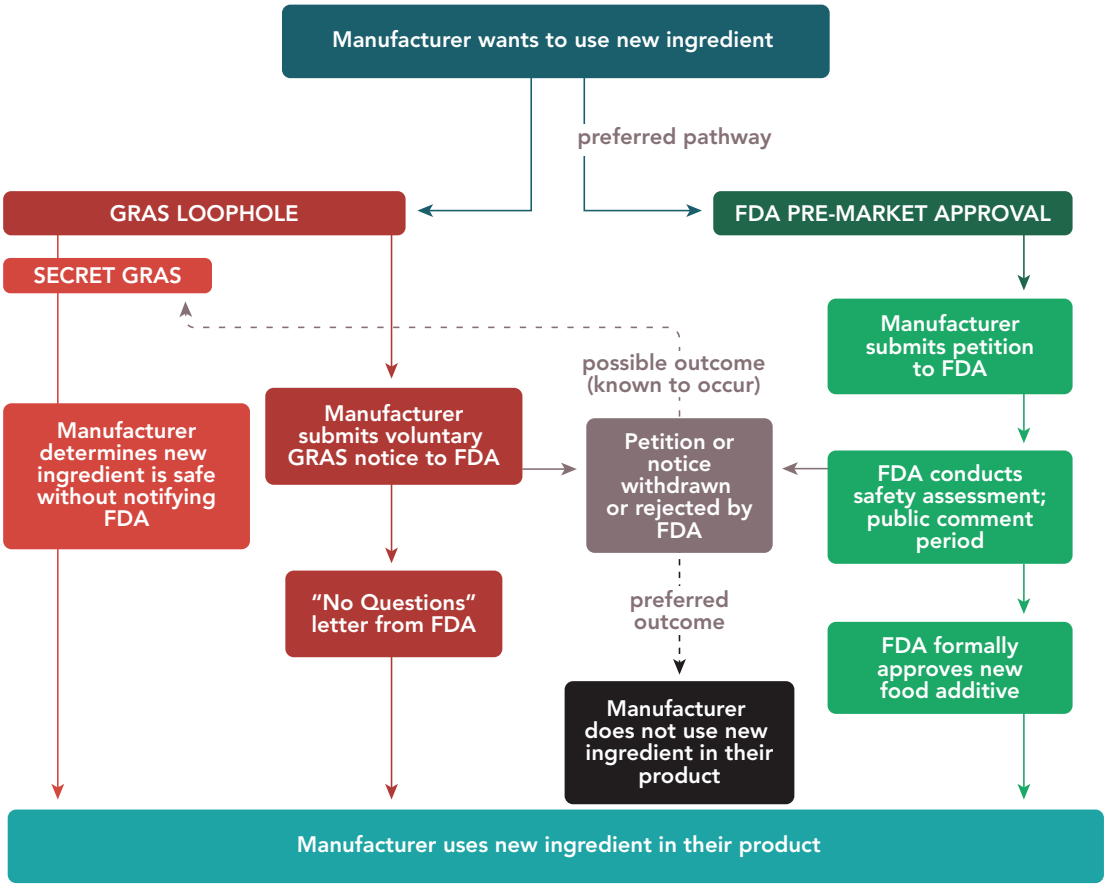


B. THE REGULATION OF FLAVOR AND SPICE INGREDIENT LABELING AND SAFETY

In the U.S., two federal agencies oversee flavor and spice labeling and safety: the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA). The USDA bears responsibility for regulating flavor labeling in meat, poultry, and some egg and fish products. But the bulk of the responsibility falls on the FDA, which regulates the safety of flavors in all packaged foods and beverages and the labeling of flavors in all other packaged foods and beverages.

Federal law requires that substances added to food—including flavor substances—be deemed safe before food companies start using them.[5-7] Specifically, there must be a "reasonable certainty" that the substance will not cause harm through its intended use, and it must not cause cancer in humans or animals.[7,8] However, there are two dramatically different ways a substance can be deemed safe and enter our food supply (Figure 3).

Figure 3. Pathways to market for new food chemicals, or new uses of existing chemicals, in the United States.



The first is through FDA premarket approval. If a food company wants to market a new food substance (or use an existing substance in a new way), it can submit a petition in which it provides the FDA with information that, theoretically, substantiates that the substance is safe under the intended use.[7] Thereafter, the FDA performs a safety assessment based on the information provided in the petition and may then formally approve it. Importantly, during this process there is an opportunity for members of the public, like CSPI, other watchdogs, and concerned citizens, to submit comments regarding the proposed use of the substance.[9] If the substance is formally approved, then it is designated and regulated as a "food additive." This is the approach Congress intended food companies to use to bring new food chemicals to market when it amended the federal Food, Drug, and Cosmetic Act in 1958. However, this is not how most new food chemicals enter our food supply currently. Instead, food and chemical companies exploit a loophole that allows them to bypass the formal FDA approval process created by Congress.

When outlining the procedures for approving new food additives in the 1958 Food Additive Amendment, Congress included an exemption for substances that are "generally recognized as safe," or GRAS.[6,10,11] This exemption allowed ingredients like vinegar, baking powder, and flour to be added to food without undergoing the formal FDA premarket approval process for food additives.[11] In addition to cutting out the FDA, this "GRAS loophole" process also excludes the public. Whereas the FDA must provide an opportunity for members of the public to submit comments regarding a food additive petition, there is no such opportunity for GRAS notices.[12] Congress hardly could have intended this exemption to allow entirely new food chemicals to be used in foods without FDA approval, yet that is exactly what is now occurring for most new food chemicals entering the food supply.

How does the GRAS loophole work? The Food Additive Amendment states that for a substance to be GRAS, the general recognition of safety should occur "among experts qualified by scientific training and experience to evaluate its safety," and be "adequately shown through scientific procedures."[6] However, it does not describe, in specific detail, what constitutes a "general recognition," what training and experience qualifies (or disqualifies) an expert, or what scientific procedures are needed for a determination. The information underlying a GRAS determination must be generally available, which ordinarily means published,[13] but as is outlined below, it is not always clear what data were used to decide that a substance is GRAS.

The interpretation and implementation of the GRAS process have evolved over time.[10,11,14] From the creation of the Food Additive Amendment through the late 1990s, the FDA largely maintained control over which substances were considered GRAS by making and periodically updating a list of GRAS substances,[11,15,16] conducting reviews into the safety of GRAS substances,[10,11] revising GRAS regulations,[11,17] and making clear that new tests establishing harm could prompt removal from the GRAS list.[17]

But even during that time period, the FDA did not have full control. The food industry considered many added substances as GRAS even when those substances were not included in the FDA's 1958 GRAS list.[10]

In 1997, the FDA gave up any claim to controlling the GRAS process and officially gave industry the authority to self-certify that a new food chemical was GRAS without any FDA oversight. The FDA created a voluntary notification system for a company to inform the FDA, if the company chose to do so, that it had determined a chemical to be GRAS.[11,12]

Of course, due to the voluntary nature of GRAS notices, companies can (and do) simply choose not to notify the FDA at all and proceed with marketing the substance. We refer to substances introduced into the food supply without FDA approval as "GRAS substances," and those introduced without even a GRAS notice as "secret GRAS" (Figure 3).

Even when a company voluntarily provides notice to the FDA of a GRAS determination, the agency can only review the information provided in the notice and raise questions about the safety determination; it does not independently perform a safety assessment or approve the substance's use.[12,18] Worse yet, the company may request for the FDA to "cease to evaluate" the notice at any time.[19] Remarkably, evidence shows that when the FDA questions the safety of a substance deemed GRAS by manufacturers, manufacturers often request that the FDA "cease to evaluate" the notice and continue to market the substance anyway, despite the FDA's questions (Figure 3).[20]

For example, the dietary supplement company Prevagen did exactly that when marketing a new substance for use in dietary supplements; this is another troubling aspect of the GRAS loophole—it applies not only to food, but also to dietary supplements, so dietary supplement companies can use the loophole to bypass other premarket review processes for new supplements.[20] In this case, despite the FDA raising multiple safety concerns with Prevagen's new dietary ingredient, Apoaequorin—a substance touted as improving memory[21]—and despite failing the FDA's supplement premarket review process for dietary ingredients as a supplement twice,[22,23] the company introduced the ingredient using the secret GRAS loophole.[24] Only after introducing the product did the company submit a GRAS notice.[25] However, it requested that the FDA cease reviewing its GRAS notice just before receiving an FDA letter outlining concerns with Apoaequorin's safety.[25,26] Despite the FDA never completing its GRAS review after raising safety concerns, Prevagen continues to market its product. Although Apoaequorin is not a flavor, any company can introduce new substances, including flavors, using the GRAS loophole to avoid addressing the FDA's safety concerns, just as Prevagen did.

Companies have introduced thousands of substances into our food via the GRAS loophole. Of the roughly 10,000 chemicals used in our food—or that can end up in our food through use in food contact substances, like food packaging—more than 3,000 have never been substantively reviewed by the FDA.[27] An estimated 1,000 of these substances entered the food supply through the secret GRAS pathway; safety decisions were made by the food industry without any notice to the FDA, meaning the FDA has no information on these substances.[27,28] As Deputy FDA Commissioner for Foods, Michael Taylor, remarked in August 2014, "We simply do not have the information to vouch for the

safety of many of these chemicals."[29] According to an analysis by the Environmental Working Group, another consumer advocacy organization, almost 99 percent of new food chemicals introduced in the U.S. since the year 2000 have entered the market via the GRAS loophole.[30]

The GRAS loophole is widely exploited to market new flavors, which is especially concerning because of the lax labeling requirements afforded this specific group of food ingredients. When GRAS flavor substances are listed as "natural flavor" or "artificial flavor," only the manufacturer knows what chemicals are present in our food, allowing industry to hide untested and unsafe food chemicals from regulators, consumers, and public health advocates, like CSPI, who might otherwise raise the alarm over dangerous chemicals.

There Are Still Problems with FDA-Approved Additives

Even when the FDA does approve a new food additive, it does not always require adequate testing. For example, the novel ingredient soy leghemoglobin was developed to replicate the color and flavor of meat in Impossible Beef, a plant-based beef substitute. Soy leghemoglobin is a protein that contains heme, an iron-containing molecule found in beef.[31] Soy leghemoglobin did not have to be approved as a flavor because Impossible deemed it to be GRAS31 and the FDA did not object.[32] However, because color additives cannot be introduced through the GRAS loophole, the company had to submit an application to the FDA to get approval to use it as a color.[32,33] The agency conducted a barebones review that did not investigate whether the ingredient might replicate some of the cancer risks associated with heme, which has been tied to cancer risks in red meat.[34]

The agency has also been slow to act on safety risks for other color additives. For example, the FDA banned the food dye FD&C Red No. 3 in January of 2025 following a 2022 CSPI petition, 35 years after the FDA determined it causes cancer and banned it from cosmetics and topical drugs.[35-37]

i. GRAS and the Flavor and Extract Manufacturers Association

The Flavor and Extract Manufacturers Association (FEMA) is a trade association of U.S. flavor manufacturers, suppliers, and users (food manufacturers) that describes itself as "the authoritative voice advancing the safe and responsible use of flavorings."[38] One way FEMA does this is by paying[iv] a panel of scientists (which FEMA calls its "Expert Panel") to perform safety evaluations leading to GRAS designations for flavor substances.[39] FEMA's member companies submit applications to have a substance reviewed by the FEMA Expert Panel. FEMA publishes these determinations and maintains a list of flavor substances that its Expert Panel has declared GRAS over the six decades during which it has operated. This list currently includes nearly 3,000 substances and is incorporated into the FDA's Substances Added to Food database (discussed below).[40] Further, this means that most of the more than 3,000 flavors in the FDA's database came to market via the GRAS loophole thanks to FEMA.

The FEMA GRAS program has been operating since 1959, the year after Congress passed the Food Additive Amendment and created the GRAS exemption. Notably, FEMA claims to have played a direct role in contributing to the 1958 Food Additive Amendment.[41,v]

[iv] FEMA states, "While the Expert Panel has been provided with financial support by FEMA it has always maintained its full independence in its operations and GRAS determinations and follows strict conflict of interest procedures."

[v] FEMA states, "As early as 1914, FEMA could 'claim to occupy the important position of being the guardian of the interests of the flavoring extract manufacturing industry of the United States…[and]…in a position to shape the future course of the extract industry of the country,' according to Thomas Lannen, FEMA's first attorney and the first U.S. food and drug lawyer. And shape the industry FEMA has done over the past 100 years, from formulating standards to fighting unfair taxation to contributing to the 1958 Food Additives Amendment and so much more."

FEMA has a number of internal policies and practices intended to ensure transparency and compliance with regulations. Yet, like many industry attempts to self-impose safety standards, the process is deeply flawed. Like an FDA review, the FEMA process is voluntary, so companies that do not have evidence to show that a chemical is safe can simply avoid FEMA or withdraw their applications (and unlike letters to the FDA, such withdrawals may not necessarily be made public). While FEMA claims to limit conflicts of interest by its experts, the organization itself is paid by its members, and therefore has a strong interest to provide positive reviews to secure repeat business, which may bias the process in ways that are difficult to document.

FEMA claims that all scientific information underlying its Expert Panel's GRAS determinations are supplied to the FDA.[39,vi] FEMA does not make its disclosures to the FDA by formally submitting voluntary GRAS notices; however, in a 2010 report, the U.S. Government Accountability Office stated that it considers the level of disclosure provided by FEMA to be analogous to that achieved through GRAS notice.[28] Further, FEMA states that its policy is to "share information on all FEMA GRAS substances with anyone upon request."

But contrary to these claims, it appears that FEMA (at least historically) did not always provide information to the FDA regarding its GRAS determinations, and it did not make such information available to anyone upon request.

About a decade ago, CSPI spent a year trying to acquire documents from FEMA and the FDA pertaining to GRAS determinations made by the FEMA Expert Panel for several substances produced by the company Senomyx. The FDA did not have any such documents in its possession. In January 2013, we sent a letter to the FDA (Appendix A) outlining the timeline and series of steps we took to acquire this information. Only after we sent this letter did FEMA finally provide us the information we requested, more than a year after we first asked. It is possible that FEMA has improved its practices since 2013, but this experience raises concerns about whether it truly implements the practices it outlines and whether the FDA is indeed in possession of the information underlying FEMA's GRAS assessments.

The criteria FEMA's Expert Panel uses to conduct safety assessments have been published in the peer-reviewed literature.[39,42,43] FEMA states that it applies the same safety standard that the FDA uses in assessing safety of food additives—that is, there must be a reasonable certainty of no harm resulting from the intended use of the substance—but recall, that is only one part of the federal safety standard. Federal law also specifies that substances that cause cancer in humans or animals must be deemed unsafe and therefore prohibited from foods. FEMA does not apply that standard. In fact, FEMA declared the flavor substance isoeugenol GRAS, despite clear evidence it caused cancer in animal tests conducted by the U.S. National Toxicology Program (NTP).[44,45] (Isoeugenol is discussed further in Chapter 2.)

FEMA has also instituted policies intended to protect against conflicts of interest biasing evaluations performed by its Expert Panel.[39] These include:

- barring Expert Panel members from having consulting relationships with FEMA member companies "regarding anything to do with flavors in the context of the FEMA GRAS Program";
- requiring Expert Panel members to provide a declaration of consulting and business relationships to the Expert Panel's legal advisor;
- preventing Expert Panel members from knowing the identity of the company responsible for a GRAS application under their review;
- prohibiting FEMA member companies from contacting the Expert Panel or participating in any Expert Panel meetings pertaining to their own applications;

[vi] FEMA states, "The scientific information serving as the basis for the Expert Panel's determinations of GRAS status is provided to FDA for all FEMA GRAS flavor ingredients. This allows the agency to include the information in its databases and to challenge any GRAS determinations that it wishes. It is important to note that the receipt by FDA of the information provided by FEMA does not constitute FDA's 'approval' of the GRAS determinations made by the FEMA Expert Panel."

- requiring Expert Panel members to appoint new members instead of FEMA; when panelists retire, the retiree suggests a replacement, and the remaining panelists review the nominee's qualifications and make the appointment;
- compensating Expert Panel members regardless of whether a GRAS determination is made;
- publishing a list of Expert Panel members;
- and barring FEMA staff members from having consulting or business relationships with FEMA member companies "regarding anything to do with flavors in the context of the FEMA GRAS program."

CSPI is skeptical that these alone are sufficient to protect against member companies biasing the outcome of Expert Panel evaluations. First, although Expert Panel members and FEMA staff cannot have consulting relationships with member companies, it is unclear how FEMA defines and applies the caveat, "regarding anything to do with flavors in the context of the FEMA GRAS program." FEMA experts and staff, thus, are permitted to have consulting and business relationships with member companies, as long as they do not discuss the FEMA GRAS program. Because the FEMA GRAS program is only one aspect of FEMA's function and safety is only one aspect of developing and marketing novel flavors, there are seemingly plenty of non-GRAS-focused reasons for which FEMA member companies may be in financial relationships with FEMA Expert Panel members or staff. A wholesale prohibition on consultation or business relationships between FEMA member companies and FEMA experts and staff would provide greater protection against conflicts of interest. Further, consultation and business relationships are only one form of competing interest. Notably lacking from the above list is a prohibition on having other financial interests in member companies (like stock ownership). Next, as far as we know, declarations made to the Panel's legal advisor are not available to the public, limiting opportunities for oversight by independent third parties (such as the FDA, CSPI, or members of the public). Lastly, having the panel self-appoint its members does nothing to prevent bias from influencing the outcome of evaluations.

FEMA, as a private organization, is not subject to any sort of third-party auditing related to these issues of which we are aware. While it is commendable that FEMA claims to implement the various measures outlined above to foster transparency and limit conflicts of interest, ultimately we have no way of knowing the extent to which these measures are implemented. FEMA may very well uphold each of these policies and procedures to their utmost and the evaluations conducted by its Expert Panel may be objective, rigorous, and scientifically sound. But there is always an unavoidable conflict of interest inherent in the current system, no matter how many voluntary safeguards FEMA claims to employ. Until such time as the GRAS loophole is closed and all flavor chemicals are formally FDA approved, there will be lingering concern about the safety of GRAS flavors.

Additional information about FEMA and an international flavor trade group can be found in Appendix B.

ii. Flavor and Spice Ingredient Labeling in the United States

In general, most foods do not need to specifically list each spice or flavor substance in the ingredient label on packaged foods and beverages.[vii] The FDA oversees labeling for most foods sold in the U.S. Under FDA rules, a flavor can be listed in the ingredient list as a "natural flavor" if it comes from a natural substance and is added to food for its flavor, not for its nutrition or other properties.[46] If a flavor is not derived from a natural source, it would have to be listed as an "artificial flavor." For example, if vanillin were extracted from the vanilla bean, it could be listed as a "natural flavor." If vanillin were created through chemical synthesis in a lab, it would be listed as an "artificial flavor."[46] In either event, the exact name of the flavor is not required to be disclosed.

[vii] One exception to this is for major food allergens, an issue that is discussed in detail in Chapter 3.

For a flavor to be considered natural, it must meet both criteria below:

- ✅ Come from one of these natural substances:
  - Fruit
  - Vegetable
  - Herb, bark, bud, root, leaf, or similar plant material
  - Meat
  - Eggs
  - Seafood
  - Dairy
  - Spice
  - Yeast
- ✅ Be in one of these forms:
  - Essential oil
  - Oleoresin
  - Essence or extractive
  - Protein hydrolysate
  - Distillate
  - Any product of roasting, heating or enzymolysis

Because the FDA allows natural flavors to be derived from any natural substance but does not require, or even encourage, companies to name the source of their "natural flavor" in ingredient lists, consumers currently have no way of knowing if a natural flavor was derived from a plant or an animal. For example, "natural vanilla flavor" could be derived from a vanilla bean, but it could also contain castoreum extract, an animal product.[47,viii] Even more counterintuitively, "natural beef flavor" could be sourced only from non-animal products and may contain no beef at all.[48,49] There are some nuances, however, when it comes to front-of-pack ingredient labeling that ultimately create even more confusion for consumers.

What qualifies as a natural or artificial flavor is different for the front of package than for the ingredient list. The front of package can only state that the food is naturally flavored when the primary flavor comes from an ingredient that people would usually assume that flavor would naturally come from.[50] For example, a vanilla ice cream flavored with castoreum extract would have to indicate on the front of its package that it is artificially flavored or flavored with castoreum extract because people would usually assume that vanilla flavor comes from a vanilla plant. However, the ingredient list could still list the castoreum extract as "natural vanilla flavor" because the castoreum extract is naturally sourced.

As a point of comparison, this differs from how the European Union regulates the term "natural flavor." As in the U.S., to use the term "natural flavouring" in the E.U., the substance must be entirely of natural origin. But unlike in the U.S., the source of the natural flavor should be identified on the labels, "except when the source materials referred to would not be recognised in the flavour or taste of the food."[51] What this means, seemingly, is that if vanilla extract were added to the product, but consumers would be unable to detect the vanilla flavor in the food, then the source could be omitted. If a source is specified, at least 95 percent of the flavoring component must be from that source. Overall, this means that in the E.U., "natural beef flavor" would be a substance derived from beef, in contrast to the U.S. where "natural beef flavor" can be derived from non-beef sources.

[viii] Regarding castoreum extract, Burdock 2007 states that it is "especially useful as an ingredient in vanilla flavored foods."

The FDA also regulates the labeling of spices. When declared in the ingredients list, "spices" specifically refers to plants in their whole, broken, or ground form.[46] There are some ingredients, like onion, garlic, and celery, that do not qualify to be declared as "spices" or "flavors" when they are ground up and added to foods. These must be listed in the ingredient list by name because, according to the FDA, they are "traditionally regarded as foods."[46]

Labeling rules are slightly different for meat, poultry, and certain fish and egg products because they are regulated by the USDA. While "artificial flavor" means the same thing in the ingredient list on packaged chicken tenders and packaged apple pie, USDA-regulated products might use the term "flavor" instead of "natural flavor."[52,53] However, neither "natural flavor" nor "flavor" can be used for a flavor substance derived from an animal source, like "lamb extract." The USDA requires companies to list that ingredient individually and specify the source on the label.[53,54] It may be frustrating for consumers who are seeking to avoid animal products to learn that it is easier to spot animal-derived flavors on the label of a meat or poultry product than on the label of plant-based products regulated by the FDA.

USDA's labeling regulations offer better transparency, accuracy, and consumer protection than the FDA's in a few additional ways. The USDA reviews product labels before the product can be marketed, a step the FDA does not require.[55] The USDA requires chemicals used to replicate smoke flavoring be declared specifically as "smoke flavor,"[52] so consumers know if a product was not conventionally smoked; E.U. regulations also require specific disclosure of smoke flavor for the same reason.[51] The FDA has no similar requirement; smoke flavor can simply be called "artificial flavor" in the ingredient list.[46] As such, only meat and poultry products are required to have specific disclosure of smoke flavor, while other foods are not required to list smoke flavor separately from other flavors.

Additional information about regulatory definitions of flavors is located in Appendix C.

Similarities between 'Flavor' in Food and 'Fragrance' in Cosmetics

Even though the food industry is not required to fully disclose flavors or spices, there is nothing stopping companies from doing so voluntarily. In fact, multiple cosmetic and personal care products companies, including major multinational corporations, have recently begun to voluntarily disclose ingredients they are legally permitted to hide.

As with food, FDA regulations currently allow personal care products, like shampoo, toothpaste, and deodorant, to use the vague catchall terms "flavor" and "fragrance" in ingredient lists instead of requiring companies to disclose each individual substance.[56] In the past decade though, some personal care products companies have adopted practices to promote transparency by voluntarily disclosing specific fragrance and flavor ingredients.[57] Unilever now discloses online all fragrance ingredients that comprise at least 0.01 percent of its personal care products by weight.[58] Procter & Gamble similarly pledged to disclose fragrance products down to 0.01 percent for its entire product portfolio, which does not include any food products, "in recognition of consumers' growing interest in knowing what ingredients are in the products they use."[59] Johnson & Johnson made a similar pledge, but only for baby products.[60] Tom's of Maine discloses the flavor ingredients of its toothpastes online.[61] There may be some food companies that have made similar pledges, but we have not seen them.

Even companies that own both food and cosmetic brands, like Unilever,[ix] have adopted transparency measures only for personal care products, not for foods. Some of the companies producing and selling fragrance for personal care products also sell flavor for foods and are FEMA members.[x] This is not surprising considering some chemicals and substances are used in both foods and cosmetics.[xi] This reinforces the fact that food companies could choose to disclose flavors. The fact that we are not seeing the food industry adopt better flavor disclosure practices leaves frustrating gaps for consumers seeking to minimize exposure to specific chemicals. We now have more knowledge than ever before about the chemicals used in our skin and hair care products but are left in the dark when it comes to foods. Of course, the cosmetics industry also has room to improve.

In addition to voluntary action by industry, there is now a law in California that requires personal care product manufacturers to disclose to the state whether their products contain certain kinds of fragrance or flavor chemicals.[62]

[ix] Unilever owns the following brands included in its "Nutrition" or "Ice Cream" brand families: Bango, Ben & Jerry's, Hellmann's, Knorr, Magnum, The Vegetarian Butcher, and Wall's.

[x] There are two FEMA member companies that have the word "fragrance" in their name: International Flavors & Fragrances (IFF; https://www.iff.com/portfolio/products) and Bell Flavors & Fragrances (https://bellff.com/)

[xi] For example, a personal care products database maintained by Environmental Working Group includes more than 200 products that specifically list vanillin as an ingredient

iii. The Scale of the U.S. Flavor Market

It is impossible to know exactly how many flavor chemicals are currently in use in the U.S. because an unknown number are secretly added to food without formal FDA approval. Nonetheless, FDA regulations include a list of some individual substances that can be used as artificial or natural flavors[63-65] and plants that the FDA has approved as spices and sources of natural flavors.[66-70] The substances listed in the regulations are those that the FDA explicitly recognizes as flavors or spices, but these lists are not comprehensive of all possible flavor substances or spices that can be used. Substances merely need to fit the definition of flavor or spice (see Chapter 1 Section B.ii.) and be declared GRAS by someone—anyone—to be used in food. In other words, other spices and flavors can be used in addition to those listed in the regulations.

The FDA keeps a Substances Added to Food database, which includes all additives and GRAS substances that are directly added to foods listed in FDA regulations.[40] The database also includes flavor substances that have been evaluated by FEMA and the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA), which would not necessarily be listed in the FDA regulations. Thus, the database gives us a better estimate of the number of flavor substances in use than the lists provided in FDA regulations. Currently, the database includes 3,046 substances listed as being used as a "flavoring agent or adjuvant."[xii] There are nine flavor substances in this database listed as "prohibited" or "no longer FEMA GRAS," meaning they are likely no longer in use. In the case of the prohibited substances, those are officially banned by the FDA, so adding them to food would be illegal. Those that are no longer FEMA GRAS have likely been abandoned by industry but are not technically illegal and could still theoretically be in use (for example, if another entity beyond FEMA declared them GRAS, which seems unlikely but is not impossible). Importantly, because the food industry is not required to notify the FDA when it markets a new flavor substance, this database and the FDA regulations do not fully capture all flavor substances currently added to foods in the U.S. Therefore, 3,046 is an underestimate of how many flavor substances are actually being added to our food. Furthermore, the list of prohibited substances is incomplete; the FDA banned seven flavors in 2018 (Chapter 2), but none of those are listed as "prohibited" in the FDA database.[xiii]

The proprietary nature of compound flavor blends is likely to be a major impediment to industry's willingness to adopt full flavor disclosure. If everyone were privy to the closely guarded secret 23 flavors of Dr Pepper—which Thrillist reports are locked in a vault in Texas[71]—theoretically, anyone could produce copycats and undercut Keurig Dr Pepper. Flavor is big business. Fortune Business Insights, a market research firm, reported that the global food flavor market was worth $14.30 billion in 2020, and forecast to increase to $20.12 billion by 2028.[72] Allied Market Research reported slightly lower global values of $12.71 billion in 2020 and a forecast 2030 value of $19.22 billion.[73] For the U.S. market, Grand View Research reported a valuation of $3.97 billion in 2016.[74] With that much money on the line, we can begin to understand why companies want to keep their flavor blends secret.

The fact that flavor is big business is further demonstrated by how commonly the terms "flavor" and "spices" appear on packaged food ingredient labels.

The USDA maintains a database of branded food and beverage products sold in the U.S. This database contained 450,659 U.S. products as of October 4, 2023.[75] To understand what percentage of products use flavor ingredients within the U.S. market, we searched the database for various flavor terms. The results of those searches can be seen in Table 1, with further detail provided in Appendix D.

[xii] Searches were performed on October 4, 2023.

[xiii] The fact that none of the seven flavor substances banned in 2018 are listed as banned in the FDA database likely has to do with the regulatory steps that FDA undertook in response to our petition. Rather than adding the seven substances to the list of substances prohibited in human food at 21 CFR § 189, FDA simply removed the seven substances from the list of approved synthetic flavors at 21 CFR § 175.515.

Table 1. Number and proportion of U.S. products in the USDA's Global Branded Food Products Database that list flavor terms on the ingredient label.[xiv]

Products with…	Count	Proportion of all Products (n=450,659)
flavor ***and/or*** spice	256,454	57%
flavor ***without*** spice	175,133	39%
flavor ***and*** spice	52,545	12%
spice ***without*** flavor	28,776	6%
any flavor	227,678	51%
natural flavor (with or without artificial flavor)	176,249	39%
only natural flavor	124,330	28%
artificial flavor (with or without natural flavor)	72,445	16%
only artificial flavor	20,526	5%
both artificial and natural flavor	51,919	12%
any spice	81,321	18%
spice ***and*** herb	1,461	0.3%
herb ***without*** spice	652	0.1%

Use of added flavor is very prevalent in the U.S. packaged foods market. We found that more than half (57 percent; n=256,454) of the products in the USDA's database contain an added flavor and/or spice. The majority of products (51 percent, n=227,678) contain flavor and 18 percent (n=81,321) contain spice.

It is notable that the term "herb" also appears on 652 packaged food ingredient labels. In fact, this term violates federal food labeling laws, which do not specify that "herb" is a permitted term. Such ingredients are required to be listed as "spice" or by a specific ingredient name.

Natural flavor is much more commonly present than artificial flavor, with 124,330 products (28 percent) listing natural flavor alone (that is, without also listing artificial flavor), compared to just 20,526 products (5 percent) listing artificial flavor alone. Another 51,919 products (12 percent) list both natural and artificial flavors. The higher prevalence of natural flavor is consistent with a trend toward increasing demand for natural flavors, which is driven by rising demand for more natural products.[72]

[xiv] Note that the number of products including the term "flavor" (n = 227,678) differs from the number of products specifically listing natural flavor, artificial flavor, or both (n = 196,775) because our search methodology underestimates the number of products using natural and artificial flavors. This is due to the fact that food manufacturers have flexibility in how they list flavor on the ingredient label. While they can simply list "natural flavor" or "artificial flavor," some manufacturers choose to provide slightly more detailed information. For example, the term "natural beef flavor" appears in 86 products in the USDA's database (Appendix D) but is not included among the results for the search "natural flavor." There are also 24 products listing "artificial beef flavor" (Appendix D). Thus, the number of products that actually contain natural or artificial flavor is higher than our estimates because it is infeasible for us to identify each possible permutation of "natural [blank] flavor" and "artificial [blank] flavor" occurring in the database. Further, since USDA-regulated products are allowed to use the general term "flavor," the simple search for "flavor" also captures those products. Thus, searching "flavor" provides a more comprehensive estimate for the prevalence of flavor, generally, in the market.

Chapter 2. Banned and Other Unsafe Flavors

The U.S. Food and Drug Administration (FDA) has the obligation to prohibit the use of flavors that it deems to be unsafe, regardless of whether the substance is an FDA-approved food additive or came to market via the GRAS loophole.[7] For food chemicals that are already in use, the FDA claims its scientists "proactively reassess a chemical when new information about its safety profile warrants reassessment."[76] However, we know this is not the case.

In 2018, CSPI and our partners succeeded in getting seven such flavor chemicals partially banned in the U.S., following a petition and lawsuit from CSPI and allied organizations. Specifically, the FDA banned the use of benzophenone, ethyl acrylate, methyleugenol, myrcene, pulegone, pyridine, and styrene as artificial flavors in food based on evidence that they can cause cancer in animals.[77-79,xv]

Each of these substances should have been deemed unsafe and banned by the FDA as soon as the cancer evidence emerged because of the statutory obligation to deem any cancer-causing additive unsafe.[7] No petition should be required to spur the FDA to perform its obligation to ban carcinogenic flavors or other food chemicals. But that is exactly what was needed.

Evidence showing that each of the seven banned substances cause cancer had been published years or decades before we submitted our petition in 2016, which led to the 2018 ban.[78] Each of these substances had been evaluated and shown to cause cancer by the U.S. National Toxicology Program (NTP) (Table 2), an interagency program of which the FDA is part.[80] Methyleugenol, for example, has been classified as "reasonably anticipated to be a human carcinogen" in NTP's Report on Carcinogens since 2002, based in part on rodent carcinogenicity studies published by NTP in 2000.[81,82] Styrene was listed as "reasonably anticipated to be a human carcinogen" in 2011 based in part on National Cancer Institute (NCI) studies published in 1979.[83,84] Nearly 40 years elapsed between the NCI studies indicating styrene's carcinogenicity in animals and its ban. Worse yet, in its response to our petition, the FDA stated it only banned styrene because industry had abandoned its use, not because of its links to cancer.[77] Each of the seven banned substances had also been classified as at least "possibly carcinogenic to humans" by the International Agency for Research on Cancer (IARC), part of the World Health Organization (WHO),[85] prior to the FDA ban, further demonstrating that the links to cancer had been well demonstrated (Table 2).

[xv] FDA banned styrene because it was no longer in use as a flavor. It was not banned based on the cancer evidence as requested in our petition.

Table 2. Information on seven carcinogenic flavor substances banned in the U.S.

Substance	NTP Report on Carcinogens Year & Conclusion	NTP or NCI Rodent Carcinogenicity Test Year & Results[xvi]	Year of IARC Evaluations & Resulting Classification
Benzophenone	--	2006, Some evidence of carcinogenic activity[86]	2013, Possibly carcinogenic to humans[87]
Ethyl acrylate	Delisted[88,xvii]	1986, Positive[89]	2019, Possibly carcinogenic to humans[90] 1999, Possibly carcinogenic to humans[91] 1986, (no classification given)[92]
Methyleugenol	2002, Reasonably anticipated to be a human carcinogen[81]	2000, Clear evidence of carcinogenic activity[82]	2023, Probably carcinogenic to humans[93] 2013, Possibly carcinogenic to humans[87]
Myrcene	--	2010, Clear evidence of carcinogenic activity[94]	2019, Possibly carcinogenic to humans[95]
Pulegone	--	2011, Clear evidence of carcinogenic activity[96]	2016, Possibly carcinogenic to humans[97]
Pyridine	--	2000, Clear evidence of carcinogenic activity[98]	2019, Possibly carcinogenic to humans[95]
Styrene	2011, reasonably anticipated to be a human carcinogen[83]	1979, Equivocal evidence of carcinogenic activity[84,xviii]	2019, Probably carcinogenic to humans[99] 2002, Possibly carcinogenic to humans[100] 1994, Possibly carcinogenic to humans[101]

NTP = U.S. National Toxicology Program, an interagency program of which the FDA is part. NCI = U.S. National Cancer Institute.
IARC = International Agency for Research on Cancer, part of the World Health Organization

Even after we submitted our petition, the FDA delayed in responding for years. The FDA filed our petition in early 2016. By law, the FDA has 180 days (6 months) to respond to petitions of this sort, but more than two years elapsed with no response.[7] Eventually, we filed a lawsuit to compel the FDA to respond.[102] Only then did the agency uphold its obligation to ban the seven carcinogenic substances.

If the FDA had been proactively monitoring the scientific evidence sufficiently while fulfilling its legal obligations, why had the agency not banned benzophenone, ethyl acrylate, methyleugenol, myrcene, pulegone, pyridine, and styrene immediately upon publication of the positive cancer studies by NTP or the classifications by NTP in the Report on Carcinogens, especially since the FDA is part of NTP? Why did the FDA ignore the IARC classifications for each of these substances? Why was a petition required to spur the agency to take action? And why did it take the FDA two years and a lawsuit to respond to our petition?

The lack of proactive action by the FDA has continued. IARC classified another flavor chemical, isoeugenol, as "possibly carcinogenic to humans" in 2023[93] based on 2010 NTP testing results (Table 2).[45] Yet isoeugenol is still authorized for use in food as artificial flavor. Why has the FDA not acted to ban isoeugenol?

[xvi] NTP testing results are reported by species and sex. These agents were each tested in both sexes of two species (rats and mice). Rather than list the results for each species and sex, we include in this table the highest classification of carcinogenic activity seen in any species and sex.
[xvii] Ethyl acrylate was listed as "reasonably anticipated to be a human carcinogen" in 1998 in NTP's Report on Carcinogens, but it was delisted following a nomination by industry because human exposure was not anticipated to be high, newer studies were negative, and the possibility that tumors previously observed were not due to ethyl acrylate specifically.
[xviii] This study was conducted by the U.S. National Cancer Institute, not NTP.

Contrary to its claims otherwise, it is clear that the FDA is not proactively ensuring the flavoring chemicals in our foods are safe.

It seems that in the past, the FDA may have done a better job of monitoring flavor safety and revoking approvals for unsafe flavors without being petitioned. Decades ago, the agency took proactive steps to ban four flavors shown to cause cancer or other serious harm:

- **Coumarin,** a chemical with a vanilla-seed-like scent,[3] and coumarin-containing tonka bean and tonka bean extract were banned from use in food in 1954 after industry told the agency these chemicals caused adverse effects.[103,104]
- **Safrole,** a flavorful component of sassafras, as well as sassafras oil, sassafras bark and the related chemicals isosafrole and dihydrosafrole were banned in 1960 based on evidence of carcinogenicity.[105,106]
- **Calamus** and its derivatives were banned in 1968 after it was shown to cause cancer in animals.[107,108] The specific chemical in calamus that is hazardous is isoasarone.[3]
- **Cinnamyl anthranilate,** a chemical that does not occur in nature, was banned in 1985 after the FDA reviewed a study from NCI showing it caused cancer.[109,110]

The most recent of these actions was in 1985. It is unclear why, after 1985, FDA stopped taking proactive steps to remove harmful flavors from the market.

Tonka Beans

Banned for Industry, Available to Consumers Online

The Atlantic reported in 2010 that some restaurants in the U.S. still use tonka beans illegally, and that they could be purchased on the internet.[111] Even today, tonka beans and tonka bean extract are readily available for purchase from online retailers like Amazon[xix] (Figure 4) and Walmart[xx] (Figure 5). It is not explicitly illegal to sell tonka beans or their extractives; it is only illegal to sell foods containing tonka beans because tonka beans contain coumarin. Nonetheless, it is concerning that consumers and restauranteurs have such easy access to a flavor substance that the FDA deemed unsafe almost 70 years ago.

The FDA sometimes falls behind even the food industry in addressing unsafe chemicals. FEMA revoked its GRAS status for styrene in 2015, three years before the FDA formally banned it. The FDA's Substances Added to Food database currently lists the following flavoring agents or adjuvants as "no longer FEMA GRAS," meaning FEMA no longer considers these flavor chemicals as GRAS:[40]

- Acetamide
- Methyleugenol (Eugenyl Methyl Ether)[xxi]
- Musk ambrette
- O-vinylanisole
- Quinoline
- Styrene

[xix] https://www.amazon.com/Motherland-Goods-Whole-Tonka-Beans/dp/B0F9B2445C/

[xx] https://www.walmart.com/ip/Tonka-Dipteryx-Odorata-Dry-Beans-Liquid-Extract-Expertly-Extracted-Trusted-HawaiiPharm-Brand-Absolutely-Natural-Proudly-made-USA-Tincture-32-Fl-Oz/1272419249

[xxi] Methyleugenol and styrene are not listed in the FDA's database as flavor agents or adjuvants, but they were used in this manner prior to the 2018 ban.

But among these chemicals, only methyleugenol and styrene have been expressly banned by the FDA, meaning FEMA is ahead of the FDA. It is worth noting that there is nothing to stop another company not affiliated with FEMA from declaring the other substances as GRAS and using them in food, so they may still be in use.

Figure 4. Image of tonka beans for sale on Amazon.com.

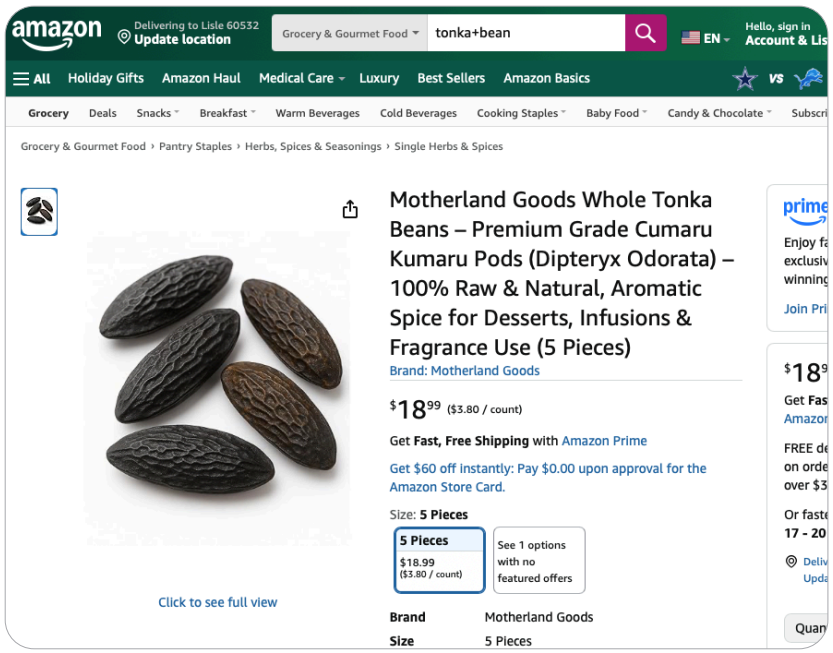
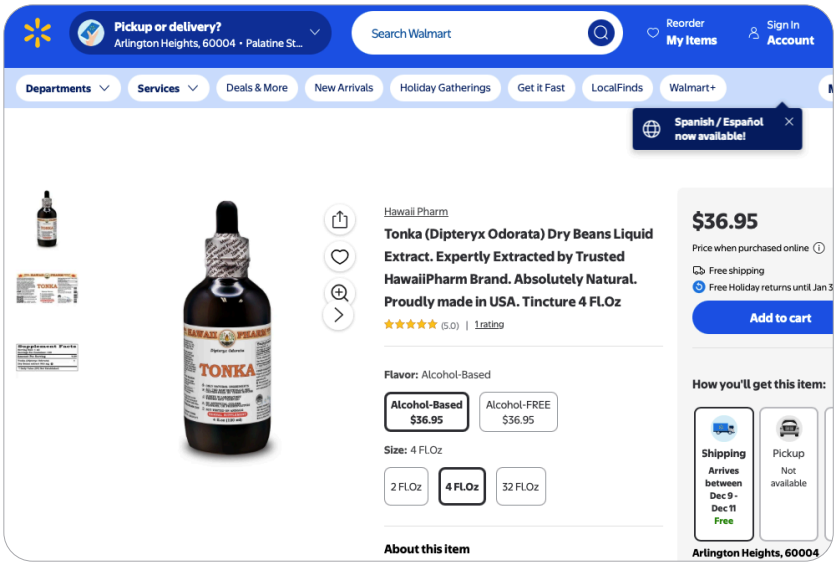


Figure 5. Image of tonka extract for sale on Walmart.com.



A. Natural Flavors are Not Inherently Safer than Artificial Flavors

In addition to its lackluster efforts of late to proactively monitor the safety of flavors, the FDA has also taken a lax approach to regulating harmful flavor chemicals when they occur naturally in flavors and spices (as opposed to being produced in a lab). The seven flavor substances banned in 2018 in response to CSPI's petition are a great example of this.

The FDA only banned *synthetic* benzophenone, ethyl acrylate, methyleugenol, myrcene, pulegone, pyridine, and styrene,[xxii] but they also occur naturally in fruits, vegetables, spices, and herbs, and some of these substances are, in part, responsible for the characteristic flavors and aromas of those plants. Similarly, the FDA only banned the use of some of the natural sources of coumarin and safrole. In addition to tonka beans, which are banned, coumarin occurs naturally in cinnamon, peppermint, green tea, and lavender.[3] Aside from sassafras oil and bark, which are banned, safrole also occurs in nutmeg, pepper, cinnamon, camphor, cocoa, coriander, mace, banana, and dill.[3] What this means is that the banned substances are still in our foods and beverages because they occur naturally in spices, natural flavors, and other food ingredients.

Herbs, spices, fruits, vegetables, and certain natural flavors—not artificial flavors—are the major sources of our dietary exposure to some of these chemicals, and this was the case even before the ban. According to analyses conducted prior to the 2018 ban, in the U.S., ingestion of methyleugenol from plants (which should include spices) and plant oils (a kind of natural flavor) was one hundred times higher than ingestion from "flavoring agents" (which we interpret as synthetic methyleugenol).[87,xxiii]

Importantly, the mere presence of these substances in our food through spices or natural flavor does not mean they pose a major risk to consumers and does not mean that consumers need to adjust their eating habits. Making such adjustments could theoretically be beneficial, but the benefits would likely be small, at least according to the FDA's risk assessments.

The FDA acknowledged that the seven substances banned in 2018 occur naturally in certain foods and, thus, natural flavor, but determined that the amount U.S. consumers are exposed to through food—taking into account all sources (artificial flavor, natural flavor, and spices)— posed a very low cancer risk.[79,xxiv] As a result, the FDA stated it banned the synthetic forms of these substances because it was obligated to do so by federal law, and chose not to take action on the natural flavor and spices.[79]

There is compelling evidence that two of these substances are genotoxic, meaning they damage DNA. This is important because, as stated by the FDA, "In cancer risk assessments, the traditional assumption for chemicals that are genotoxic is that there is no threshold exposure level below which there is no risk of cancer and that there is a risk of cancer at any level of exposure."[79] Thus, any reduction in exposure to such chemicals would be beneficial (but the benefit may not be large). The evidence of genotoxicity is particularly strong for methyleugenol[79,93] and styrene.[99] The FDA regarded methyleugenol as potentially genotoxic in its risk assessment. Since the FDA did not assess the risk of cancer from styrene, it did not specify whether it regarded styrene as a genotoxic carcinogen. But we suspect the agency would have classified it as such, considering IARC reported that there is strong evidence that styrene is genotoxic. What is notable, then, is how the FDA's opinion and approach differs from that of European regulators in this case. Whereas the FDA dismissed the risk from methyleugenol as minimal and declined to regulate naturally occurring methyleugenol, the E.U. acknowledged that no safe dose could be set for methyleugenol and recommended that steps should be taken to reduce exposure.[112] As described in the next section, the E.U. has taken such steps, in part by setting maximum levels on methyleugenol and some other naturally occurring hazardous chemicals present in natural flavors. We consider the E.U. approach more protective.

Regardless of the regulatory approach used, the most important point to take from all of this is that natural flavors and spices are not inherently safer than artificial flavors. The same chemicals can and do occur in both types of flavor substances and spices. In fact, natural flavor and spices can be the predominant source of dietary exposure compared to artificial flavor.

[xxii] FDA said, "Each of these synthetic substances has a natural counterpart in food or in natural substances used to flavor foods. The FDA's revocation of the listings providing for the use of these synthetic flavor substances and adjuvants does not affect the legal status of foods containing their natural counterparts or of flavoring substances extracted from such food, often labeled as 'natural flavors'."

[xxiii] In the U.S., ingestion of methyleugenol from plants and oils was 80.5 micrograms per day, while ingestion from synthetic methyleugenol was 0.8 micrograms per day, leading to a total dietary exposure of 81.3 micrograms per day in the U.S. according to IARC's exposure assessment based on studies conducted in 2007-2010.

[xxiv] The FDA did not assess the risk of cancer associated with styrene because the agency determined that styrene was no longer in use as a flavor.

B. Banned & Restricted Flavors: Europe vs. the U.S.

Unlike the U.S., the E.U. has no GRAS loophole or secret GRAS. All food additives and most flavors must be formally approved before being added to food in the E.U.[113,114] In the E.U., the term "flavouring substances" refers to flavors that are specific, defined chemicals, like vanillin, while the term "flavouring preparations" refers to substances derived from vegetable, animal or microbial origin, like vanilla extract, which are not specific chemicals but rather mixtures of many chemicals.[51] "Flavouring preparations" do not need to be approved so long as they are produced from food, but "flavouring preparations" not derived from foods, as well as "flavouring substances," must be evaluated and approved. This means that vanillin had to be approved, but vanilla extract did not need to be approved before use in the E.U. The E.U. maintains a publicly available database of approved "flavouring substances," although it does not include "flavouring preparations" or smoke flavors.[114] It would be impossible for the FDA to produce a similar list for the U.S.; due to the secret GRAS pathway of the GRAS loophole (see Figure 3), the FDA does not know definitively and exhaustively what substances are used in our foods. We reviewed E.U. flavor regulations to identify more examples of flavor substances and preparations that may be present in foods in the U.S. and pose health concerns. Beyond reviewing specific chemicals, we also conducted a broader comparison of the FDA's and the E.U.'s regulatory approach to flavors to better understand which jurisdiction provides greater protection to consumers overall. We found that while both the U.S. and E.U. regulations could be improved in various ways, the E.U.'s approach offers greater protection to consumers (Table 3).

Table 3. Comparison of flavor safety and disclosure regulations in the United States versus the European Union.

Flavor-Related Regulation	European Union	United States	Relevant Report Sections
Industry may self-certify the safety of flavors	No *(though flavors produced from foods do not need to be assessed before use)*	Yes	Chapter 1, Section B.i. and Chapter 2, Section B
Source materials for natural flavors must be disclosed	Yes *(unless the source would not be recognized in the flavor of the food)*	Sometimes *(USDA-regulated products only and, in such products, only flavors derived from animals)*	Chapter 1, Section B.ii.
Employs a systematic regulatory approach to limit exposure to naturally occurring harmful flavor chemicals	Yes	No	Chapter 2, Section B.vi.
Use of smoke flavor must be disclosed	Yes	Sometimes *(USDA-regulated products only)*	Chapter 1, Section B.ii.
Composition of smoke flavor is regulated	Yes	No	Chapter 2, Section B.vii.

i. Flavors Explicitly Banned in the E.U., but not the U.S.

European regulations explicitly prohibit the use of several substances. These include four flavors also banned in the U.S. (methyleugenol, coumarin, safrole, and pulegone[51]) as well as several others that are seemingly still permitted for use in the U.S. These are:[xxv,xxvi]

- **Aloin,** a substance found in aloe vera, among other plants, belongs to a class of chemicals that increase the risk of cancer.[115] Aloe is FDA-approved for use in natural flavors in the U.S.[63]
- **Capsaicin** is responsible for the spiciness in hot peppers.[116] The European Commission's Scientific Committee on Food (SCF) could not establish a safe level of exposure for capsaicin based on evidence that it might cause cancer in humans and animals.[117] Therefore, while peppers are allowed in Europe, pure capsaicin cannot be added to foods. In the U.S., capsaicin is not an FDA-approved flavor,[118] but it is considered GRAS by FEMA.[40,118,119]
- **Estragole** occurs naturally in tarragon, chervil, and pine.[3] In 2001, SCF concluded that estragole is carcinogenic and genotoxic, so the committee could not establish a safe level of exposure.[120] In the U.S., estragole is FDA-approved for use in foods.[64]
- **Hydrocyanic acid,** also called hydrogen cyanide or prussic acid, can cause poisoning at doses that can be found in derivatives of stone fruits (such as cherries and peaches) and almonds used for flavor.[121] Hydrogen cyanide is acutely toxic at levels humans are not likely to experience from food, typically, but human fatalities have occurred following consumption of stone fruit kernels.[121] Chronic exposure to hydrocyanic acid may be associated with other adverse effects.[121] Due to lack of adequate data, the European Food Safety Authority (EFSA) was not able to establish a safe dose for hydrogen cyanide when it reviewed the chemical in 2004. The FDA limits the content of hydrocyanic acid in cherry pits, cherry laurel leaves, elder tree leaves, and peach leaves to 25 parts per million when used in natural flavor[63] and requires bitter almond extractives to be free from hydrocyanic acid in order to be GRAS.[67] But hydrocyanic acid is not banned per se (although this seems to signal that the FDA would not condone the direct use of hydrocyanic acid as a flavor substance). The FDA considers both apricot and peach kernel to be GRAS.[68] Conversely, the E.U. does not directly limit the amount of hydrocyanic acid allowed in stone fruit-derived natural flavors.
- **Hypericine,** or hypericin, is found in St. John's wort.[3] SCF noted a lack of data on the safety of hypericine when it reviewed the substance in 2002.[122] The FDA does not expressly prohibit use of hypericine in flavor, but it does specify that St. John's wort can be used as a flavor only for alcoholic beverages, and that it must be free of hypericine.[63]
- **Isoasarone**[xxvii] is the substance responsible for the toxicity of calamus that, as discussed above, the FDA banned in 1968. SCF could not establish a safe exposure limit due to evidence that isoasarone is carcinogenic and potentially genotoxic.[123] Use of a certain kind of calamus is also banned in the E.U.[51,xxviii] While calamus and its derivatives are banned in the U.S., isoasarone is not explicitly banned.

[xxv] CSPI is not an expert in the regulatory history of these or other flavors in the E.U. Thus, we cannot attest to the specific rationale used to ban these substances, although it is reasonable to suspect that the health effects detailed here are possible reasons for the bans.

[xxvi] This regulation also included a ban on agaricic acid, which is a mycotoxin, a toxic substance produced by a species of fungus, and is described as "tasteless" (https://drugs.ncats.io/drug/2XE342S7L6). Given that description, it is unclear whether this substance or this fungus are used in the U.S. as flavors, but it seems unlikely. Therefore, we excluded it from this list.

[xxvii] Isoasarone is another name for β-asarone according to Burdock 2010.

[xxviii] Particularly, Annex IV, Part A of the E.U. flavor regulation prohibits the use of the tetraploid form of calamus.

- **Menthofuran** is related to pulegone (one of the flavors banned by the FDA in 2018). Pulegone can be converted in the body to menthofuran, which might be responsible for some of pulegone's toxic effects.[96,124] When EFSA reviewed the safety of pulegone and menthofuran together in 2008 it declined to establish an acceptable daily intake in large part because these two chemicals had not been adequately tested for safety. In the testing that had been done, there was evidence they may harm the liver.[124] Since then, NTP completed its rodent testing of pulegone and found clear evidence of carcinogenicity (Table 2). In the U.S., menthofuran is not an FDA-approved lavor[125] but it is allowed in food because it has been deemed GRAS by FEMA.[40]
- **Quassin** is a bitter compound that occurs in the natural flavor substance quassia.[63,126] In its 2002 evaluation, the SCF raised concerns about reproductive effects and inadequate testing of quassin, noting that exposure in humans from alcoholic beverages could be similar to the doses at which negative effects were observed in animals. In the U.S., quassia is FDA-approved as an additive.[63]
- **Teucrin A** is a compound found in germander that can cause liver toxicity at levels near to which the SCF determined the European population could be exposed through alcoholic beverage consumption.[127] Germander is approved by the FDA for use as a flavoring in alcohol in the U.S.[63]
- **Thujone,** is a potentially carcinogenic substance that also causes neurotoxicity and, according to FEMA, is believed to be the cause of adverse neurological effects historically associated with absinthe consumption.[128-130] A 2021 FEMA review states that the direct addition of thujone to food is prohibited in the U.S., but thujone does not appear in the list of banned additives in U.S. regulations[129,131] or in FDA's Substances Added to Food database. Thus, it is unclear whether this is truly the case.[xxix] Regardless, federal regulations do specify that foods formulated with natural flavors derived from certain plants—wormwood, cedar, oak moss, tansy, and yarrow—must be thujone-free.[63] Sage also contains thujone,[3,129] but U.S. regulations do not set limits on thujone content of sage, sage derivatives, or foods containing sage or its derivatives.

ii. Flavors Removed from the E.U. List of Approved Flavors, but Allowed in the U.S. via the GRAS Loophole

Absence or removal from the E.U. list of approved "flavouring substances" is sufficient to prohibit the use of a flavor chemical in the E.U. Several substances deemed GRAS by FEMA in the U.S. have been removed from the E.U. list due to safety concerns raised by EFSA. These substances are listed in Table 4.

[xxix] CSPI reached out to FDA in October 2023 to clarify the regulatory status of thujone. We have not received a response.

Table 4. Substances deemed GRAS by FEMA that are prohibited in the E.U. based on removal from the E.U. list of approved "flavouring substances" due to safety concerns raised by EFSA.[xxx]

Substance Name* (CAS #)	Approval Status in U.S.	Year Removed from E.U. List†	Health Concern
perillaldehyde [FDA] ♦ *p*-mentha-1,8-dien-7-al [EFSA] (2111-75-3)	FDA-approved[64] FEMA GRAS (#3557)‡[132]	2015[133]	Genotoxicity in animals[xxxi,134]
2-hydroxymethyl-6,6-dethylbicyclo(3.1.1)hept-2-enyl formate [FDA] myrtenyl formate [EFSA] (72928-52-0)	**NOT** FDA-approved⁑[135] FEMA GRAS (#3405)[136]	2016[137]	Genotoxicity of a related substance in animals[xxxii,134]
2,6,6-trimethyl-1 and 2-cyclohexen-1-carboxaldehyde [FDA][xxxiii] ♦ 2,6,6-trimethyl-1-cyclohexen-1-carboxaldehyde [EFSA] (432-25-7; 432-24-6; 52844-21-0; 977045-71-8)	**NOT** FDA-approved[138] FEMA GRAS (#3639)[139]		
4,5-epoxy-(E)-2-decenal [FDA] ♦ 4,5-epoxydec-2(trans)-enal [EFSA] (188590-62-7; 134454-31-2)	**NOT** FDA-approved[140] FEMA GRAS (#4037)[141]	2017[142]	Genotoxicity in animals[143]
4-hydroxy-2-butenoic acid gamma-lactone [FDA] ♦ furan-2(5H)-one [EFSA] (497-23-4)	**NOT** FDA-approved[144] FEMA GRAS (#4138)[145]	2019[146]	Genotoxicity in animals and in studies conducted with human cells[147]
delta-damascone (57378-68-4)	**NOT** FDA-approved[148] FEMA GRAS (#3622)[149]	2020[150]	Genotoxicity[xxxiv,151]
alpha-damascone** ♦ (43052-87-5)	**NOT** FDA-approved[152] FEMA GRAS (#3659)[153]		
cis-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)but-2-en-1-one [EFSA] ** (23726-94-5)	FEMA GRAS (#3659)[153]		
trans-alpha-damascone [FDA] trans-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)but-2-en-1-one [EFSA] (24720-09-0)	**NOT** FDA-approved[154] FEMA GRAS (#4088)[155]		
4-methyl-2-phenyl-2-pentenal [FDA] ♦ 4-methyl-2-phenylpent-2-enal [EU] (26643-91-4)	**NOT** FDA-approved[156] FEMA GRAS (#3200)[157]	2025[158]	Genotoxicity caused by a related substance in human cells[xxxv,159]

* A single substance might be called different names by FDA, EFSA, FEMA, and others. When they differ, we list the names used by FDA and EFSA. We also include CAS numbers to further identify these substances. CAS numbers are unique identifiers for chemical substances that are widely used globally for the purpose of chemical identification.[160] A substance may have multiple CAS numbers; we list each of the CAS numbers used by FDA, the EU, and FEMA for each substance. FEMA numbers are also useful identifiers. See footnote below for additional information about FEMA numbers.

† Each of these substances still have entries in the EU Flavourings Database (https://ec.europa.eu/food/food-feed-portal/screen/food-flavourings/search). This does not mean that they are legal to use. Each of the respective entries in that database for these substances (except 4-methyl-2-phenylpent-2-enal) states that these are not permitted in foods in the E.U. The entry for 4-methyl-2-phenylpent-2-enal has evidently not yet been updated to reflect the decision to remove it from the list.

♦ This symbol denotes substances that are known to occur naturally in foods. These substances can therefore be listed on food ingredient labels as "natural flavors" if they are derived from natural sources. These include perillaldehyde, 2,6,6-trimethyl-1 and 2-cyclohexen-1-carboxaldehyde (natural only), 4,5-epoxy-(E)-2-decenal , 4-hydroxy-2-butenoic acid gamma-lactone, alpha-damascone, trans-alpha-damascone, and 4-methyl-2-phenylpent-2-enal.[3,161] These are, or may, also be produced synthetically, meaning they could also be hidden in ingredient lists as "artificial flavor." Whereas myrtenyl formate and delta-damascone are not reported to occur naturally in foods,[3] suggesting they are exclusively artificial flavors.

⁑ As noted in Chapter 1, the FDA maintains a Substances Added to Food Database, which includes substances deemed GRAS by FEMA.[40] Listing in this database is not an indication that a substance is approved by the FDA; it merely indicates that the FDA is aware that the substance is used in foods. Substances formally approved by the FDA are listed in FDA regulations as well as this database. Each of the substances in this table is listed in the FDA database, but only one (perillaldehyde) has been formally approved as a food additive by FDA. Because FDA approval is not required for flavors in the U.S. due to the GRAS loophole, the substances listed as "Not FDA-approved" are allowed in food in the U.S.

‡ FEMA assigns unique numbers to flavors its panel has deemed GRAS. Those numbers are listed here for reference. FEMA also maintains a flavor library, which is a database of substances it has deemed GRAS. References included in this table refer to specific entries in that library.

** FEMA considers alpha-damascone and cis-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)but-2-en-1-one to be synonymous, as indicated by the fact that it lists the CAS numbers for both to a single entry in its flavor library (meaning only one FEMA number is assigned), but the E.U. regulates them as distinct chemicals. We have included each as a separate entry in this table because the E.U. considers them distinct.

Ruling out genotoxicity is the first step in EFSA's procedure for assessing flavor safety. If genotoxicity cannot be ruled out then the substance cannot be considered safe in the E.U.[162,163] Since this is the first step in the evaluation and because it is a very protective (strict) standard, it is not surprising that each of the substances listed in Table 4 were withdrawn from the E.U. list of approved flavors due to concerns about genotoxicity.

Overall, these substances help illustrate that the GRAS system in the U.S. is broken because it allows the food industry to introduce and continue using unsafe flavor chemicals years after they have been demonstrated to be unsafe.

iii. 2,4-Hexadienal: A Restricted Flavor in the E.U., Allowed in the U.S. via GRAS Loophole

The flavor chemical 2,4-hexadienal (also called hexa-2(trans),4(trans)-dienal, among other synonyms) is restricted, but not banned, in the E.U. over safety concerns. It was classified by IARC as possibly carcinogenic to humans in 2012 based on what IARC determined was "sufficient evidence" of carcinogenicity in animal studies completed by NTP in 2003 (under NTP's evidence classification system, NTP concluded that there was "clear evidence of carcinogenic activity" in male and female rats and mice).[87,164] IARC specifically noted that there is moderate evidence that tumors observed in the NTP animal studies were caused through a genotoxic mechanism and that the mechanistic evidence provides "some additional support" for the relevance of the animal results to humans. EFSA first raised concerns about the safety of 2,4-hexadienal in 2008 due to evidence of carcinogenicity and genotoxicity.[165] After this first evaluation, industry submitted additional information at the request of EFSA, and EFSA published an updated safety evaluation in 2014 that confirmed the safety concern. Industry submitted additional studies to EFSA in 2016 in response to EFSA's concerns. This led the E.U. to limit the uses of 2,4-hexadienal in 2017, pending further evaluation by EFSA.[166] That evaluation was published in 2018, and EFSA concluded that the new results did in fact rule out concerns for genotoxicity, allowing it to be further evaluated for safety by the EFSA panel.[167] However, this does not necessarily mean that 2,4-hexadienal will be deemed safe by EFSA (as noted above, ruling out genotoxicity is only the first step in the safety evaluation process), and it remains to be seen if and how IARC will interpret the new genotoxicity data.

Regardless, the U.S. Congress and courts preclude the FDA from deeming a food additive safe if it causes cancer in animals. Notably, 2,4-hexadienal is not an FDA-approved food additive,[168] but instead it is a FEMA GRAS substance.[169] As with isoeugenol, FEMA has deemed 2,4-hexadienal GRAS despite the fact that it caused cancer in animal studies conducted by NTP. In effect, this further shows that FEMA abuses the GRAS loophole to market chemicals that would likely be illegal if assessed through the food additive premarket approval process as intended by Congress.

Like several of the flavors included in Table 4, 2,4-hexadienal occurs naturally in some foods and is also produced synthetically,[3] so it can be hidden in ingredient lists as "natural flavor" or "artificial flavor" depending on whether it was naturally derived or manufactured.

[xxx] Other chemicals were also withdrawn from the E.U. list after EFSA raised safety concerns, but we do not include them here because they are not listed in the FEMA Flavor Library or FDA Substances Added to Food database, meaning it is not clear whether or not they are used in the U.S. These substances include alpha-damascenone (Commission Regulation (EU) 2020/1681); myrtenyl-2-methylbutyrate and myrtenyl-3-methylbutyrate (Commission Regulation (EU) 2016/637); benzene-1,2-diol (Commission Regulation (EU) 2024/2856; and 3-acetyl-2,5-dimethylthiophene (Commission Regulation (EU) 545/2013). Additional chemicals were withdrawn from the E.U. list because EFSA requested additional safety information and either industry failed to supply the requested data by the specified deadline or indicated they had abandoned them (i.e., stopped using them in food in the E.U.) (Commission Regulation (EU) 2024/234). We do not list these substances in this report for brevity.

[xxxi] EFSA evaluated this flavor group again in 2017 and 2019. It did not reverse the conclusion on perillaldehyde in either instance.

[xxxii] EFSA often groups chemically similar flavors together and evaluates them as a group. In this case, EFSA determined that these chemicals belong to the same group as p-mentha-1,8-dien-7-al, which is representative of the whole group. As such, EFSA concluded there is a potential safety concern for these chemicals. EFSA evaluated this flavor group again in 2017 and 2019. It did not reverse the conclusion on myrtenyl formate or 2,6,6-trimethyl-1-cyclohexen-1-carboxyaldehyde in either instance.

[xxxiii] EFSA regulates 2,6,6-trimethyl-1-cyclohexen-1-carboxaldehyde (CAS 432-25-7) and 2,6,6-Trimethylcyclohex-2-ene-1-carboxaldehyde (CAS 432-24-6) separately (where the latter is approved, but the former is not), the FDA and FEMA group them together, as indicated by the fact that the FEMA library lists both CAS numbers but provides a single FEMA number.

[xxxiv] The chemical structures for these chemicals indicate possible genotoxicity. EFSA requested additional data from industry, which provided equivocal evidence of genotoxicity in animals, which ultimately led EFSA to conclude that it could not rule out genotoxicity.

[xxxv] EFSA requested additional information from food companies, which indicated that 4-methyl-2-phenylpent-2-enal was no longer in use, presumably in the E.U., which led to its removal from the E.U. list of approved flavors

iv. Flavors Banned in the U.S. but not the E.U.

Benzophenone, ethyl acrylate, and myrcene were among the seven carcinogenic flavors banned by the FDA in 2018, but they remain legal in the E.U. Additionally, tonka bean and sassafras bark, discussed earlier in this chapter, are prohibited from addition to food in the U.S., but are seemingly not banned or restricted in the E.U.

v. Flavors Banned in both the U.S. and the E.U.

Of the seven carcinogenic substances the FDA banned in 2018, only two—methyleugenol and pulegone—are explicitly banned in the E.U. Two others—styrene and pyridine—are absent from the E.U. list of approved flavors, which means they are implicitly banned because premarket approval is required in the E.U. Similarly, isosafrole and dihydrosafrole, which were banned in the U.S. alongside safrole in 1960, are also absent from the E.U. list, meaning they are implicitly banned there.

vi. Regulation of Naturally Occurring Toxic Flavors in the E.U. Compared to the U.S.

As discussed in Chapter 2, Section A, some of the flavors that are banned or restricted in the U.S. or E.U. occur naturally in foods. When a specific substance is banned from foods in either the U.S. or the E.U., typically it is just the individual chemical that is banned; the bans do not extend to include all natural flavors that naturally contain the substance. So, for example, the FDA only banned synthetic methyleugenol from foods in 2018; it did not ban basil extract, which will naturally contain methyleugenol. The E.U. also has not banned basil extract or other natural flavor preparations that inherently contain methyleugenol, so in that way, the U.S. and E.U. regulations are the same. However, the E.U. has limited the amount of methyleugenol (and the other explicitly banned chemicals) allowed in food resulting from its inherent occurrence in natural flavors, while there are no such limits in the U.S. In doing so, the E.U. took into account "both the need to protect human health and their unavoidable presence in traditional foods."[51] In contrast, FDA regulations implicitly acknowledge the fact that some natural flavor substances are toxic (by virtue of banning some of them, like tonka bean extract), but only sometimes imposes limits on specific toxic chemicals occurring in natural flavors, such as thujone and hydrocyanic acid. Thus, it does not seem that the FDA has sought to address this issue systematically like the E.U. has. The E.U.'s more systematized approach is superior to the FDA's more diffuse approach. It would seemingly be beneficial for the FDA to undertake an effort to identify undesirable substances, their sources, and the main contributors to dietary exposure, and then establish maximum levels in a manner similar to the E.U.

Notably, neither E.U. nor U.S. regulations limit the content of any of these naturally occurring toxic flavor substances if they are present in foods due to the use of herbs and spices. This is despite evidence that, at least in the case of methyleugenol, herbs and spices might be the predominant sources of exposure.

vii. Smoke Flavor Safety in the E.U. Compared to the U.S.

As noted in Chapter 1, E.U. regulations require the specific disclosure of smoke flavor on food ingredient labels, similar to USDA-regulated products (but not FDA-regulated products).[51] This is framed as a means of ensuring that consumers are not misled into thinking a food has been smoked. The E.U. also regulates the method of manufacture and composition of smoke flavor and thermal process flavors (meaning, those produced by heating certain ingredients), specifically limiting the content of 4,8-DiMeIQx, PhIP, benzo[a]pyrene, and benz[a]anthracene,[51,170] whereas no such specifications exist in U.S. regulations to our knowledge. PhIP, benzo[a]pyrene, and benz[a]anthracene are substances produced by the cooking of meat or combustion—like burning meat or wood—that are listed as "reasonably anticipated to be a human carcinogen" in NTP's Report on Carcinogens.[171, 172] While 4,8-DiMeIQx belongs to the same chemical class as PhIP, it is not included in the Report on Carcinogens.

European consumers seem to enjoy better protection from harmful flavorings than U.S. consumers. The FDA must do more to close the gap (Chapter 4).

Chapter 3. Vague Disclosure Puts Allergic Consumers at Risk & Undercuts Consumer Choice

Consumers may need or want to avoid certain ingredients due to allergies or religious or ethical reasons. Vague flavor and spice disclosure may preclude consumers from accessing the information they need to identify foods containing such ingredients. In this chapter, we identify some flavors and spices that may raise such concerns.

A. Allergenic Flavors and Spices

Allergic reactions occur when a person's immune system responds to a certain substance resulting in effects on the respiratory system (like anaphylaxis), skin (like hives), or the gastrointestinal system (like vomiting).[173] These reactions can be life-threatening. To help consumers identify and avoid foods to which they are allergic, federal law currently requires nine specific allergens to be identified on food labels if present. These so-called nine major allergens are: milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, soybeans, and sesame.[173] But there are many other foods that are known to cause allergic reactions less frequently, including many that can be used as flavors or spices.

The U.S. Food and Drug Administration (FDA) asserts that more than 160 foods have been identified to cause food allergies,[174] based on a 1996 review of the evidence by Hefle et al.[175] The nine major allergens were defined as such due to the high prevalence of people allergic to them. Sesame was added to the list of major allergens in 2021, while the other eight have required labeling since 2004. In 2004, the original eight allergens accounted for 90 percent of food allergies and serious allergic reactions in the U.S. Comparatively, prevalence of allergy to other foods is low. Nonetheless, low prevalence does not mean reactions are any less severe. The 59 foods listed in Table 5 are the less common allergenic foods that were identified by Hefle et al. as having been associated with anaphylaxis, asthma, and/or laryngeal edema, which the authors identified as potentially life-threatening. All the substances in Table 5 can be used as sources of natural flavors, according to the U.S. regulatory definition of "natural flavor." Seven are explicitly listed as spices in FDA regulations. Seven of the foods listed have also been named by the Food Allergy Research and Resource Program (FARRP) at the University of Nebraska as "other priority allergens."[176,xxxvi]

There were many other foods identified in Hefle et al.'s review as being associated with other types of non-life-threatening allergic reactions that are known to be permitted sources of spices and natural flavors. The non-exhaustive list provided in Table 5 is intended to simply highlight the problem—that the FDA allows industry to hide food allergens behind vague terms, putting consumers at risk of potentially life-threatening allergic reactions.

[xxxvi] FARRP also includes sesame among its "other priority allergens," whereas its primary priority allergens, which it calls "the big eight," are the original eight major allergens. Since sesame is now a major allergen and subject to mandatory labeling in the U.S., we excluded it from Table 5.

Table 5. Less common allergens causing life-threatening reactions according to Hefle et al, 1996.[175]

Food	Documented Life-Threatening Allergic Reactions	Permitted as Undisclosed Source of Natural Flavor[xxxvii,46]	Listed as a "Spice" in U.S. Regulations[46,66]	FARRP "Other Priority Allergen"[176]
Abalone	Yes	Yes		Yes
Amaranth	Yes	Yes		
Annatto	Yes	Yes		
Apple	Yes	Yes		
Balsam of Peru	Yes	Yes		
Banana	Yes	Yes		
Barley	Yes	Yes		
Beans	Yes	Yes		
Beef	Yes	Yes		
Buckwheat	Yes	Yes		Yes
Cabbage	Yes	Yes		
Carrot	Yes	Yes		
Celery	Yes	Yes	Yes (seed)	Yes
Chamomile	Yes	Yes	Yes	
Chicken	Yes	Yes		
Chocolate and cocoa	Yes	Yes		
Clams	Yes	Yes		Yes
Coriander	Yes	Yes	Yes	
Cottonseed	Yes	Yes		
Cucumber	Yes	Yes		
Cuttlefish	Yes	Yes		Yes
Fennel	Yes	Yes	Yes	
Grapes	Yes	Yes		
Honey (sunflower)	Yes	Yes		
Hops	Yes	Yes		
Kiwi	Yes	Yes		
Lettuce	Yes	Yes		
Lentils	Yes	Yes		
Limpet	Yes	Yes		Yes
Maize	Yes	Yes		
Mango	Yes	Yes		
Millet seed	Yes	Yes		
Mushrooms	Yes	Yes		
Mustard	Yes	Yes	Yes	Yes
Oats	Yes	Yes		
Orange	Yes	Yes		
Parsley	Yes	Yes	Yes	
Pea	Yes	Yes		

[xxxvii] The substances marked "Yes" implicitly meet the regulatory requirements to be permitted as a source for natural flavor. The regulations do not explicitly list these as approved sources of natural flavor.

Peach	Yes	Yes		
Pineapple	Yes	Yes		
Plum	Yes	Yes		
Poppy seed	Yes	Yes	Yes	
Pork	Yes	Yes		
Potato	Yes	Yes		
Psyllium[177,xxxviii]	Yes	Yes		
Rice	Yes	Yes		
Royal jelly[178,xxxix]	Yes	Yes		
Rye	Yes	Yes		
Soybean oil	Yes	Yes		
Squid	Yes	Yes		Yes
Strawberry	Yes	Yes		
Sunflower seed	Yes	Yes		
Sunflower oil	Yes	Yes		
Swiss chard	Yes	Yes		
Tomato	Yes	Yes		
Tragacanth gum[179,xl]	Yes	Yes		
Watermelon	Yes	Yes		
Wine	Yes	Yes		
Yeast	Yes	Yes		

It is possible that the specific allergenic substances within these foods—typically a protein—would not be present in derivatives used for flavoring foods, but consumers with allergies may wish to avoid any food ingredient derived from the foods to which they are allergic to be absolutely certain they are not ingesting an allergen.

By not requiring labeling for other known food allergens while simultaneously allowing the use of the vague ingredient terms "spices" and "natural flavors," the FDA allows the food industry to hide known allergens from consumers who need that information to protect themselves.

B. Animal-derived Flavors and Ethical Concerns

Consumers may choose to avoid specific or all animal products for religious, ethical, or other reasons, but the FDA's lack of disclosure requirements for natural flavors opens the possibility for animal products to be hidden in an ingredient list. This makes it impossible for consumers to know with certainty that the products they buy are free from the animal-derived substances they want to avoid. To identify some animal-derived flavors currently permitted or condoned by the FDA, we reviewed FDA regulations and Flavor and Extract Manufacturers Association (FEMA) documents. The substances we identified are listed in Table 6. We did not seek to identify all animal-derived flavors that exist; we merely sought to illustrate that such products exist and may be in use.

[xxxviii] Psyllium appears to be used primarily for non-flavoring purposes in foods, but it has been noted as being used for "sensory improvement," per Belorio and Gomez 2020. Further, it is a plant thus, like the other substances in this table, is implicitly permissible as a source for natural flavor. Therefore, it warrants inclusion in this table.

[xxxix] Royal jelly is a bee-derived substance that apparently has a flavor, per Collazo et al. 2021.

[xl] Tragacanth gum has been affirmed as GRAS by FDA when used as an emulsifier, formulation aid, stabilizer, and thickener in food. Whether it is used in flavor is unclear, but because it is a plant-derived substance, it could be used as a source for natural flavor.

To further identify animal-derived flavors on the market, we reviewed the product catalogs of several randomly selected flavor companies. Firmenich offers seafood-derived flavor substances—including from fish, crustacean shellfish, and molluscan shellfish—and substances derived from bee products.[180] Givaudan offers flavors from 11 different species of seafood.[181] Nikken Foods sells 12 different extracts derived from fish or shellfish that meet the FDA and USDA definitions of "natural flavor."[182] On its website marketing these products, Nikken encourages its customers to use these substances to "add clean tasting notes, authentic seafood and umami to your formulations."[182] Jeneil sells cheese-derived flavor substances.[183] It states, "most of [our] flavors can be declared as 'Natural Cheese Flavor' or 'Natural Flavor'."[183]

Presumably, these cheese flavors and any other flavors derived from milk, fish, or crustacean shellfish would need to include the major allergen disclosure, so consumers seeking to avoid animal products would be able to identify foods containing those ingredients. However, since molluscan shellfish (like clams and oysters) and ingredients from other animals are not subject to mandatory allergen labeling, the molluscan shellfish flavors and remaining animal-derived substances we have identified could be hidden behind "natural flavors."

Table 6. Examples of animal-derived flavor substances either listed in FDA regulations[69] or otherwise seemingly in use per industry (FEMA) documentation.

Substance	Description or Method of Manufacture	FEMA Name and Number
Ambergris[xli]	Byproduct of the intestinal tract of sperm whales[3,184]	Ambergris tincture (FEMA #2049)[185]
Beeswax	Produced by bees[3]	Beeswax, White (FEMA 2126)[186]
Butter Acids	Isolated from butter[3]	Butter Acids (FEMA 2171)[187]
Butter Esters	Produced from butter acids[3]	Butter Esters (FEMA 2172)[188]
Castoreum	Glandular secretion from beavers[3]	Castoreum extract (FEMA 2261)[189] Castoreum, liquid (FEMA 2262)[190]
Civet	Glandular secretion from civet cats[3]	Civet absolute (FEMA 2319)[191]
Musk (Tonquin musk)	Glandular secretion from musk deer[3]	Musk Tonquin (FEMA 2759)[192]

Chapter 4. Recommendations to Policymakers & Industry

Federal, state, and local policymakers and industry can—and should—take steps to promote greater safety, transparency, and accountability for flavors and the flavor industry.[xlii]

A. Federal Policymakers

Federal policymakers should:

- **Mandate full disclosure of flavors and spices (via FDA and USDA regulation or Congressional legislation):** Require full disclosure of all ingredients, including spices and flavors, on packaged food and meat/poultry product ingredient labels. We recognize that compound flavors can contain more than one hundred individual ingredients, making full on-pack disclosure logistically challenging. Thus, full disclosure mandates could allow online disclosure, but should favor on-pack disclosure.

[xli] While still legal to use per FDA regulation, it is illegal to possess ambergris according to the U.S. National Oceanic and Atmospheric Administration.
[xlii] Some of our recommendations, if implemented, would render other recommendations obsolete.

- **Close the GRAS loophole (via FDA regulation or Congressional legislation):** Require all flavor substances and other food chemicals to come to market via food additive petitions, as we believe was intended by Congress when the Food Additive Amendment was passed in 1958.
- **End secret GRAS (via FDA regulation or Congressional legislation):** Fully closing the GRAS loophole is the ultimate goal, but making it compulsory to notify the FDA of any GRAS determinations and ensure all data are publicly available prior to marketing new substances would be a major step in the right direction. Such reform would have to account for the thousands of secret GRAS ingredients already on the market.
- **Require companies using the term "natural flavor" to specify source materials (via FDA and USDA regulation):** Rather than allowing the food industry to name flavors in the ingredient list based on the taste the substances are intended to emulate, the FDA should require companies to label natural flavors based on their source material. This change would ensure that consumers can make fully informed decisions.
- **Set maximum levels for toxic substances that occur naturally in spices and natural flavors (via FDA regulation):** The FDA should set maximum levels of use for hazardous chemicals that occur naturally in spices and natural flavors, such as methyleugenol, to offer greater protection to consumers.
- **Improve post-market monitoring of food chemicals (via FDA oversight):** The FDA should implement systems to proactively reevaluate the safety and use of food chemicals. Currently, the FDA has the authority to reassess safety of existing chemicals, but it is not obligated to do so and seemingly only rarely does so on its own.
- **Develop a comprehensive food chemical database (via FDA oversight):** The FDA's current inventories of food chemicals are incomplete because of the secret GRAS pathway within the GRAS loophole. A publicly available database would shed light on the secret GRAS substances currently in use.
- **Align ingredient labeling terminology between FDA- and USDA-regulated foods: (via FDA and USDA regulations):** Currently, FDA and USDA regulations allow for different terms to be used to describe the same substances. While the USDA allows the general term "flavor" as a synonym for natural flavor, no such term is permitted in FDA-regulated products. Additionally, the USDA mandates specific disclosure of added smoke flavor when present, but the FDA does not. These inconsistencies may create confusion among consumers.
- **Provide the FDA with more resources dedicated to food chemical safety (via Congressional legislation):** Increasing funding and resources available to the FDA to review the safety of food chemicals should better enable the agency to fulfill its premarket and post-market oversight responsibilities. If the FDA is empowered to increase the speed at which it responds to food chemical safety issues—including ruling on food additive petitions—perhaps exploiting the GRAS loophole will become a less attractive option to food companies.

B. State and Local Policymakers

Regulation of food chemical safety and labeling has historically been carried out predominantly by the FDA, but due to failures by the FDA to adequately protect consumers, states have begun to take action. For example, in October 2023, California banned the use of four specific food chemicals in foods sold in-state.[193] A similar bill has been introduced in New York.[194] While neither of these bills pertains to flavors, they demonstrate that states have the ability to act on behalf of consumers when it comes to food safety and may increasingly do so. As such, states or localities could:

- **Collect and publish secret information:** If federal policymakers continue to condone the secret GRAS pathway of the GRAS loophole, states could require that food manufacturers disclose to state agencies certain information about the ingredients in any products sold in the

state. State agencies could publish this information. Simply requiring disclosure of ingredient names would pull back the curtain on secret GRAS and eventually lead to the creation of a comprehensive list of all chemicals added to foods, similar to the recommendation for federal policymakers described above. States could go further and require industry to disclose regulatory and safety information (which substances in their products are GRAS, safety information used in making GRAS determinations, information on the individuals involved in making GRAS determinations, etc.). Although some of this information may be publicly available already, at least in the case of FEMA GRAS substances, the existence of secret GRAS and the lack of a comprehensive database leave major gaps in our understanding of the entire food chemical universe and undermines our confidence in the safety of our food supply. Notably, this recommendation would promote transparency not just for flavor, but for all food chemicals.

- **Ban dangerous chemicals.** Like California, states can pass laws banning individual dangerous chemicals from being included in foods sold in the state. This could cause food companies to reformulate if the market in the state is large enough.
- **Mandate disclosure of flavors and spices:** States could require companies to disclose which flavor substances and spices are used in their products.

C. Industry

Industry should voluntarily:

- **Implement full flavor and spice disclosure:** The flavor and food industries should be more transparent, taking cues from some cosmetics companies, by voluntarily disclosing the compositions of flavor blends to consumers. Ideally, this would mean full disclosure on the food ingredient label itself. We recognize that compound flavors, just like fragrances, can contain so many ingredients that full disclosure on the package is not possible. Online disclosure is a reasonable first step. We also recognize that food companies that purchase compound flavor blends from flavor companies, rather than formulate flavors themselves, may be legally precluded from disclosing the ingredients by name because it is proprietary information owned by the flavor company. But this is no different than the situation the cosmetics industry finds itself in with proprietary fragrance blends. The food industry can work within its supply chain to overcome these challenges just like some cosmetics companies have.
- **Stop exploiting the GRAS loophole:** The flavor and food industries should seek formal FDA approval for all new food chemicals in keeping with the legislative intent of the 1958 Food Additive Amendment. Industry likely uses the GRAS loophole because it is easier and faster to self-declare something GRAS than go through the formal FDA approval process (see federal policymaker recommendation above regarding FDA resources to address this issue). Industry should apply to the FDA for approval of new food chemicals, rather than self-affirm them as GRAS. Thoroughly vetting the safety of the chemicals in our foods is not something that should ever be rushed nor solely carried out by those who stand to make money from the chemicals.
- **Stop using secret GRAS:** At a bare minimum, when introducing new chemicals via the GRAS loophole, industry should commit to providing notice to the FDA and refrain from using these chemicals until the FDA issues its "no questions" conclusion. We are pleased that the Flavor and Extract Manufacturers Association (FEMA) says it is committed to alerting the FDA of its GRAS notices, but by our own experiences a decade ago, the extent to which FEMA and individual companies in the flavor and food industries make their own GRAS determinations is unclear. Neither the FDA nor the public should be left wondering what is in our foods.
- **Publish GRAS information:** All information pertaining to GRAS determinations or food additive petitions, including the underlying data and the names, affiliations, and conflicts of interest for participants in GRAS panels, should be published online in a publicly accessible format. This will allow third parties to independently audit the safety of GRAS substances and the processes followed in making those determinations.

Acknowledgements

We want to thank the Smith Edmonds Family Foundation and the John Sperling Foundation for their generous donations to CSPI that made this work possible. We are tremendously appreciative of the thoughtful feedback provided by our CSPI colleagues, Peter Lurie, Jannah Tauheed, Stephanie Rogus, Alla Hill, Nancy Fink, Eva Greenthal, Irene Ulrich, Adrienne Crezo, Zack Goldstein, and Jorge Bach, as well as our partners Thomas Gremillion (Consumer Federation of America), Lisa Lefferts, Tom Neltner (Environmental Defense Fund), and Maricel Maffini.

Appendices

A. CSPI 2013 CORRESPONDENCE WITH FDA REGARDING FEMA GRAS



January 31, 2013

Dr. Dennis Keefe
Director, Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
CPK-2 Bldg. Room 3044
4300 River Road
College Park, MD 20740

Dear Dr. Keefe:

We are writing to share both our experience and the experience of another scientist with the Flavor and Extract Manufacturers Association's (FEMA) GRAS (generally recognized as safe) program that we believe illustrate an important failure of the current GRAS system. We urge the Food and Drug Administration (FDA) to consider ways to increase the rigor, availability, transparency, and acceptance of GRAS reviews.

FDA has essentially delegated GRAS-review authority for flavors, flavor enhancers, and related substances to FEMA. The FEMA GRAS program exists only with the oversight and participation of the FDA, as noted by FEMA.[1]

FDA has noted that the Federal Food, Drug, and Cosmetic Act has several criteria that must be met before the intended use of a substance in food can be considered GRAS: that its safety be established scientifically (or by common use prior to 1958), and that the basis for concluding it is safe must be *generally accepted, publicly available, and transparent to experts* (emphasis added).[2] FDA has further stated that a GRAS substance is distinguished from a food additive on the basis of the "common knowledge" about the safety of the

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[1] Page 269 in Hallagan, John B. and Richard L. Hall. "Under the conditions of intended use – New developments in the FEMA GRAS program and the safety assessment of flavor ingredients." Food and Chemical Toxicology 47: 267-278, 2009. Also personal communication with John B. Hallagan, November 30, 2012. The qualifications and objectivity of FEMA's expert panels is a separate matter.

[2] General Comments of the Department of Health and Human Services (HHS) on the Government Accountability Office's (GAO) Draft Report Entitled, "Food Safety: FDA Should Strengthen Its Oversight of Food Ingredients Determined to be Generally Recognized As Safe (GRAS)" (GAO-10-246), included in Appendix IV of GAO-10-246, February 2010.

1220 L Street, NW, Suite 300 • Washington DC 20005-4053 • tel 202 332-9110 • fax 202 265 4954 • www.cspinet.org

substance for its intended use, and the "widespread awareness of the data and information about the substance."[3]

However, our experience shows that those criteria are not being met. The criterion of public availability is particularly important when dealing with novel substances such as sweetness-enhancing compounds, since without it, safety cannot be considered to be generally accepted.

In a recent interview, Marianna Naum, in the Office of the Deputy Commissioner for Foods and Veterinary Medicine, said, "Since you're talking about general recognition of safety, you have to be talking about familiarity with the ingredient in the scientific community. I do think it is important for us to keep in mind that these ingredients aren't necessarily new ingredients. We are just finding a new use for it. I think it is a misconception of the GRAS program. These are mostly old ingredients used in new ways."[4]

Obviously, familiarity with the ingredient in the scientific community cannot exist when dealing with a new ingredient, for which the information underlying the GRAS determination is not publicly available.

CSPI has been attempting for over *one year* to obtain the scientific information that forms the basis for the FEMA's determination that compounds developed by Senomyx are GRAS.[5] Unfortunately we have not been able to obtain the information despite our best efforts, including:

- filing a Freedom of Information Act (FOIA) request (1/18/12, FOIA request number 2012-485) with the FDA
- providing clarifying information (the CAS, FEMA, and JECFA numbers and chemical names for the substances of interest) to FDA as FDA requested (4/16/12)
- meeting in person with FEMA representatives (11/30/12)
- sending numerous emails and making numerous phone calls to FEMA representatives (1/3/12 – 1/22/13)

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[3] "Guidance for Industry: Frequently Asked Questions About GRAS, December 2004, at http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm061846.htm. The answer to question 4 states, "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. As FDA discussed in a proposed rule to establish a voluntary notification program for GRAS substances (62 Fed. Reg. 18938; April 17, 1997), the data and information relied on to establish the safety of the use of a GRAS substance must be generally available (e.g., through publication in the scientific literature) and there must be a basis to conclude that there is consensus among qualified experts about the safety of the substance for its intended use. Thus, the difference between use of a food additive and use of a GRAS substance relates to the widespread awareness of the data and information about the substance, i.e., who has access to the data and information and who has reviewed those data and information."

[4] Food Safety News, December 18, 2012.

[5] Senomyx Inc. develops taste modifiers that may enable food manufacturers to reduce levels of salt, sugar, artificial sweeteners, and monosodium glutamate (MSG). CSPI wanted to review the safety information on Senomyx's sweetness-enhancing substances.

A summary documenting our correspondence with FEMA in an attempt to obtain the information is attached to this letter.

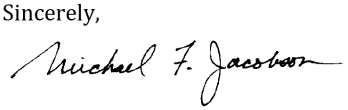
We recently learned that another scientist, Dr. Susan Schiffman, retired director of the Duke University Taste and Smell Lab and former Professor of Medical Psychology in the Department of Psychiatry at Duke University Medical School, currently a consultant, also asked FEMA for the scientific information underlying the GRAS determination on a sweetness-enhancing compound developed by Senomyx, but FEMA declined to send her the information.

Information on the identity and safety of substances in the food supply should not be a secret and should not require Herculean efforts to obtain. Even the FDA apparently does not have any information on eight flavor-enhancing compounds developed by Senomyx, other than rough exposure estimates for four of the compounds.[6] FEMA's delays in releasing the information foil our ability to evaluate and inform the public about the safety of those substances. Meanwhile, FEMA touts the transparency of its GRAS program.[7]

This inability to obtain information in a timely way about the safety of GRAS substances means that the basis for the GRAS status is not common knowledge and that there is not widespread awareness of or familiarity with the data and information about the substance. Hence, there cannot be a general recognition of safety. We urge FDA to reconsider the GRAS status of any such substance. We call on FDA to publish all FEMA notices pursuant to the proactive disclosure provisions of the Freedom of Information Act as described by the Department of Justice and encouraged by the Attorney General and the President.[8] Furthermore, we urge the FDA to seriously review its acceptance of the current FEMA GRAS-review process and consider instituting major reforms.

Thank you for considering these comments.

Sincerely,





Michael Jacobson, Ph.D.
Executive Director

Lisa Y. Lefferts, M.S.P.H.
Senior Scientist

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[6] Email from Sharon R. Dodson of FDA to Alison Brown of CSPI on August 10, 2012, attaching letter to Alison Brown from Sharon R. Dodson dated February 21, 2012 re: FOIA request 2012-485 and an enclosure with exposure information on 4 compounds.

[7] Page 267 in Hallagan, John B. and Richard L. Hall. "Under the conditions of intended use – New developments in the FEMA GRAS program and the safety assessment of flavor ingredients." Food and Chemical Toxicology 47: 267-278, 2009. Also personal communication with John B. Hallagan, November 30, 2012.

[8] Department of Justice Guide to the Freedom of Information Act: Proactive Disclosures. Available at http://www.justice.gov/oip/foia_guide09/proactive-disclosures.pdf

Attachment: Correspondence between FEMA and CSPI regarding Senomyx's flavor enhancers

KEY:

AB: Alison Brown, CSPI (Research Associate)
CG: Christie Gavin, FEMA (Owner and Managing Director of Verto Solutions, which manages FEMA)
JH: John Hallagan, FEMA (General Counsel, former Science Director)
LL: Lisa Lefferts, CSPI (Senior Scientist)

CSPI: Center for Science in the Public Interest
FEMA: Flavor and Extracts Manufacturers Association
RIFM: Research Institute for Fragrance Materials
Correspondence is via email unless otherwise noted

1/3/12 CSPI's Alison Brown (AB) emails FEMA's Christie Gavin (CG) about gaining access to the RIFM-FEMA database, asks about fee.
1/10 CG replies to AB that CSPI does not meet the criteria for access to the database, and would be pleased to talk about what is being sought
notes in files (undated) titled "Christie Gavin FEMA" about CSPI interested in knowing about Senomyx compounds deemed GRAS.
1/10 AB emails FEMA's John Hallagan (JH) inquiring about status of Senomyx GRAS approvals by FEMA
1/11 JH: will get back to you by end of week
1/17 JH refers to phone conversation that morning w/AB and sends 2 publications w/background on FEMA GRAS program. Says will get back shortly w/other info discussed.
1/24 AB thanks JH, says she is checking on the status of the other information requested, i.e., more details of Senomyx's GRAS approvals by FEMA, including the scientific data upon which approvals were based. She notes that GRAS 24 and 25 reports published in Food Technology don't provide information being sought.
3/5 AB email to JH following up and getting info discussed. Notes that FDA responded that it could find no information to fulfill our FOIA request
3/17 JH says he'd like to meet to share the information, and can provide a detailed explanation of the evaluation process and a description of the scientific information used to establish GRAS status. Suggested 2 dates in March
3/21 AB notes that FEMA says it provides its safety assessment information "for inclusion in its publicly available databases." Says after reading documents, would like to meet to discuss any questions
4/5 AB tells JH that, per phone conversation, we are waiting to receive a list of the Senomyx compounds along with the corresponding FEMA codes
4/5 JH apologizes for the delay, kids are on spring break, will get back once back at work

4/11 AB says understood, we look forward to receiving the list of compounds along with corresponding FEMA codes. Also came across another flavor enhancer compound and asked for info on that (PureCircle and Prinova, called NSF-02)
4/11 JH says a letter containing the info we discussed is attached. (Letter identifies chemical name, FEMA number, JECFA number, CAS number for 8 compounds, and provides other information about FEMA and the FEMA GRAS program generally)
4/12 AB thanks JH, asks about the other flavor enhancer she mentioned (NSF-02), is that in the compounds listed in your letter? Also would like the names of the sponsors of each of the chemicals listed and information on conflicting interests of each of the members of FEMA's current Expert Panel. Also what is your availability in upcoming weeks for our meeting to discuss the scientific evidence evaluating the first flavor enhancer compound on the list you provide.
4/17 JH: the other substance that AP asked about is not in the list in the letter that he sent her. FEMA does not identify FEMA GRAS substances by the applicant for GRAS status or the manufacturer/marketer. He is going on travel and will contact AB in early May to set up a time to meet. At that time we can discuss the other substance that AB asked about and begin the process of sharing the information on the substances on the list in his letter.
8/8 AB: Although quite a bit of time has gone by, we would still like to discuss details of the Senomyx research for the following 8 compounds (lists)
8/8 AB tells her supervisor (Michael Jacobson) that JH was agreeable to speak over the phone about each Senomyx compound but, to his strong advisement, he preferred to go over each compound step-by-step. At this point, she says we need to set up a meeting for him to go over the scientific data of each Senomyx compound.

CSPI's Lisa Lefferts (LL) begins contacting FEMA
10/17 I LL asks JH for a meeting if that is only way to get the information
10/18 JH says he is currently traveling and will call after gets back to the US on Monday to set up a time, will be in DC next month and can compare calendars
10/31 LL emails JH asking if 11/19 will work to meet
10/31 JH proposes 11/28-30, LL confirms a time on 11/30
11/28 LL reconfirms and says "I trust that at the meeting you will be able to provide me with the documentation supporting the GRAS determination for each of the Senomyx substances."
11/30 LL meets with JH, CG, and also Sean Taylor (Scientific Director of FEMA and Scientific Secretary to the FEMA Expert Panel) and Kelly Poole (Director of Government Relations for Verto Solutions, which manages FEMA). Provide background information on organizational structure and GRAS and explain how each Senomyx compound is used. LL asks for toxicological information for two of the compounds which are sweetness enhancers. JH says they would provide FEMA's summaries for those 2 compounds in the "next couple of weeks."
12/3 JH sends Codex flavor guideline as discussed at meeting, but not FEMA's GRAS reviews.
12/5 LL requests original studies in addition to FEMA summaries. Also asks for advice on how to word FOIA to obtain info from FDA (in response to JH's comment during meeting about importance of wording). Confirms that he will be sending a group safety assessment document.

12/7 LL asks questions about FEMA's poundage survey provided at meeting
12/12 JH responds to Qs about FEMA poundage survey, says will provide info on 2 Senomyx compounds as soon as they can
12/21 LL asks if any progress retrieving summaries, noting it has been 3 weeks since meeting
12/27 JH sends summary JECFA report and says is going through process to get study reports and will provide be in touch after first of year
1/7/13 LL thanks JH for JECFA report and asks about status of FEMA summaries and underlying studies
1/7 JH says he will check on the status today, he thinks the copying is done but needs to check.
1/8 LL: Thanks JH and asks what he found out about the copying.
1/17 JH sends more detailed JECFA report and says he will be in touch soon to set up a meeting to give me the studies
1/22 LL thanks JH for the report, says making another special trip to meet with you prior to receiving the information is unnecessary, please mail the information
1/30 JH apologizes for delay, is traveling, will ask FEMA office to box up studies and send them, and will let LL know when can expect them
(current as of 1/30/13)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

APR 24 2013

Michael F. Jacobson, Ph.D.
Executive Director

Lisa Y. Lefferts, M.S.P.H.
Senior Scientist

Center for Science in the Public Interest
1220 L. Street, N.W.
Suite 300
Washington, D.C. 20005-4053

Dear Dr. Jacobson and Ms. Lefferts:

This replies to two letters from the Center for Science in the Public Interest; these letters are dated January 31, 2013, and March 25, 2013. In your January 31st letter you share your experiences with the Flavors and Extract Manufacturers Association (FEMA) generally recognized as safe (GRAS) review process and your attempts in obtaining information about certain flavor-enhancing substances that have been added to the FEMA GRAS list. You call upon FDA to increase the vigor, availability, transparency, and acceptance of GRAS reviews. Additionally, you call on FDA to publish all FEMA notices, to "seriously review" FDA's acceptance of the current FEMA GRAS review process, and consider instituting major reforms. The March 25 letter is a cover letter that encloses the January 31st letter.

As you are aware, embedded in the Federal Food, Drug, and Cosmetic Act (FD&C Act) is an exemption from pre-market approval for the intentional use of substances that are generally recognized as safe or GRAS. Thus the FD&C Act allows for independent determinations that the intended use of a substance is GRAS.

In your January 31st letter, you state that data FEMA relied upon to conclude that the intended uses of certain flavor-enhancing substances are not publicly available. You discuss your attempts to obtain safety data from FEMA concerning certain flavor-enhancing substances, produced by Senomyx. FDA is aware that you have had further correspondence with FEMA subsequent to the January 31 letter and that FEMA sent you documents on February 4 and 11, 2013.

You call upon FDA to increase the vigor, availability, transparency and acceptance of GRAS reviews. As you know, FDA has established and maintains a voluntary GRAS Notification Program. This program operates in accordance with the FD&C Act. We invite all interested parties to participate in the program and submit their GRAS determinations to us. We routinely engage in scientific and regulatory discussions with our stakeholders. FDA's GRAS program is transparent; we publish our response letters and notifiers' complete GRAS notices on the web. Within the limits of our resources, the GRAS notification program has increased FDA's

knowledge of GRAS substances added to the food supply and we have taken action against unapproved food additives. As you are well aware, FDA does not have the authority to require mandatory GRAS submissions or data submissions upon request or to otherwise change its GRAS program in ways that you have suggested. Such authorities require new legislation.

With regard to your suggestions that FDA review the FEMA GRAS process, consider major reforms, and publish FEMA's notices, we reiterate that FDA does not have the authority to require such changes by FEMA, or anyone's, processes for determining whether the intended use of a substance is GRAS. Nevertheless, we are prepared to take action should we become aware of the use of unapproved food additives, especially those that present a hazard to the public.

We appreciate your interest in helping to ensure the safety of ingredients added to food and we are gratified to know that you are willing to share your concerns with us.

Sincerely,

Dennis M. Keefe, Ph.D.
Director,
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition

B. ADDITIONAL INFORMATION ABOUT FLAVOR TRADE GROUPS

The Flavor and Extract Manufacturers Association (FEMA) has over 100 member companies.[195] These include several major food corporations like Coca-Cola, Keurig Dr Pepper, Mondelez International, Mars Wrigley, PepsiCo, and Nestlé. There are also two tobacco companies that belong to FEMA, Philip Morris and Reynolds, although the FEMA Expert Panel does not evaluate flavor ingredients for use in tobacco products.[39] In addition to organizing its Expert Panel, FEMA is involved in several other activities, including advocacy on behalf of the flavor industry by representing "members' interest in laws and regulations involving taxes, trade secret protection, workplace safety, environmental protection, and product safety." FEMA says, "In proactively representing the industry's interests, FEMA seeks to avoid the imposition of unreasonable restraints and burdens on the industry, while protecting the public interest." It also protects its member companies' intellectual property.[196,197]

FEMA is also a founding member of the International Organization of the Flavor Industry (IOFI), an international trade group formed in 1969.[198,199] Its members include both flavor companies as well as other national and regional trade associations. IOFI's mission is to promote "the global trade of safe, responsibly produced flavorings" through use of science, advocacy, and communication.[200]

C. FLAVORING AGENTS, ADJUVANTS, AND ENHANCERS

Federal regulations include functional definitions for two types of flavor substances:[201]

- **"Flavoring agents or adjuvants:** Substances added to impart or help impart a taste or aroma in food."
- **"Flavor enhancers:** Substances added to supplement, enhance, or modify the original taste and/or aroma of a food, without imparting a characteristic taste or aroma of its own."

Strictly speaking, flavor enhancers are not permitted to be captured under the umbrella terms "artificial flavor" or "natural flavor," and as such, these substances are outside the scope of this report. However, we are aware of at least one instance in which a company claimed that its flavor enhancers could be grouped under the term artificial flavor. That company was Senomyx, the same one discussed in Chapter 1 and Appendix A. In 2013, CSPI sent a letter to the FDA asking that the agency notify Senomyx and other companies making similar substances that "taste modifiers" cannot be categorized as artificial flavors and must be disclosed by name.

D. METHODS FOR CALCULATING PRODUCT COUNTS FROM USDA'S BRANDED FOOD PRODUCTS DATABASE

Using the search tips provided by the USDA for searching its Branded Food Products Database, we developed and entered the search terms listed in Table A1 into the "ingredients" search function in the online version of the database. Searches were performed on October 4, 2023, and were limited to the U.S. market, with no restrictions on date, trade channel, brand owner, or food category.

- Using these search results, we calculated the number of products that contained:
- Natural flavor with or without artificial flavor: Search #2 + Search #5
- Artificial flavor with or without natural flavor: Search #3 + Search #6
- Exclusively natural flavor: Search #2 - Search #4 - Search #6
- Exclusively artificial flavor: Search #3 - Search #4 - Search #5
- Both artificial flavor and natural flavor: Search #4 + Search #5 + Search #6
- Flavor and/or spice: Search #10 + Search #11 + Search #12

Table A1. Search terms and results from the USDA Global Branded Food Products Database

Search Number	Search Term	Count
1	"flavor"	227,678
2	"natural flavor"	136,952
3	"artificial flavor"	69,938
4	+"natural flavor" +"artificial flavor"	10,115
5	"natural and artificial flavor"	39,297
6	"artificial and natural flavor"	2,507
7	"spice"	81,321
8	+"spice" +"herb"	1,461
9	+"herb" -"spice"	652
10	+"spice" +"flavor"	52,545
11	+"spice" -"flavor"	28,776
12	+"flavor" -"spice"	175,133
13	”natural beef flavor”	86
14	”artificial beef flavor”	24

References

[1] American Chemistry Society. *Flavor Chemistry Research at the USDA Western Regional Research Center*. 2013. Accessed: October 4, 2023; Available: https://www.acs.org/education/whatischemistry/landmarks/usda-flavor-chemistry.html.

[2] U.S. Food and Drug Administration. *Guidance for Industry: Questions and Answers Regarding Food Allergen Labeling*. 2022. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-questions-and-answers-regarding-food-allergen-labeling-edition-5.

[3] Burdock, G.A. *Fenaroli's Handbook of Flavor Ingredients*. 6th ed. 2010, Boca Raton, FL, USA: CRC Press, Taylor & Francis Group.

[4] Hallagan, J.B., R.L. Hall, and J. Drake. *The GRAS provision - The FEMA GRAS program and the safety and regulation of flavors in the United States*. Food Chem Toxicol, 2020. 138: p. 111236.

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