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Navigating the U.S. Food Additive Regulatory Program

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Abstract: The Food Additives Amendment of 1958 is the foundation for the U.S. food additive regulatory program, which oversees most substances added to food. This article is a comprehensive review of the program, including original analysis of pre- and postmarket safety standards for various categories and subcategories of substances and their uses; assigning the more than 10000 substances currently allowed in human food to those categories; and analyzing the U.S. Food and Drug Administration's (FDA) review of more than 1900 petitions and notifications received from 1990 to 2010. Overall, federal agencies made approximately 40% of the 6000 safety decisions allowing substances in human food. These decisions allowed an estimated 66% of the substances currently believed to be used in food. Manufacturers and a trade association made the remaining decisions without FDA review by concluding that the substances were generally recognized as safe (GRAS). Robust premarket safety decisions are critical since FDA has limited resources to monitor potentially significant scientific developments and changing uses of a substance after it enters commerce and only has access to published data or data submitted to it. In the late 1990s, FDA moved from promulgating rules for its decisions for food contact and GRAS substances to reviewing manufacturer safety decisions and posting the results of the review on the agency's website. This shift appears to have encouraged manufacturers to submit their decisions to FDA for review but has limited public opportunity to provide input.

Introduction

In the more than 50 y since the U.S. Congress enacted, and President Eisenhower signed into law, the Food Additives Amendment of 1958 (Public Law 85-929, 72 Stat. 1784), Americans' diet has changed dramatically. Consumers have higher expectations for quality, safety, and convenience while insisting that they have easier access to a greater diversity of food tailored to their particular lifestyles and needs. They want all of this at a reasonable cost. As a result of these driving forces as well as scientific developments and a global economy, our food supply has become more diverse and more processed and is produced farther away from where it is consumed than it was 50 y ago (Rulis and Levitt 2009; Floros 2010). A food science and technology professional from 1958 may recognize most of the food in today's supermarkets but might be surprised by the complexity of the food production system. Substances ranging from drugs in animal feed to pesticides to food additives are added to food to cultivate it, preserve it, process it, contain it, make it more appealing, and enhance its flavor, texture, and color; these substances serve a crucial role in meeting consumers' expectations and needs (IFT 2011).

Given the complexity of the current food production system, food science and technology professionals and policy makers have a greater responsibility and a tougher challenge than ever to understand the regulatory status of substances added to food as well as the regulatory program designed to ensure their use is safe. For purposes of this article, the authors refer to this program as the "food additive regulatory program" even though, as detailed below, its scope reaches far beyond the legal definition of food additives. This program includes nearly 1900 sections and more than 1200 pages of the Code of Federal Regulations (CFR) addressing substances added to food. These CFR provisions do not even begin to tell the whole picture, since thousands of substances are addressed through nonrule actions by FDA or are not reviewed by FDA at all. In an effort to provide assistance, the U.S. Food and Drug Administration (FDA) provides access to this vast amount of information through at least 4 searchable databases, including its "Everything Added to Food in the United States" (EAFUS) database. Despite its name, EAFUS includes less than half of all substances allowed by FDA and less than 10% of the substances allowed by the agency in the past 10 y. Moreover, none of the databases include the thousands of substances that are not required to be reviewed by FDA.

This article is designed to assist food science and technology professionals and others to navigate the food additive regulatory program to more fully understand the program's structure and operation. It builds on 3 existing resources: "Food Regulation: Law, Science, Policy, and Practice" by Neal D. Fortin (2009), "Making Decisions about the Risks of Chemicals in Foods with Limited Scientific Information," an Institute of Food Technologists Expert Report (2009), and "FDA's food ingredient approval process: Safety assurance based on scientific assessment" (Rulis

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and Levitt 2009). The current article expands on the information provided in these resources and attempts to provide a systematic, comprehensive, and broad review of the food additive regulatory program, including novel analysis of the program's current status and recent trends.

As a systematic review and to provide background for the article, Section "Defining Food and Food Additives" introduces the terms food and food additives and explains key concepts needed to apply those terms. Section "Categories and Subcategories of Substances Added to Food" provides detailed descriptions of those terms, especially the categories and subcategories of substances added to food. Section "Safety Determination Standards" compares the standards that food manufacturers, additive suppliers, and importers (hereinafter referred to as "manufacturers") or federal agencies must use to determine whether a substance is safe for its intended use. Section "Number of Affirmative Safety Decisions and Substances Allowed for Human Food" provides estimates of the number of affirmative safety decisions made and the number of substances currently allowed in each category and subcategory. Section "Manufacturer's Postmarket Responsibilities" explains the manufacturers' postmarket responsibilities for ensuring that substances added to the foods they make, market, and sell are and remain safe. Section "Trends in FDA Reviews for Human Food Since 1990" highlights how changes in the regulatory system during the last 20 y have impacted FDA's review of substances added to food. Section "Methodology" explains the methodology the authors used to develop estimates and assess trends. Section "Conclusions" provides the authors' conclusions.

Due to the length of the article and the diverse experiences of readers, the authors sought to make each section and each major table as independent as possible without unnecessary duplication. Readers who are familiar with the program may find it helpful to jump ahead to Section "Safety Determination Standards" and refer back to Sections "Defining Food and Food Additives" and "Categories and Subcategories of Substances Added to Food" as needed to better understand the categories and subcategories.

Throughout this article, the authors use as an example a typical microwave-ready, frozen children's meal to highlight and explain how the food additive regulatory program functions. They chose the meal because it is commonly available and has diverse components and ingredients that reflect the different parts of the regulatory program. The meal consists of breaded chicken nuggets, macaroni and cheese, corn, and chocolate pudding. The food sits in a polyethylene terephthalate plastic tray covered by a sheet of clear plastic with a separate internal plastic bag and has a freezer shelf life of up to 2 y. The box's ingredient list identifies 68 items which range from whole grain flour to microcrystalline and carboxymethyl cellulose. Where relevant, the authors use this meal to explain the regulatory status of the additives and potential additives.

Defining Food and Food Additives

The U.S. Congress defined "food" to mean "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article" (21 USC §321(f)). FDA clarified by defining "food" to include human food, pet food, animal feed, and substances migrating to food from food contact articles (21 CFR §170.3(m)). The sample frozen meal is food, including substances in the packaging that may get into the food at the production facility, during up to 2 y of storage, and when it is microwaved.

Given these definitions of food, all food additives are food. What then is a food additive? The obvious answer is that a food additive is something added to food. However, the statutory definition is far from obvious:

> "The term 'food additive' means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include
> (1) a pesticide chemical residue in or on a raw agricultural commodity or processed food; or
> (2) a pesticide chemical; or
> (3) a color additive; or
> (4) any substance used in accordance with a sanction or approval granted prior to September 6, 1958, pursuant to this chapter, the Poultry Products Inspection Act [21 USC §451 et seq] or the Meat Inspection Act of March 4, 1907, as amended and extended [21 USC §601 et seq.];
> (5) a new animal drug; or
> (6) an ingredient described in paragraph (ff) in, or intended for use in, a dietary supplement." (21 USC §321(s))

From this one sentence definition, it is difficult to discern what is and is not considered a food additive. The definition is both broader and narrower than it may appear.

On the one hand, it is broader in 2 ways. First, the term "food additive" includes all the common ingredients in the frozen children's meal, such as the wheat flour and the cheese in macaroni and cheese. These common ingredients that have been used for centuries are not what we normally think of as "food additives." Next, the term also includes substances whose use may reasonably be expected to result in them becoming a component of food, even if the manufacturer does not intend for them to become part of the food (21 USC §321(s)). These substances are often called "indirect food additives" or "food contact substances" and include thousands of substances used in food packaging and on the equipment used for processing and storing food. Therefore, "food additive" may include substances in or on packaging, such as components of the clear plastic film that covers the frozen children's meal, as well as substances used in or on food processing equipment, such as lubricating oil or cleaning chemicals, to the extent that their components may migrate into food.

Expanding the meaning of food additive further is the definition's inclusion of any source of radiation, which is used to inspect, heat, or treat some foods or packaging even though it is not a substance per se (21 USC §321(s) and 21 CFR Part 179).

On the other hand, the broad inclusive definition is matched by 3 broad exclusions from the food additive definition. First, substances "generally recognized as safe" (GRAS) among experts who are qualified by scientific training and experience to evaluate safety under conditions of intended use are excluded from the definition of food additives (21 USC §321(s)). These substances are commonly known as "GRAS substances." They range from

common food ingredients in use before 1958, like the wheat in the sample frozen meal, to FDA-reviewed, newly engineered substances made using biotechnology or nanometer-scale materials.

Second, the U.S. Congress excluded from the definition of food additive, substances that were sanctioned by the FDA or the U.S. Dept. of Agriculture (USDA) before the Food Additives Amendment of 1958 was enacted. These "prior-sanctioned substances" were grandfathered into the food additive regulatory program (21 USC §321(s)). FDA has documented most but not all of these approvals.

Third, the U.S. Congress also excluded from the definition certain categories of substances and established distinct programs and standards for managing them. In the Food Additives Amendment of 1958, it excluded pesticide chemicals and pesticide chemical residues in raw agricultural commodities. Later the U.S. Congress excluded color additives (1960), drugs in animal feed (1968), and dietary supplements (1994) (21 USC §321(s)).

Currently, FDA's Office of Food Additive Safety (OFAS), in the agency's Center for Food Safety and Applied Nutrition (CFSAN), regulates food additives, GRAS substances, color additives, and prior-sanctioned substances used in human food. FDA's Center for Veterinary Medicine (CVM) regulates drugs in animal feed and additives to animal feed and pet food. The Environmental Protection Agency (EPA) sets standards for pesticide chemicals or residues in food which FDA enforces.

One final, important concept to recognize is what constitutes a food additive and where a substance falls in the spectrum of categories: the category or subcategory of a substance is primarily based on its intended use. Intended use means more than just what type of food in which the substance will be used. It also denotes the intended function of the substance in that food. This means that a single substance may fit within multiple categories or subcategories. Consider these 2 examples:

1. Carbon dioxide would be categorized as (a) a pesticide chemical or residue if used in the airspace above food commodities to control insects (40 CFR §180.1049); (b) as a GRAS substance for animal feed (21 CFR §582.1240); or (c) as a GRAS substance for human food if used as a leavening agent, processing aid, propellant, aerating agent, or gas (but not as a pesticide) when used in accordance with good manufacturing practices (21 CFR §184.1240).
2. Diatomaceous earth—the silica skeletal material from a type of algae called diatoms—would be categorized as (a) a pesticide chemical or residue due to its role as an insect-control agent on growing crops, food commodities after harvest (if food is removed or covered), and animals (40 CFR §180.1017); (b) a food additive for animal feed if used as a carrier or anti-caking agent (21 CFR 573.340); or (c) a GRAS substance for human food if used as part of a filtration media (FDA 2002).

Categories and Subcategories of Substances Added to Food

The Food Additives Amendment of 1958 amended the Federal Food Drug and Cosmetic Act of 1938 (FFDCA) to establish the U.S. food additive regulatory program (Public Law 85-929, 72 Stat. 1784, 21 USC §348). Central to the program was the definition of "food additives" as described in Section "Defining Food and Food Additives." The definition excluded substances specified in the professional parlance as "GRAS substances." It also excluded pesticide chemicals or residues used in, on, or in association with raw agricultural commodities and substances whose use was previously sanctioned or approved pursuant to the FFDCA, the Poultry Products Inspection Act or the Meat Inspection Act (21 USC §321(s)). Overall, with the 1958 legislation, the U.S. Congress recognized 4 distinct categories of substances added to food and established requirements for each:

- Food additives
- GRAS substances
- Pesticide chemicals or residues; and
- Prior-sanctioned substances.

After 1958, the U.S. Congress adopted 3 laws that made significant changes to the statutory definition of food additives:

- The Color Additive Amendments of 1960 created a new regulatory program for FDA to manage "color additives" whether in food, drugs, or cosmetics and exempted them from the definition of food additives (Public Law 86-618, 74 Stat. 397).
- The Animal Drug Amendments of 1968 exempted drugs in animal feed approved after 1938 from the definition of food additives (Public Law 90-399, 82 Stat. 342).
- The Dietary Supplement Health and Education Act of 1994 created a new FDA-based regulatory program to manage "dietary supplements" and exempted these from the definition of food additives (Public Law 103-417, 108 Stat. 4325). Generally, these substances are items not intended to be "conventional food" or intended as the sole item of a meal.

As a result of these laws, by 1994, the U.S. Congress had established 7 distinct categories of substances added to food. If a manufacturer intends to use any substance, directly or indirectly, in food it must fall into one of these categories; otherwise, it must not be used or even marketed as it would be considered a contaminant or unapproved food (or color) additive and, therefore, the food would be adulterated. FDA has broad authority to protect Americans from adulterated food (21 USC §§331, 321, 342, and 348 and 21 CFR §181.5).

FDA's and EPA's implementation of these laws (and additional changes to the laws) generated subcategories within these categories. Table 1 provides a current listing of the 7 categories with the key subcategories used in this article. Each is described in more detail below.

To help make sense of these categories and subcategories, refer again to the microwave-ready, frozen children's dinner meal described in the introduction. At the end of each category or subcategory, the authors explain what additives may be in the sample frozen meal described in the introduction section. Table 2 summarizes those explanations.

Table 1–Categories and subcategories of substances added to food

1. **Food additives**
   - A. Direct food additives
   - B. Indirect food additives (few additions after 1997)
   - C. Substances covered by FCS notifications (began in 1997)
   - D. FCSs below threshold of regulation (began in 1995)
   - E. Radiation sources
2. **GRAS substances**
   - A. Common food ingredients in use before 1958
   - B. Manufacturer self-determined
   - C. Association expert panel-determined
   - D. FDA-listed (ended in 1973)
   - E. FDA-affirmed (began in 1973 and effectively replaced after 1997)
   - F. Substances covered by FDA-reviewed GRAS notification (began in 1997)
3. **Prior-sanctioned substances (federally sanctioned before 1958)**
4. **Color additives (began in 1960)**
5. **Pesticide chemicals or residues (modified in 1996)**
6. **Drugs in animal feed (modified in 1968)**
7. **Dietary supplements (began in 1994)**

Table 2–Categorization of substances potentially associated with sample frozen, microwave-ready children's meal

Category and subcategory	Ingredients/Substances
Food additives	
Direct food additives	Carrageenan, butylated hydroxytoluene, modified food starch, and possibly some of the natural flavor
Indirect food additives	Polyethylene terephthalate. Other unknown but likely to include additives in or on packaging and equipment used to make the food, such as paperboard, inks, adhesives, glues, coatings, and antimicrobials
Substances covered by food contact substance (FCS) notifications	Unknown but may include additives in or on packaging and equipment used to make the food that are not in other categories or subcategories
FCSs below threshold of regulation	Unknown but may include additives in or on packaging and equipment used to make the food that are not in other categories or subcategories
Radiation sources	Final product not treated with ionizing radiation; however, it may have been used on packaging or individual ingredients or additives. Unknown whether other forms of radiation were used on the food
"Generally recognized as safe" (GRAS) substances	
Common food ingredients in use before 1958	34 ingredients including chicken breast, water, bleached wheat flour, whole wheat flour, salt, spices, soybean oil, whey protein, and yeast
Manufacturer self-determined	Unknown but most likely microcrystalline and carboxymethyl cellulose, soy protein concentrate, and soy protein isolate
Association expert panel-determined	Extractives of turmeric and paprika, carboxymethyl cellulose, and some flavoring
FDA-listed	Disodium phosphate, monocalcium phosphate, sodium acid pyrophosphate, sodium caseinate, sodium phosphate, cellulose gum, and, possibly, some of the spices and natural flavor
FDA-affirmed	Citric acid, garlic powder, guar gum, gum arabic, lactic acid, maltodextrin, potassium chloride, sodium bicarbonate, whey protein concentrate, yeast extract, soy lecithin, beta carotene, dextrose, dried sweet whey, acetic acid esters of mono- and diglycerides with maltodextrin, and, possibly, some of the natural flavor
Substances covered by FDA-reviewed GRAS notifications	Unknown but may include additives used to make the food that are not in other categories or subcategories
Prior-sanctioned substances	Unknown, possibly some used in manufacture of paper and paperboard
Color additives	Annatto, beta carotene, turmeric and red cabbage extract
Pesticide chemicals or residues	Unknown but may include residues of pesticides used in or on raw agricultural commodities in the meal, such as the corn, wheat, sugar, spices, and soybean
Drugs in animal feed	Unknown but chicken feed may have contained antibiotics and arsenic-based drug
Dietary supplements	Not applicable because the meal is conventional food

Note: Categorization based on 68 ingredients identified on label, the type of packaging, and knowledge of additives associated with the ingredients and packaging. Many substances, especially FCSs and processing aids, not required to be identified on the label. "Unknown" means that some of the ingredients or substances from these categories may have been used, but their use cannot be determined based on the label.

1. Food Additives are substances "the intended use of which results or may reasonably be expected to result, directly or indirectly, in [their] becoming a component or otherwise affecting the characteristics of any food," provided that the substances' use does not fall under one of the other 6 categories described below. The "food additive" category includes substances intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food as well as radiation sources (21 USC §321(s) and 21 CFR §170.3).

The food additives category consists of the following 5 subcategories:

1A. Direct Food Additives are substances intentionally added directly to food and whose use has been expressly approved by FDA usually in response to food additive petitions from manufacturers. The subcategory includes substances known as "secondary directs" that have a technical effect in food during processing but are not intended to have an ongoing technical effect in the food. A substance does not affect the characteristics of food if it only protects the contents of the package, preserves a food's shape, or prevents moisture loss from the food (21 CFR §170.3). Before authorizing a new food additive by an administrative rule, such as in response to a food additive petition, FDA publishes its approvals as regulations in the CFR after notifying the public via the *Federal Register* of the proposal, providing an opportunity for the public to comment, and responding to those comments in a final rule published in the *Federal Register* (21 USC §348(c)). The regulations are codified at 21 CFR Parts 172, 173, 180, and 189 for all human food and 21 CFR Parts 573, 579, and 589 for animal feed and pet food only. The direct food additives subcategory is still the primary method for new food additive approval as specified in the statute even though it is not commonly used today.

However, the process of getting FDA approval of a petition is time consuming and a manufacturer will typically pursue direct food additive status for a substance only if it cannot qualify as a GRAS substance. A common reason why a substance is ineligible to be a GRAS substance is when the key safety studies are unpublished. From 2000 to 2010, FDA received 37 direct food additive petitions for 12 distinct substances used for human food (see Section "Trends in FDA Reviews for Human Food Since 1990"). Although written as a primary category in the law, in practice, the direct food additives subcategory now serves as a category of last resort for substances used in food that do not fall clearly into any other category or subcategory described below.

Regarding the sample frozen meal, according to the label, the direct food additives appear to consist of carrageenan (a gum), butylated hydroxytoluene (a preservative in the vegetable oil used to fry the chicken), modified food starch, and possibly some of the natural flavor. It may contain other substances not required to be specifically identified on the label such as natural flavors and extracts and substances used as additives in one of the ingredients or that have no functional or technical effect on the final product. For more information on label requirements, see 21 CFR §101.100.

1B. Indirect Food Additives are substances not intentionally added directly to food but which may reasonably be expected to become a component of food and whose use has been expressly approved by the FDA (21 CFR §170.3). Generally, these are substances used in or on food packaging or the equipment used for processing or handling food. The regulations governing indirect food additives appear at 21 CFR Parts 174 through 178 for human food and 21 CFR §570.14 for animal feed and pet food. These

regulations were promulgated pursuant to a food additive petition. As with direct food additives, FDA must notify the public in the *Federal Register* of the opportunity to submit comments and publish its approval as a regulation in the CFR (21 USC §348(c)). From 2000 to 2010, FDA has received 6 indirect food additive petitions and 1 after 2001 (see Section "Trends in FDA Reviews for Human Food Since 1990"). Most of the activity shifted to the food contact substance (FCS) notification subcategory described below.

Regarding the sample frozen meal, the indirect food additives are not required to be identified on the label, but they likely consist of additives in packaging and equipment used to make the food, such as polyethylene terephthalate (#1 PETE plastic), other plastics, paperboard, inks, adhesives, glues, cleaning products, antimicrobials, and coatings, that, if capable of migrating into the food should be covered by an indirect food additive regulation, a FCS notification, or a FCS below the threshold of regulation described below.

1C. Substances Covered by FCS Notifications are substances "intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in such food" and that were the subject of a Food Contact Notification (FCN) to which FDA did not object (21 CFR §170.3(e)(3)). While "technical effect" is not defined, the term generally means the substance does not affect the characteristics of food so as to make the substance a direct food additive. This category has essentially replaced the indirect food additive subcategory for new substances.

The U.S. Congress created this subcategory with the Food and Drug Administration Modernization Act of 1997 (Public Law 105-115, 111 Stat. 2296). A new section 409(h) was added to the FFDCA, which replaced the premarket approval procedure for indirect food additives with a premarket notification procedure. FDA began accepting FCNs in 2000 when it proposed rules for its Premarket Notification for FCS program (21 CFR §§170.100–170.106, 67 FR 35724, May 21, 2002). FDA finalized the regulations implementing the new procedure in 2002. Under the program, FDA reviews notifications from a manufacturer that has decided that the intended use of a FCS is safe. FDA has 120 d to object to a properly submitted notification. If FDA fails to act, the notification is essentially treated as approved and the manufacturer can use the FCS consistent with the FCN. If FDA has no objections, it typically issues a "no objection" letter. If the agency has concerns, a manufacturer will typically withdraw the notification rather than have FDA formally object (Kahl 2010). Manufacturers may withdraw a notification without prejudice (21 CFR §§170.100–170.106). FDA posts affirmative decisions (or ones FDA has not objected to) on its website and describes the chemical and its use limitations and lists the name of the manufacturer (FDA 2011a). It does not post the manufacturer's notification or the contents of the agency's letter to the manufacturer on the website. Congress prohibited FDA from posting information on the notice prior to making a decision (21 USC §348(h)(4)). FDA's decision applies only to substances described in the notice from the manufacturer that submitted it. Competitors may not rely on the decision but can submit their own notification for the same substances and uses.

FCNs get a quicker response from FDA than indirect food additive petitions (described above) because FDA's inaction on an FCN would essentially serve as consent and FDA does not have to go through the process of issuing a new regulation. Therefore, this subcategory has largely replaced the indirect food additive subcategory for new substances indirectly added to food, as well as FCSs below the threshold of regulation (described below), and appears to have encouraged manufacturers to choose to submit FCNs for substances that they might otherwise have self-determined to be GRAS substances. From 2000 to 2010, FDA reviewed more than 1000 FCNs and issued no-objection letters for 778 of them (see Section "Trends in FDA Reviews for Human Food Since 1990").

Regarding the sample frozen meal, substances covered by FCS notifications are not identified on the label, but they likely consist of substances similar to indirect additives described above.

1D. FCSs below Threshold of Regulation are substances used in food contact articles, for example, food packaging or food processing equipment, which migrate or may be expected to migrate into food at levels so low that FDA determines they are exempt from regulation as a food additive (21 CFR §170.39). FDA adds substances based on its affirmative review of a manufacturer's notification, called a Threshold of Regulation (TOR) exemption request (FDA 2011b).

FDA established this FCSs below Threshold of Regulation subcategory in 1995, 2 y before the U.S. Congress created the substances created by FCS notifications subcategory described above (60 FR 36582, July 17, 1995). For a substance to qualify for this subcategory, FDA must find that it has not been shown to be a carcinogen; has no technical effect in or on the food into which it migrates; has no significant adverse impact on the environment; and has no other health or safety concerns. FDA assumes there to be no other health or safety concerns if the dietary exposure is at or below 1.5 micrograms of the substance per person per day or if the substance is already regulated as a direct food additive and the dietary exposure is at or below 1% of the existing acceptable daily intake for the substance (Rulis and Levitt 2009; FDA 2011c).

As with substances covered by FCS notifications, after making a decision, FDA posts affirmative decisions on its website and describes the chemical and its use limitations and lists the name of the manufacturer (FDA 2011d). FDA does not post the manufacturer's notification or the contents of the agency's letter to the manufacturer on its website. Manufacturers made extensive use of this subcategory when it was launched in 1995. However, because FDA is not required to respond in 120 d, this subcategory appears to have largely been replaced by the substances covered by FCS notifications subcategory described above (Keller and Heckman 2001; FDA 2005). From 2000 to 2010, FDA affirmatively reviewed only 30 of these notifications (see Section "Trends in FDA Reviews for Human Food Since 1990").

Regarding the sample frozen meal, FCSs below the threshold of regulations are not identified on the label, but they likely consist of substances similar to indirect additives described above.

1E. Radiation Sources are machines such as x-ray tubes or radioactive elements that produce radiation used for inspecting food, controlling food processing, irradiating food, heating food (including microwaves), and treating food packaging. FDA publishes its approvals as regulations in the Code of Federal Regulations after notifying the public via the *Federal Register* and providing an opportunity for the public to comment (21 USC §348(c)). The regulations appear at 21 CFR Part 179.

Regarding the sample frozen meal, it is not known to consumers whether or not the ingredients comprising the meal were irradiated. The law requires final products treated with ionizing radiation to be labeled; however, radiation sources may have been used on the packaging or individual additives without triggering the labeling requirement.

2. GRAS Substances are substances "generally recognized, among experts qualified by scientific training and experience to

evaluate the safety as having been adequately shown . . . to be safe under conditions of their intended use" (21 USC §321(s)). General recognition of safety can be based on a substance's common use in food prior to 1958 or on scientific procedures. If a safety determination relies on scientific procedures, the determination "shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information" ("ordinarily" is not defined) (21 CFR §170.30(b)). The key feature of the GRAS category is that anyone, as long as they are experts qualified by scientific training and experience, not just FDA, may decide that a substance's use is safe and begin marketing it and adding it to food. If a manufacturer makes a determination that use is safe in accordance with 21 CFR §170.30, it has no explicit legal obligation to notify FDA.

A substance is GRAS for a specific use. As noted earlier, a single substance may have multiple uses, some of which may fit into the drugs in animal feed, pesticide chemicals or residues, food additives, or color additives categories, and some of which may qualify as GRAS.

The GRAS substances category consists of 6 subcategories. The first 3, common food ingredients in use prior to 1958, manufacturer self-determined GRAS substances, and association expert panel-determined GRAS substances, have been in place essentially unchanged since the early 1960s.

The remaining 3 subcategories reflect FDA's modification of the GRAS program which evolved from "FDA-listed GRAS substances" from 1958 to 1973, to "FDA-Affirmed GRAS substances" from 1973 to 1997, to the current "FDA-Reviewed GRAS notifications" subcategory in effect since 1997 (24 FR 9368, November 20, 1959, 62 FR 18938, April 17, 1997). With each of these changes, FDA's earlier decisions remained valid unless formally reversed, affirmed, or modified.

Before passage of the Food Additive Amendment of 1958, FDA presented to Congress a list of substances that the agency considered GRAS. After passage of the law, FDA published its initial version of FDA-listed GRAS substances (23 FR 9511, December 9, 1958) and added to the list over the years. In 1973, FDA replaced the listing approach with the GRAS affirmation process for FDA-affirmed GRAS substances, primarily to encourage firms to submit their GRAS determinations and enable the agency to address any safety issues with the new food substances. A successful GRAS affirmation petition provided incentive and reassurance to the manufacturer and its customers that FDA agreed with the safety determination.

Implementation of the GRAS affirmation process, however, broke down due to lack of resources and, perhaps, lack of priority within the agency. The GRAS affirmation process was created by the agency, not statute, and accordingly lacked statutory deadlines and mandates. The backlog of affirmation petitions increased every year until finally in 1997 when FDA proposed replacing affirmations with a notification process. Although FDA had not finalized its proposed regulations for GRAS notifications, the agency began almost immediately accepting notifications and refused further GRAS affirmation petitions (Kahl 2010; 62 FR 18938, April 17, 1997).

The FDA-reviewed GRAS notifications subcategory represents a major change in the FDA's food additive regulatory program because the agency's decision is in the form of a letter to the notifier which is posted on its website but lacks the publication or comments period associated with a proposed regulation (FDA 2006a). The process also represents a shift from petitions—where FDA made the formal safety decision—to manufacturer notifications—where a manufacturer makes the safety decision described in a notification, and FDA reviews the decision and issues a "no question" or "insufficient basis" letter (FDA 2009a). Despite the differences in process, the common element of all 3 subcategories is that FDA publishes its decision, and all manufacturers are entitled to rely on it—not just the manufacturer submitting the petition or notice (McQuate 2011) (75 FR 81536, December 28, 2010). Details on the GRAS subcategories are as follows:

2A. Common Food Ingredients in Use before 1958 are substances that are added to food that were commonly consumed before 1958 and are of natural biological origin. For example, a potato added to broth to make a can of soup would be considered a substance added to food and more specifically, a common food ingredient (21 CFR §170.30(d)). FDA adopted 2 regulations (21 CFR §182.1 for human food and 21 CFR §582.1 for animal feed) to generically designate staples of the American diet as GRAS. Included among these substances are salt, pepper, vinegar, monosodium glutamate, baking powder, flour, fruits, vegetables, meat, poultry, and seafood. No additional GRAS notification or food additive petition or determination on the part of FDA is required.

Regarding the sample frozen meal, common food ingredients include 34 of the 68 listed ingredients including chicken breast, water, bleached wheat flour, whole wheat flour, salt, spices, soybean oil, whey protein, and yeast.

2B. Manufacturer Self-determined GRAS Substances are those substances that manufacturers determine are GRAS independent of or absent FDA's review or approval. A manufacturer's decision must be consistent with 21 CFR §170.30 and should consider FDA's guidance, especially its "Toxicological Principles for the Safety Assessment of Food Ingredients" (FDA 2007) (also known as the "Redbook"). However, a manufacturer is not obligated to notify FDA of its decision to add a substance to food or of the way it intends to use the substance in food (21 USC §348 and 62 FR 18938, April 17, 1997). There is also no explicit legal obligation for the manufacturer to follow the Redbook. In some cases, such as with certain spices and flavors as well as with FCSs, a substance also does not have to be specifically identified on the product label (21 CFR §101.22).

A manufacturer can make a decision based on the safety assessment performed by its own employees or an expert panel it selects and convenes; however, the determination must be one accepted by experts in the field in order to satisfy the general recognition of safety requirement. If FDA learns of the decision and disagrees with it, the agency could take enforcement action claiming the firm violated the law by introducing into commerce an unapproved food additive. As a recent example, in October 2009 FDA sent a letter to 4 manufacturers of certain alcohol drinks with added caffeine. FDA gave them until April 2010 to submit a GRAS notification under item F below. One manufacturer submitted a GRAS notification. FDA found it insufficient in November 2010 and warned all 4 manufacturers to stop adding caffeine to alcohol drinks (FDA 2010a). They apparently complied within the 30 d FDA gave them. At least one has reformulated the product without caffeine.

Regarding the sample frozen meal, manufacturer self-determined GRAS substances appear to include microcrystalline carboxymethyl cellulose, soy protein concentrate, and soy protein isolate since they do not appear on any lists for the other categories or subcategories. It may contain other manufacturer self-determined GRAS substances not required to be identified on the label.

2C. Association Expert Panel-Determined GRAS Substances are substances found to be GRAS by an expert panel

that is selected and convened by an association to evaluate potential GRAS substances that have been submitted by manufacturers seeking approval. It is not a distinct subcategory created by the rules. Rather it is a variation of the manufacturer self-determined GRAS substances subcategory where the manufacturer relies on the decision by the association's expert panel. The authors treated it separately because the expert panel publishes its affirmative decisions, allows all manufacturers to rely on the decision, and has a long track record of making many decisions. The association expert panel must follow 21 CFR §170.30 to enable a manufacturer to rely on the panel's safety decision.

Currently, the authors are aware of only one organization, the Flavor and Extract Manufacturers Association (FEMA), which has such a panel assessing GRAS substances in human food in a sustained and systematic manner. FEMA established an expert panel in the early 1960s and has systematically reviewed and published its findings evaluating the safety of flavors and extracts in human food since then (FEMA 2011). FEMA also submits its decisions and supporting documentation to FDA, but the agency does not conduct a formal evaluation of FEMA's findings. FEMA publishes the decisions of its expert panel so others may rely on them. In July 2011, FEMA published its 25th report in *Food Technology Magazine* (Smith and others 2011).

There is a second association that makes decisions that manufacturers routinely rely on for GRAS determinations. The Association of American Feed Control Officials (AAFCO) adopts ingredient definitions for animal feed and pet food and publishes these definitions annually in its "Official Publication" (OP). Although neither FDA's CVM nor AAFCO calls the OP definitions "GRAS determinations," they operate as such under the law. AAFCO definitions are accepted by FDA and state and local officials enforced their laws for animal feed and pet food using the OP to determine whether a substance's use is permitted. The AAFCO's ingredient definitions are largely based on "no objection" letters sent to AAFCO by FDA's CVM in response to requests from AAFCO or manufacturers, but neither CVM nor AAFCO describes these substances as GRAS. In practice, manufacturers and regulators rely on them in the same way a food manufacturer would rely on GRAS determinations. CVM and AAFCO documented this program in an April 2007 Memorandum of Understanding (FDA-AAFCO 2007). This program is likely to go through significant changes because CVM began accepting official voluntary GRAS notifications in late 2010 from manufacturers as described below.

Manufacturers could also rely on the international standards set by the Codex Alimentarius Commission, which are based on the safety assessments by the Joint Expert Committees on Food Additives (JECFA). JECFA is a joint committee of the United Nation's Food Agriculture Organization (FAO) and the World Health Organization (WHO). An ingredient's safety standard published by Codex should meet the GRAS definition of generally recognition as safe.

Regarding the sample frozen meal, flavor and extract manufacturer association expert panel-determined GRAS substances include extractives of turmeric and paprika, carboxymethyl cellulose, and some flavoring. It may contain other association expert panel-determined substances not required to be identified on the label.

2D. FDA-Listed GRAS Substances are substances determined by FDA to be GRAS and expressly allowed to be added to food. FDA publishes its approvals as regulations in the CFR after notifying the public via the *Federal Register* and providing an opportunity for the public to comment. Any manufacturer can rely on these decisions. These regulations appear at 21 CFR Part 182 for human food and 21 CFR Part 582 for animal feed and pet food.

In 1973, when FDA adopted its GRAS Affirmation rule (discussed below), FDA stopped adding new FDA-listed GRAS substances and began to reassess its previous decisions, usually replacing them with new regulations pursuant to the new rule. As a result, the number of FDA-listed GRAS substances has gone down since 1973.

Regarding the sample frozen meal, FDA-listed GRAS substances include disodium phosphate, monocalcium phosphate, sodium acid pyrophosphate, sodium caseinate, sodium phosphate, cellulose gum, and, possibly, some of the spices and natural flavor. It may contain other FDA-listed GRAS substances not required to be identified on the label.

2E. FDA-Affirmed GRAS Substances are substances determined by FDA to be GRAS and expressly allowed to be added to food pursuant to the agency's GRAS affirmation regulation, usually in response to a manufacturer's voluntary GRAS Affirmation Petition. FDA adopted this rule in 1973, essentially replacing the GRAS listing program (21 CFR §170.35). Under the affirmation program, FDA would, of its own accord or in response to a petition, publish its approvals as regulations in the CFR after notifying the public via the *Federal Register* and providing an opportunity for the public to comment. The regulations appear at 21 CFR Part 184 for human food and 21 CFR Part 584 for animal feed and pet food.

In 1997, FDA ceased accepting new GRAS affirmation petitions and directed new and prior petitioners to submit a notification through FDA's new voluntary GRAS Notification Program described below. This shift created the new subcategory of "Substances Covered by FDA-Reviewed GRAS Notifications." FDA completed its review of a few of the previously submitted GRAS affirmation petitions and no longer devotes resources to reviewing or affirming the petitions (FDA 2004). From 2000 to 2010, FDA did not receive any GRAS affirmation petitions (see Section "Trends in FDA Reviews for Human Food Since 1990").

Regarding the sample frozen meal, FDA-affirmed GRAS substances include citric acid, garlic powder, guar gum, gum arabic, lactic acid, maltodextrin, potassium chloride, sodium bicarbonate, whey protein concentrate, yeast extract, soy lecithin, beta carotene, dextrose, dried sweet whey, acetic acid esters of mono- and diglycerides with maltodextrin, and, possibly, some of the natural flavor. It may contain other FDA-affirmed GRAS substances not required to be identified on the label.

2F. Substances Covered by FDA-Reviewed GRAS Notifications are substances described in notifications submitted by manufacturers pursuant to FDA's proposed GRAS Notification Program. In 1997, FDA proposed this program to replace the GRAS Affirmation Petition Program described above with a more streamlined voluntary approach. This new program is similar to the FCS Notification Program described earlier.

Under the GRAS notification program, a manufacturer voluntarily submits a notification to FDA announcing and justifying its safety decision. The agency evaluates the notification and then provides a response indicating that it either had no questions or that there was an insufficient basis for the manufacturer's GRAS determination. Before receiving FDA's written response, a manufacturer can withdraw its notice without prejudice. FDA publishes the manufacturer's notifications and the contents of its letter to the manufacturer including any limitations on use (FDA 2011e). FDA's evaluation applies to the substance's use described in the notification so competitors may rely on it. However, many of the substances are described in a manner that makes it difficult for a competitor to match the product in terms of

proprietary manufacturing processes or by narrowly defining product specifications.

Despite not finalizing the 1997 proposed rule, FDA operates this program based on its proposal (62 FR 18938, April 17, 1997). CFSAN began accepting notifications for additives to human food in 1998 and CVM began accepting notifications in 2010 for animal feed and pet food (FDA 2009b, 2010b). In a March 2010 report, the U.S. Government Accountability Office criticized FDA's handling of this program and its failure to finalize the rule (GAO 2010). In late 2010, FDA requested additional comments on the proposed rule and indicated that it plans to finalize the rule in 2012 (75 FR 81536, December 28, 2010). The primary differences between the FCS and GRAS notification programs (both set up in the late 1990s) are that the GRAS notification program

- is created by FDA rather than Congress;
- does not have deadlines by which FDA must complete its review of a manufacturer's safety decision (although FDA set an unenforceable goal of 90 d) (62 FR 18938, April 17, 1997, 21 CFR §170.104);
- allows existence of notifications to be made public before FDA makes its decisions (excluding confidential business information) (62 FR 18938, April 17, 1997, 21 CFR §170.102);
- provides the nonconfidential portions of the actual notification and contents of the decision letter;
- allows other manufacturers to rely on the notice and not just the manufacturer submitting it (21 CFR §170.100(a)); and
- allows the manufacturer to summarize the data and information that are the basis of the safety decision rather than provide FDA with primary biological and chemical data (62 FR 18938, April 17, 1997 and 21 CFR §170.101(b)).

The final difference is significant since it fundamentally changes the nature of FDA's review. With GRAS notifications, FDA reviews a comprehensive discussion of the science data but not the underlying biological and chemical data. Instead of conducting an independent assessment, FDA's role is to identify potential flaws with the manufacturer's safety decision.

This program has been popular with manufacturers since they can usually get a more timely response from FDA than they may have received under the previous GRAS affirmation program. From 2000 to 2010, FDA received 330 GRAS notifications.

Regarding the sample frozen meal, substances covered by GRAS notifications do not appear to have been used based on the product label. However, not all substances covered by FDA-reviewed GRAS notifications are required to be identified on the label.

3. Prior-Sanctioned Substances are substances that FDA or USDA affirmatively approved before September 6, 1958, for use in food pursuant to the FFDCA, the Poultry Products Inspection Act, or the Meat Inspection Act (21 USC §321(s)). These substances were "grandfathered" into the food additive regulatory program and FDA cannot revoke this status. FDA has listed those approvals of which it is aware at 21 CFR Part 181 but acknowledged that "not all of these sanctions and approvals can be ascertained because of the destruction of old records and the retirement of personnel involved in these matters" (37 Fed. Reg. 16407, August 12, 1972). According to an industry expert, there are existing approvals that FDA has not captured in these regulations.

While prior-sanctioned substances cannot be regulated as food additives, FDA can override prior approval if it finds that a substance's use is "injurious to health" and, therefore, adulterated (21 CFR §181.1). At this time, 120 substances remain in the prior-sanctioned substances category based on those listed in the regulations.

Regarding the sample frozen meal, prior-sanctioned substances do not appear on the list of ingredients. However, it may contain other prior-sanctioned substances not required to be identified on the label such as FCSs and processing aids.

4. Color Additives are substances that are capable (alone or through reaction with other substances) of imparting color when added or applied to a food. The FFDCA requires FDA approval of all color additives, usually in response to a color additive petition (21 USC §321(t)(1)). The regulatory requirements for color additives are similar to those of food additives, but there are no GRAS or prior-sanctioned substance exceptions. This category does not include substances that FDA determines are used or intended to be used solely for purposes other than coloring. For example, cranberry juice will impart a red color when added to white grape and pear juice but is not regulated as a color additive if added for its flavor or juice content.

All color additives must be approved in order to be used in food. To approve a color additive, FDA publishes its approvals as regulations in the CFR after notifying the public via the *Federal Register* and providing an opportunity for the public to comment (21 USC §379e). The regulations appear at 21 CFR Part 73 for color additives exempt from certification, 21 CFR Part 74 for color additives subject to certification, 21 CFR Part 81 for provisional color additives, and 21 CFR Part 82 for certified provisionally listed colors. Certified colors are often referred to as "artificial food colors" or "synthetic colors" because they are synthesized from petroleum, tar, or other substances. FDA analyzes each batch of certified colors to ensure it complies with the standards in 21 CFR Part 80. Color additives exempt from certification are typically derived from plants or insects. From 2000 to 2010, FDA received only 4 color additive petitions for food uses.

Regarding the sample frozen meal, the color additives appear to be annatto, beta carotene, turmeric, and red cabbage extract because they are noted in the ingredients as colors. It does not contain any certified color additives.

5. Pesticide Chemicals or Residues are substances intended to prevent, destroy, repel, or mitigate any pest or to serve as a plant regulator, defoliant, or desiccant used in or on a raw agricultural commodity such as raw produce, grains, meat, or eggs or applied to food contact surfaces other than food packaging that has an ongoing antimicrobial effect on the surface (7 USC §136(u) and 21 USC §321(s)). This category is unusual because EPA, not FDA, makes the safety decision and approves the use of a pesticide as well as establishes a "tolerance" (the maximum allowable residue of the pesticide in food). EPA publishes its approvals as regulations in the CFR after notifying the public via the *Federal Register* and providing an opportunity for the public to comment (21 USC §346a). FDA is responsible for enforcing the tolerances (21 CFR §170.19 and §570.19) when pesticide chemical residues show up in processed agricultural commodities. Manufacturers may only use these substances in a manner consistent with a pesticide label approved by EPA and the tolerance (7 USC §136a).

Note that the line between pesticide chemicals or residues (regulated by EPA) and preservatives or antimicrobials (regulated by FDA as food additives or GRAS substances) is complicated and is based on a detailed understanding of their uses. For direct use on food, if applied to unprocessed food, the substance is regulated by EPA. If used on processed food, the substance is regulated by FDA. A food is still considered unprocessed if it is only being

washed, colored, waxed, hydro-cooled, refrigerated, shelled (if a nut), handled to removed leaves, stems, and husks, fumigated, or packed. A food is considered processed when it is canned, frozen, cooked, pasteurized, irradiated, milled, peeled, ground, chopped, sliced, or cut. For use on food contact surfaces, EPA regulates a substance controlling pests (including microbes) only if used on the surface of equipment such as a conveyor, grinder, or countertop, and the use provides an ongoing sanitizing effect on the surface. FDA regulates it if used on food packaging, does not have an ongoing antimicrobial effect, or penetrates beyond the surface (FDA 1999).

Unlike the tolerance levels for substances covered by other categories, pesticide chemicals or residue tolerances (and exemptions) must be regularly reassessed to determine their safety pursuant to amendments to the FFDCA made by the Food Quality Protection Act of 1996 (FQPA) (Public Law 104-170, Section 103) (7 USC §136a(g)). The U.S. Congress directed EPA to reassess the tolerances within 10 y of the original enactment (21 USC §346a(q)(1)) and further required a reassessment of all pesticide's safety by 2022 with an additional review every 15 y using the detailed and rigorous standards in the FQPA (7 USC §136a(g)(1)(A)). EPA completed its first round in 2007 reviewing 9721 tolerances for 581 pesticides (EPA 2011a).

Regarding the sample frozen meal, pesticide chemicals or residues may be present from pesticides used in or on produce or crops in the meal, such as the corn, wheat, sugar, spices, and soybeans, or from sanitizing the surfaces of equipment used to prepare the food. Pesticide chemicals or residues may be present but only below the tolerance limit established by EPA and do not have to be listed on the product's label.

6. Drugs in Animal Feed are substances intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in animals that are expressly approved by FDA (21 USC §§321(g) and 321(v)). Technically, this category only applies to drugs in animal feed that were approved after 1938, which essentially includes all approved drugs in animal feed (Cantin 2011). FDA publishes its approvals as regulations in the CFR after notifying the public via the *Federal Register* and providing an opportunity for the public to comment (21 USC §360b). The regulations appear at 21 CFR Part 556 for tolerances for residues of new drugs in animal feed in food, 21 CFR Part 558 for new drugs in animal feed for use in animal feeds, and 21 CFR §516.1215 for conditional approval for one minor animal species—catfish.

Regarding the sample frozen meal, drugs in animal feed such as antibiotics and arsenic-based substances may have been used in the chicken feed to prevent disease and promote growth. These substances are not required to be listed on the product's label.

7. Dietary Supplements are products, other than tobacco, intended to supplement the diet that bear or contain one or more "dietary ingredients." These products are not intended to serve as a conventional food or as the sole item of a meal. They are intended to maintain structure and function of the body but not remedy a specific disease or illness. The dietary ingredients in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites (21 USC §321(ff) and FDA 2009c). A manufacturer must notify FDA of new dietary ingredients (any dietary ingredient not sold in the U.S. before October 15, 1994). However, it does not need FDA's review or approval before marketing or selling them in the United States if the new dietary ingredient has been in the food supply in a form that has not been chemically altered (21 CFR Part 190). If the new dietary ingredient is not eligible for this exemption, the company must submit a premarket notification prior to introducing into commerce a dietary supplement containing the new dietary ingredient. FDA has 75 d to review the notification and will reject the notification when it fails to provide the necessary safety information (21 U.S.C. §350b(a)). An absence of a response from FDA does not constitute a finding by the agency that a new dietary ingredient or dietary supplement that contains a new dietary ingredient is safe or not adulterated (21 CFR Part 190).

FDA may determine that a dietary supplement or dietary ingredient is adulterated and block its marketing or sale if the agency finds that the ingredient or supplement

A. "presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use";
B. "is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury";
C. is declared by the Secretary [of the Department of Health and Human Services] "to pose an imminent hazard to public health or safety . . . [in which case] the Secretary shall promptly after such declaration initiate a proceeding . . . to affirm or withdraw the declaration"; or
D. "is or contains a dietary ingredient that renders it adulterated . . ." (21 USC §342(f) and 21 USC §334).

Some of the substances categorized as dietary ingredients may also be categorized as food additives or GRAS substances if added to conventional foods. The essential difference is that dietary supplements are not conventional foods or the sole item of a meal or diet.

Regarding the sample frozen meal, dietary supplements or ingredients are not present because the meal is conventional food.

In summary, a single meal is likely to contain substances belonging to each of the categories and subcategories described above. Referring back to the microwave-ready, frozen children's dinner meal, half of the 68 ingredients identified on the label were common food ingredients in use before 1958. The remainder included 16 FDA-affirmed GRAS substances, 8 FDA-listed GRAS substances, 4 direct food additives, 4 color additives (including red cabbage extract approved as a vegetable juice), and 3 apparent manufacturer self-determined GRAS substances.

Although a substance used in food must fall under one of the previous categories and subcategories, there are situations when a substance may be present in food but not fit into one of the categories. This could occur, for example, because there was no intent to use it. These substances are generally considered contaminants. They may be naturally occurring ones, such as aflatoxins on peanuts, or they may be so widespread in the environment that they often end up in food products. Contaminants are not subject to the food additive definition. FDA regulates contaminants under the general adulteration provisions of 21 USC §342(a)(1). Formal tolerance for unavoidable contaminants can be established under 21 USC §346. Examples of unavoidable contaminants are mercury, a common contaminant in fish, and polychlorinated biphenyls (PCBs) and lead which can enter from FCSs. FDA has set a formal tolerance under 21 USC §346 for only one contaminant, PCBs (21 CFR §109.30). It also set labeling requirements for ornamental and decorative ceramic ware that contains lead to warn against use for food-handling purposes (21 CFR §109.16).

As should be clear, FDA's food additive regulatory program has evolved significantly since the U.S. Congress first established it

over 50 y ago. The program was complex from the beginning and has become more so as FDA crafted alternatives to respond to new scientific developments, to make the program more rigorous, and to make it more efficient to administer.

Safety Determination Standards

The U.S. Congress requires that manufacturers and FDA (and, for pesticides, EPA) ensure that substances added to food are safe (21 USC §331 and §342). Whether FDA, EPA, an association, or a manufacturer makes the final decision about a substance's safety, understanding the standards that will be used to make the safety determination is crucial.

In the Food Additives Amendment of 1958, the U.S. Congress required that FDA deny a petition to approve a food additive "if a fair evaluation of the data . . . fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe" (21 USC §348(c)(3)). The U.S. Congress stated that "the term 'safe' as used . . . has reference to the health of man or animal" (21 USC §321(u)). Given this vague definition, the U.S. Congress established limits and factors for FDA to employ in making a decision on whether or not to allow a substance in food. These limits and factors include:

- **Mandatory Factors.** Under the law, FDA shall consider:
  - "The probable consumption of the additive and of any substance formed in or on food because of the use of the additive;
  - [T]he cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet; and
  - [S]afety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data" (21 USC §348(c)(5)).
- **Cancer.** "No additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal" (21 USC §348(c)(3)(A)). This is commonly known as the Delaney Clause—named after U.S. Congressman James Delaney from New York who sponsored the measure in 1958.
- **Tolerance Limits.** If the maximum amount of a substance that can be found or used in food is not safe, then FDA must establish a tolerance limit to assure safety. The tolerance limit (other than for pesticides) must also not be higher than "reasonably required to accomplish the physical or other technical effect for which such additive is intended" (21 USC §348(c)(4)).

Unfortunately, these limits and factors do not provide a clear framework for determining safety. FDA has interpreted the statutory requirements to better define this framework, in some cases employing the legislative history for assistance, and effectively creating 3 elements of the safety standard that FDA and manufacturers must use to make the safety determination. Table 3 summarizes how the 3 elements apply to each of the categories and subcategories.

- **Must be reasonably certain of no harm.** While the language of the Food Additives Amendment of 1958 was not entirely clear on the definition of safety, its legislative history is more illuminating. The key piece of legislative history is the Senate Committee on Labor and Public Welfare Report entered into the U.S. Congressional Record on August 18, 1958. Describing the concept of safety, the report states "[s]afety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not—and cannot—require proof beyond any possible doubt that no harm will result under any conceivable circumstance." In addition, the committee report also states that "in our opinion the bill is aimed at preventing the addition to the food our people eat of any substances the ingestion of which reasonable people would expect to produce not just cancer but any disease or disability" (U.S. Senate Committee on Labor and Public Welfare 1958). Based on this legislative history, FDA defined safe or safety to mean "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use" and applied this definition to all food additives and GRAS substances (21 CFR §170.3(i); Rulis and Levitt 2009).

  This definition has endured and become synonymous with safety in foods under FDA's jurisdiction. It is important to note that this definition does not balance the risks and the benefits of a substance. The benefits must not be considered (61 FR 3119, January 20, 1996; Rulis and Levitt 2009). The definition does not define "harmful," but based on the legislative history, FDA considers harm to be "the capacity to injure or otherwise damage the health of individuals consuming the additive" (61 FR 3119, January 20, 1996). Most substances added to food must meet this standard. The 2 major exceptions: drugs in animal feed and prior-sanctioned substances. For drugs in animal feed, FDA must find that the drug is safe and effective—essentially a risk-benefit analysis of the impact on the animal's health (21 USC §321(v) and 64 FR 40746, July 28, 1999). However, any drug residue in human food would be evaluated for safety for humans and the food could be deemed adulterated if the residue was found unsafe (21 USC §360b). Prior-sanctioned substances were essentially grandfathered into the program because of their approval before 1958, and the standard for their pre-1958 approval is unknown. FDA has the authority to reverse the original decisions regarding prior-sanctioned substances to ensure the use is reasonably certain not to be harmful, but it must do so through rulemaking (21 CFR §181.1).

  The definition of safety is more stringent for 2 categories: pesticide chemicals or residues and color additives. For pesticide chemicals or residues, under rigorous amendments added by the Food Quality Protection Act of 1996, EPA must also consider nondietary exposure for which there is reliable information and must ensure protection of infants, children, and other vulnerable subpopulations (21 USC §346a). For color additives, FDA defined safe to mean that there must be "convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive" (21 CFR §70.3(i)). Convincing evidence is required for colors in food, but that term is not explicitly used for other substances added to food.
- **Must not cause cancer in animals or humans.** The Delaney Clause applies to color additives and to food additives. It does not apply to prior-sanctioned substances, dietary supplements, and pesticide chemicals and their residues. Prior-sanctioned substances were approved before the Delaney Clause was adopted in 1958. For pesticides, the U.S. Congress amended the definition of food additive to exempt

Table 3–Current safety standards for substances added to food

Category and subcategory	Safety standards: Must be reasonably certain of no harm[a]	Safety standards: Must not cause cancer in animals or humans[b]	Safety standards: Must use Good Manufacturing Practices (GMP)[c]	Who makes and reviews the safety decision?	Does public have[d] opportunity to comment before decision made?[d]
Food additives					
Direct food additives	Yes	Yes	Yes	FDA	Yes
Indirect food additives					
Radiation sources	Yes	Yes	Yes[e]	FDA	Yes
Substances covered by food contact substance (FCS) notifications	Yes	Yes	No	Manufacturer with FDA review	No
FCSs below threshold of regulation[f]	Yes	Yes[g]	No	Manufacturer with FDA review	No
"Generally recognized as safe" (GRAS) substances[h]					
Common food ingredients in use before 1958	Yes	Yes[i]	Yes	FDA and manufacturer	No
Manufacturer self-determined	Yes	Yes[i]	No	Manufacturer with no FDA review	No
Association expert panel-determined	Yes	Yes[i]	No	Expert panel for association	No
FDA-listed FDA-affirmed	Yes	Yes[i]	Yes	FDA	Yes
Substances covered by FDA-reviewed GRAS notifications	Yes	Yes[i]	No	Manufacturer with FDA review	No[j]
Prior-sanctioned substances	No	No	Yes	FDA or USDA before 1958	No
Color additives	Yes with convincing evidence	Yes for human/Limited for animal feed[k]	Yes	FDA	Yes
Pesticide chemicals or residues	Yes[l]	No	Yes	EPA	Yes
Drugs in animal feed	Generally yes[m]	Limited[n]	Yes	FDA	Yes
Dietary supplements	No[o]	No	Yes	Manufacturer with FDA review for new dietary ingredients	No

[a] Specifically, "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use" (21 CFR §170.3(i)).
[b] Specifically, the Delaney Clause states "[n]o additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests, which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal" (21 USC §348(c)(3)(A)).
[c] If the relevant rules did not contain an explicit requirement to use GMP, the item was marked "no."
[d] "Yes" means FDA systematically provided a notice of the opportunity to comment and made relevant information available to the public before the agency made a final decision. Regulations always have this opportunity.
[e] GMP is specified for ionizing radiation only (21 CFR §179.25).
[f] For FCS below the Threshold of Regulation Substances, FDA presumes there are no health or safety concerns if a substance has not been shown to be a carcinogen and the exposure is less than 1.5 micrograms per person per day or if the substance is currently regulated as a direct additive and would be used at or below 1% of acceptable daily intake (ADI). FDA may rebut the presumption if the proposed use "may pose a public health risk" (21 CFR §170.39).
[g] For FCS Below the Threshold of Regulation Substances, the prohibition against carcinogenicity is more stringent than the Delaney Clause. 21 CFR §170.39(a)(1) states that a FCS below the threshold of regulation cannot have been shown to, "be a carcinogen in humans or animals, and there is no reason, based on the chemical structure of the substance, to suspect that the substance is a carcinogen." There are additional limits on carcinogenic impurities as well.
[h] For substances not used before 1958, assessment by "scientific procedures shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data." Assessment based on common use in food before 1958 "shall ordinarily be based upon generally available data and information" (21 CFR §170.30(b) & (c)).
[i] Delaney Clause is an element of safety and Congress intended GRAS substances to be at least as safe as food additives.
[j] For FDA-reviewed GRAS notifications, FDA typically posts the notice on its website and informally accepts comments. The 1997 proposed rule does not require this posting.
[k] Color additives may not induce cancer when ingested by man or animal (21 USC § 379e(b)(5)(B). The Delaney Clause extends not only to the color additive but any component or impurity that is the causative agent for the cancer (21 CFR §70.50). In animal feed, color additives are exempt from the Delaney Clause where no measureable residues in food producing animals can be found (21 USC §379e(b)(5)(B)).
[l] For pesticide chemicals or residues, EPA must also consider aggregate exposure to the chemicals and residues including all anticipated dietary exposures and all other exposures for which there is reliable information (21 USC §346a(b)(2)(A)(ii)).
[m] For drugs in animal feed, safety is not defined. The drug in animal feed must be safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling (21 USC §321(v)).
[n] Delaney clause does not apply for drugs intended for nonfood producing animals and for drugs intended for use in food producing animals with short-term therapeutic use that leave no measureable residues (21 USC §348(c)(3)(A)).
[o] For dietary supplements, FDA may block the marketing or sale for several reasons including whether it "presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use" (21 USC §342(f)).

pesticide residues in processed foods from the definition, and therefore from the Delaney Clause, in the Food Quality Protection Act of 1996 (Public Law 104-170, 110 Stat. 1489) as part of a major rewrite of existing pesticide standards (Section 402 of FQPA).

The Delaney Clause also partially applies to animal drugs and color additives used in animal feed or pet food. In the 1960s, Congress allowed carcinogens to be added to animal feed if the substance is not harmful to the animal. If the animal is used for human food, then no residue is allowed in any edible portion of the animal after slaughter or in any food derived from the living animal based on approved measurement methods (21 USC §348; 21 USC §379e(b)(5)(B)).

Based on the authors review of the legislative history, since the Delaney Clause is an element of safety and Congress intended GRAS substances to be at least as safe as food additives, GRAS substances are subject to the requirements of the Delaney Clause (U.S. Senate Committee on Labor and Public Welfare 1958). However, at least one expert has informally indicated to the authors that the Delaney Clause is not an element of safety and, therefore, only applies to food additive petitions.

- **Must use Good Manufacturing Practices (GMP).** All substances must be made consistent with the general GMP requirements contained within 21 CFR Part 110 to ensure that the food is sanitary and clean. FDA has interpreted the statutory requirements regarding tolerance limits to mandate the use of additional GMP for most substances added to food (21 USC §346 and §346a). While many of the regulations for specific substances use the term GMP without defining it, FDA has defined the term for some types of substances. Some examples include:

- *Direct food additives*. GMP means:
  - The quantity of the substance added to food does not exceed the amount reasonably required to accomplish its intended physical, nutritive, or other technical effect in food.
  - Any substance intended for use in or on food is of appropriate food grade (USP 2011) and is prepared and handled as a food ingredient (21 CFR §172.5).
- *FDA-affirmed GRAS substances (indirect additives only)*. GMP includes the following restrictions:
  - The quantity of any food additive substance that may be added to food as a result of use in articles that contact food shall not exceed, where no limits are specified, that which results from use of the substance in an amount not more than reasonably required to accomplish the intended physical or technical effect in the food contact article; shall not exceed any prescribed limitations; and shall not be intended to accomplish any physical or technical effect in the food itself, except as such may be permitted by regulations.
  - Any substance used as a component of articles that contact food shall be of purity suitable for its intended use.
  - Must not render food injurious to health or otherwise unfit for consumption (21 CFR §174.5).
- *Pesticide chemicals or residues*. GMP essentially means removing any residue from the raw agricultural commodity during processing, such as by peeling or washing and so long as the concentration of the residue in the processed food when ready to eat is not greater than the tolerance prescribed for the raw agricultural commodity (unless the higher level is covered by a tolerance prescribed for the processed food) (21 CFR §170.19).

FDA explicitly requires GMP for most categories of substances added to food. For substances covered by a notification for FDA review, while there are no explicit GMP requirements, FDA believes that the contents of the submissions and, therefore the safety review, define GMP. There are no explicit GMP requirements for

- non-ionizing radiation sources;
- manufacturer self-determined GRAS substances; and
- association expert-panel determined GRAS substances.

However, the safety standards themselves are only a part of the safety equation: who makes the safety decision and whether the public has an opportunity to review and comment on the potential decision may be just as important because the standard contains ambiguities, especially regarding the terms "harm," "harmful," "reasonable," "convincing," and "competent." While there is extensive FDA guidance as well as legal and scientific precedent explaining which studies are needed and how they should be conducted to evaluate the safety of a substance that help reduce the ambiguities, the guidance and, to some extent, the precedent are not binding on manufacturers, especially when they make a safety decision without FDA review (FDA 2007). Agency and public scrutiny are generally expected to increase the quality and thoroughness of the decision, especially when industry competitors, academics, and public interest organizations have an opportunity to critique the petition or notification and impact FDA's decision. The fifth column in Table 3 explains who makes the decision. The sixth column describes whether the public, including the industry and public interest stakeholders, have an opportunity to comment before the decision is made. Only the rulemaking process provides the public with a formal opportunity to comment. While FDA does not provide a systematic opportunity to comment on notifications it receives for review, FDA has adopted the practice for voluntary GRAS notifications only by posting the notice for public review before posting its final decision.

Number of Affirmative Safety Decisions and Substances Allowed for Human Food

With a solid understanding of the types and origins of affirmative safety decisions made, understanding the prevalence of the categories and subcategories provides useful context. However, quantifying the prevalence of the different categories and subcategories of substances added to food within the regulatory system is difficult. FDA does not track every substance that is added to food, which makes it impossible to calculate with certainty the exposure to such substances and whether such exposures present any risk. The authors concluded that the best metrics to understand prevalence are estimates of the number of current affirmative safety decisions as a measure of regulatory activity and the number of substances allowed based on those decisions as a measure of how many substances consumers might encounter in their food.

The authors developed 4 methods to estimate the number of affirmative safety decisions made and the number of substances currently allowed in human food. The methods apply to human food and not animal feed or pet food because it is difficult to make an estimate from the AAFCO ingredient definitions (described in Section "Categories and Subcategories of Substances Added to Food"). Section "Methodology" describes each method in more detail.

All estimates are based on the information available as of January 11, 2011. A summary of each method follows:

- **CFR Sections Method.** The number of current CFR sections provides a rough estimate of the number of affirmative safety decisions FDA and EPA have made for color additives, drugs in animal feed, pesticide chemicals or residues, prior-sanctioned substances, direct food additives, indirect food additives, FDA-listed GRAS substances, and FDA-affirmed GRAS substances. For these categories and subcategories, FDA's decision to allow the use of a substance in human food is promulgated as a regulation and codified in the CFR. The number of unique CAS numbers referenced in the CFR sections for a category or subcategory provides a reasonable estimate of the number of substances allowed. It is important to note that one CFR section may contain more than one substance. Because one CFR section may contain more than one substance, it is important to note that when trying to understand FDA's role in allowing or reviewing substances coming to market, looking at the number of substances together with the number of decisions provides the most useful view. In many cases, a single CFR section with multiple substances constituted one decision, however there are some instances where additional substances were added to a CFR section through an additional decision. For this reason, the authors believe their method of counting decisions undercounts FDA's role to a modest degree. In contrast, the authors' method of counting substances overcounts FDA activity since a single CFR section may cover hundreds of substances.
- **Notifications to FDA Method.** The number of "no question" or "no objection" determinations to the notifications submitted by manufacturers of their affirmative safety decisions provides an excellent estimate of the number of

affirmative decisions made by FDA for substances covered by FCS notifications and FDA-reviewed GRAS notifications as well as FCSs below the threshold of regulation. For these subcategories, FDA evaluates notifications and publishes its determinations on its website. The number of substances is based on the number of affirmative decisions after eliminating duplicates.

- **FEMA Reports Method.** To determine the number for the association expert panel subcategory, the authors referred to the FEMA expert panel that makes safety decisions for flavors and extracts such as spices that may be GRAS substances. It publishes affirmative decisions in *Food Technology Magazine.* The number of affirmative decisions and substances allowed were drawn from these reports. The FEMA panel has been making safety decisions since the early 1960s.
- **Author Estimate Method.** To determine the number of manufacturer self-determined GRAS substances approved for use, the authors interviewed several consultants for and representatives of the food industry and obtained their private estimates of manufacturer GRAS self-determinations. The authors complemented these interviews with a review of various notifications and reports. The rough estimate produced through this method is as follows: 1000 current affirmative safety decisions on 1000 current substances allowed. Based on discussions with experts, the number of decisions is unlikely to be lower than 500 of each decisions and substances and could be several times larger.

Note that the following categories and subcategories were not included in Table 4 or the estimates for the reasons provided:

- *Dietary supplement category.* Because any dietary ingredients in use before 1994 do not need to be reported to FDA, any estimate of the number of these substances would be speculative. Based on a review of GRAS notifications to FDA, some of these substances are also allowed in human food.
- *Radiation sources subcategory of food additives.* This category covers sources of energy and does not represent substances added to food. There are 6 CFR sections covering 13 types of sources.
- *Common food ingredients in use before 1958 (subcategory of GRAS substances).* These are common food ingredients such as flours, vinegar, fruits, vegetables, and meat of natural biological origin that were commonly used before 1958 that FDA gave a blanket approval to in its rules without identifying specific substances (21 CFR §182.1 for human food and 21 CFR §582.1 for animal feed).
- *Drugs in animal feed.* These substances are used in animal feed or pet food.

Based on the 4 methods described above, Table 4 provides the estimated number of current affirmative safety decisions that allow substances to be used in food (column 2) and the estimated number of substances currently allowed to be used in food (column 3) in the United States. The categories of substances are in shaded cells with bold typeface and the subcategories of substances are in unshaded cells. The relative contribution of each category or subcategory to the overall totals is listed in parentheses. The estimates may add up to more than 100% due to rounding. The table also explains where the decisions are published (if published).

As of January 11, 2011, the authors estimated 6204 current affirmative safety decisions allowing substances to be used in food. More than 2/3 of the decisions dealt with GRAS substances. Food additives made up 20% of the total decisions. Association expert panel-determined GRAS substances constituted 63% of all GRAS substance decisions and 44% of all decisions. Within the food additives category, decisions regarding FCS notifications made up 69% of all food additives. Substances other than food additives and GRAS substances made up the remainder.

Regarding the number of substances currently allowed in food, the authors estimate that 10787 were allowed as of January 11, 2011. Whereas food additives made up 21% of all decisions, they constitute nearly half of all substances. This increase is largely due to indirect food additives which made up only 3% of all decisions but 28% of all substances. The difference is primarily the result of the long lists of substances in individual CFR sections. For example, one CFR section, 21 CFR §175.105, for adhesives covered 1266 substances. More than 11 CFR sections covered more than 100 substances each. FDA used this approach most often on listings from the 1960s. GRAS substances constituted only 43% of the total, while the other substances constituted less than 8% of the total. Within the GRAS substances category, the association expert panel-determined GRAS substances subcategory constituted 25% of the total number of substances.

Figure 1A provides a visual representation of the estimated 6204 current affirmative safety decisions grouped by who made the final safety determination (see Table 3, column 5, and Table 4, column 2). The size of each slice is based on its relative contribution to the total. The "Flavors and Extract Manufacturers Expert Panel Determined" slice represents the 2702 affirmative safety decisions made by that association's expert panel. The "Manufacturer Determined" slice represents the estimated 1000 self-determinations made by manufacturers that were not submitted to FEMA or FDA for review or approval. The "Federal Agency Reviewed or Approved" slice represents the 2502 affirmative safety decisions in the remaining categories and subcategories including FDA decisions promulgated as CFR sections, FDA or USDA prior sanctions, FDA reviews of manufacturers' FCS or GRAS notifications that result in "no question" or "no objection" letters from the agency, and EPA pesticide decisions. FDA made 1921 of the 2502 federal agency decisions with EPA making the remainder. FDA was credited with the prior-sanctioned substance decisions promulgated as CFR sections by the agency even if USDA may have made the initial decision before 1958. Overall, federal agencies make or review 40% of all current affirmative safety decisions. FDA has made 40% fewer decisions than the FEMA expert panel.

Figure 1B expands on Figure 1A by providing details on the "Federal Agency Reviewed or Approved" slice. There are 3 main subgroups in this slice separated by the extended lines: "FDA GRAS Substances," "FDA Food Additives," and "Other FDA Substances." Other FDA Substances consists of color additives, prior-sanctioned substances, and EPA-approved pesticide residues (which FDA enforces). The size of each of these subgroup's slices is based on the relative contribution to the estimated 6204 current affirmative safety decisions. The 1275 FDA food additive safety decisions make up slightly more than half of all 2502 federal agency-reviewed decisions. Decisions involving FDA GRAS substances and EPA approved pesticide residues each represent 23% of the federal agency-reviewed decisions. Color additives and prior-sanctioned substances constitute the balance.

To show the changes to FDA's review of GRAS substances and indirect food additives/FCSs over more than 50 y, the authors added segments to the relevant slices marking significant dates on the axis starting with 1958 in the center and 2011 on the outer

Table 4–Number of current affirmative safety decisions and number of substances currently allowed in human food as of January 11, 2011.

Category and subcategory (human food only)	Estimated nr of affirmative decisions (% of total)	Estimated nr of substances allowed (% of total)	Estimation method[a]	If decision is published, where is it published?
Food additives	**1275 (21%)**	**5292 (49%)**		
Direct food additives	230 (4%)	1483 (14%)	CFR Sections	21 CFR Parts 172, 173, 180, and 189
Indirect food additives	171 (3%)	3007 (28%)	CFR Sections	21 CFR Parts 174 to 178
Substances covered by food contact substance(FCS) notifications	773 (13%)	701(7%)	Notifications to FDA	FDA publishes its decision but not the manufacturer notification on its website
FCSs below threshold of regulation	101 (1.6%)	101 (0.9%)	Notifications to FDA	FDA publishes its decision but not the manufacturer notification on its website
"Generally recognized as safe" (GRAS) substances	**4284 (69%)**	**4646 (43%)**		
Manufacturer self-determined	1000 (16%)	1000 (9%)	Authors Estimate[b]	Not published
Association expert panel-determined (flavors and extracts only)	2702 (44%)	2702 (25%)	FEMA Reports[c]	Panel publishes periodically in *Food Technology Magazine*[d]
FDA-listed	85 (1.4%)	437 (4%)	CFR Sections	21 CFR Part 182
FDA-affirmed	230 (4%)	270 (3%)	CFR Sections	21 CFR Part 184
Substances covered by FDA-reviewed GRAS notifications	267 (4%)	237 (2%)	Notifications to FDA	FDA publishes its decision and the manufacturer's notification on its website
Prior-sanctioned substances	**12 (0.2%)**	**120 (1.1%)**	CFR Sections	FDA lists known decisions at 21 CFR Part 181
Color additives	**52 (0.8%)**	**148 (1.4%)**	CFR Sections	21 CFR Parts 70 to 82
Pesticide chemicals or residues	**581 (9%)**	**581 (5%)**	CFR Sections	EPA posts at 40 CFR Part 180
Overall total	**6204 (100%)**	**10787 (100%)**		

Notes:
See Section "Categories and Subcategories of Substances Added to Food" for explanation of categories and subcategories.
Shaded cells with bold typeface represent numbers in each category and percentages of total decisions or substances.
Unshaded cells represent numbers in each subcategory and percentages of total decisions or substances.
[a] See Section "Methodology" for a detailed description of estimation methodology.
[b] Based on the authors' discussions with manufacturers and their consultants. See Section "Methodology" for more information.
[c] Expert panel established in the early 1960s by the Flavor and Extract Manufacturers Association (FEMA).
[d] Based on the 24th report which was published in June 2009.

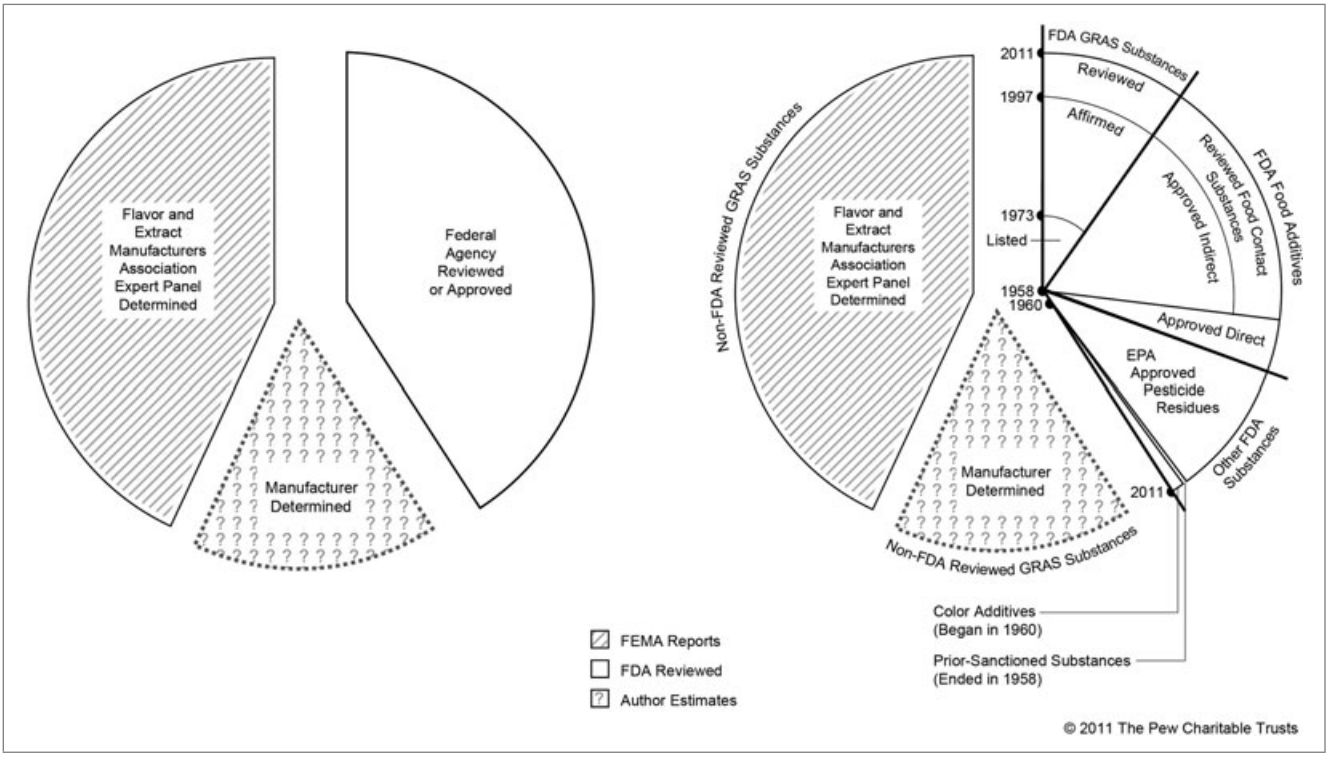


Figure 1–(A) Relative contribution to the total estimated number of current affirmative safety decisions for substances in human food grouped by organization making the final decision. (B) Relative contribution to the total estimated number of current affirmative safety decisions for substances in human food grouped by organization making the final decision and showing the relative contribution of the specific categories and subcategories in the "federal agency reviewed or approved" slice with significant dates along the axis with 1958 in the center and 2011 at the outer perimeter.

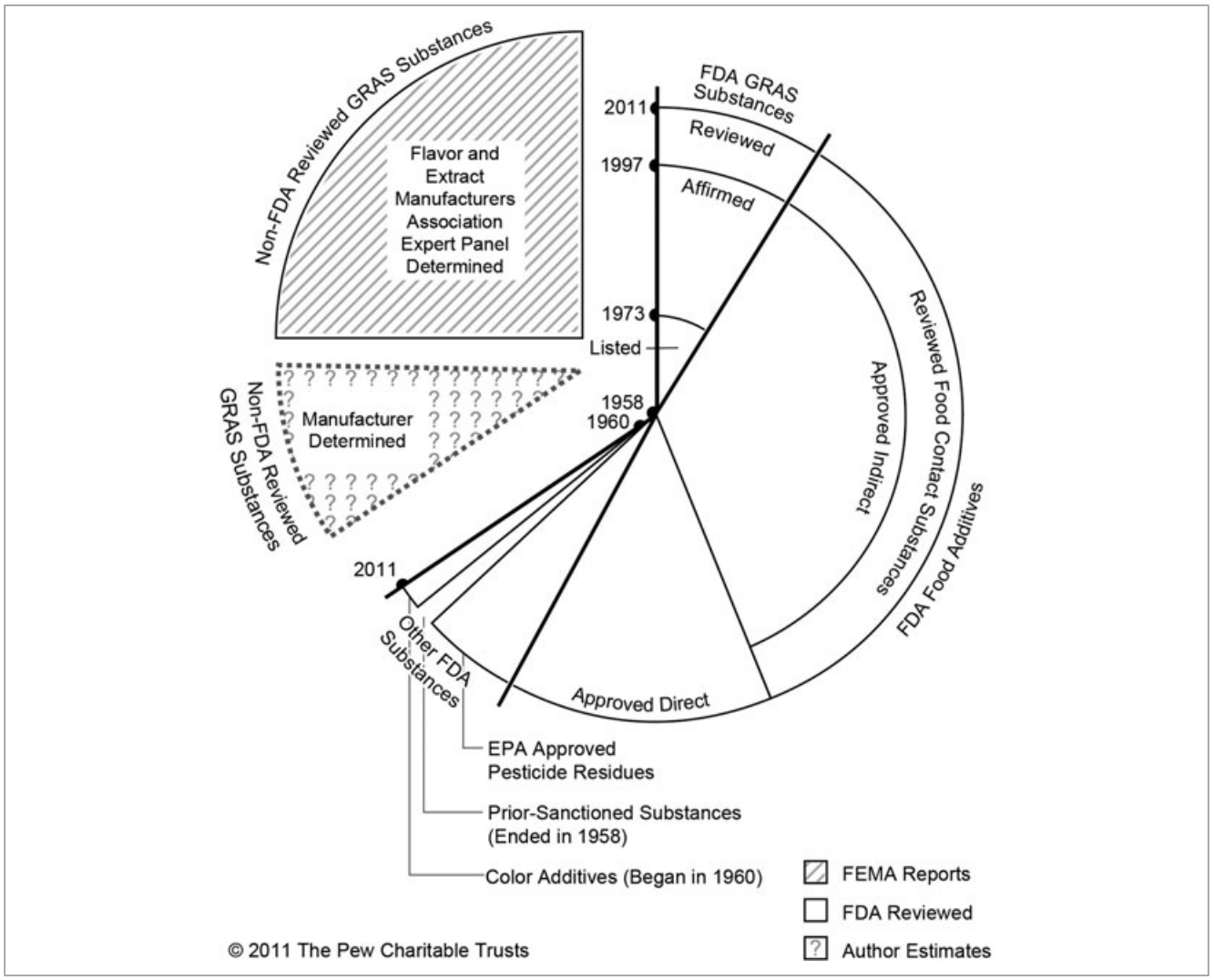


Figure 2–Relative contribution to the total estimated number of substances currently allowed in human food grouped by organization making the final decision and showing the relative contribution of the specific categories and subcategories in the "federal agency reviewed or approved" slice with significant dates along the axis with 1958 in the center and 2011 at the outer perimeter.

perimeter. FDA approved listings of GRAS substances in CFR sections from 1958 to 1973 (identified as "Listed"). The agency shifted to affirming substances as GRAS in CFR sections from 1973 to 1997 (identified as "Affirmed") and replaced the affirmation process with a review of voluntary GRAS notifications begun in 1997, where decisions were documented by letters to the manufacturer and a posting on FDA's website instead of CFR rules (identified as "Reviewed"). For indirect food additives and FCSs, FDA approved indirect food additives in CFR sections from 1958 to 1997. Although it has continued to use this process since 1997, FDA largely replaced it with the FCSs below threshold of regulation subcategory in 1995 and the FCS notification subcategory enacted by the U.S. Congress in 1997 and operational in 2000. For simplicity, the authors grouped these changes together and used 1997 to identify their general beginning.

Figure 2 is similar to Figure 1B. The distinction is that the size of the slices is based on the number of substances current allowed rather than the number of current affirmative safety decisions. The slices change dramatically when estimating the number of substances allowed in food, excluding common food ingredients. FDA decisions covered approximately 66% of the estimated 10787 substances. The discrepancy between the number of safety decisions and the number of substances exists because a single CFR section may contain multiple substances.

Manufacturer's Postmarket Responsibilities

Once a substance is determined to be safe for its intended use by the appropriate decision-maker, as described in the previous sections, a manufacturer must fulfill certain postmarket responsibilities. While all manufacturers have a general duty to ensure their food products are not poisonous or deleterious, important distinctions exist between the responsibilities specific to each category of substances added to food (21 USC §331 and §342).

There are 4 major types of postmarket responsibilities that manufacturers must comply with and these responsibilities are summarized in Table 5:

A. Comply with conditions used as the basis of the safety determination. Generally, a manufacturer must ensure that it complies with the conditions used as the basis of the safety determination. For example, if the safety determination was explicitly based on a particular manufacturing process, the manufacturer must use that process. Similarly, if the decision was based on a

Table 5–Summary of manufacturer's postmarket responsibilities.

Category and subcategory	Comply with conditions used as basis of safety determination	Conduct hazard analysis for food facilities[a]	Report new research on hazards[b]	Report adverse health reactions
Food additives				
Direct food additives	Yes, per CFR section	Confirm use is approved[c]	No	If serious[d]
Indirect food additives				
Substances covered by FCS notifications	Yes, per FDA's decision and manufacturer's notification[e]	Only if handling food other than FCSs[f]	No	If serious and handling food other than FCSs[d,f]
FCSs below threshold of regulation				
GRAS substances				
Manufacturer self-determined	Yes, per its safety decision[e]	Confirm use is approved[c]	No	If serious[d]
Association expert panel-determined	Yes, per panel's safety decision[e]			
FDA-listed	Yes per CFR section[e]			
FDA-affirmed	Yes, per CFR section[g]			
Substances covered by FDA-reviewed GRAS notification	Yes, per FDA decision and manufacturer's notification[e]			
Prior-sanctioned substances	Yes, per CFR section or USDA or FDA approval[e]	Confirm use is approved[c]	No	If serious[d]
Color additives	Yes, per CFR section	Confirm use is approved[c]	No	If serious[d]
Pesticide chemicals or residues	Yes, per CFR section	Required	Yes	Yes
Drugs in animal feed	Yes, per CFR section	Required	No	Yes
Dietary supplements	Yes	Yes	No	If serious adverse event[h]

[a] Based on the FDA Food Safety Modernization Act (Public Law 111-353), 21 USC §350g requires hazard analysis. FDA is developing regulations to implement these requirements (75 FR 81536, December 28, 2010).
[b] Research results received after the safety decision or approval is final.
[c] FSMA states that hazard analysis only applies to "unapproved food and color additives" (21 USC §350g(b)(1)(A)). The word "unapproved" suggests that facilities may need to confirm that all substances added to food are allowed by the food additive regulatory program.
[d] Report to FDA "if reasonable probability of serious adverse health consequences" (21 USC §350f).
[e] However, a manufacturer is not prohibited from making a safety determination for a FCS below the threshold of regulation or GRAS substance (other than an FDA-affirmed GRAS substance with specific limitations) that is contrary to the existing one, as long as the determination meets the requirements for GRAS status.
[f] Requirement only applies to persons with registered food facilities. It does not include facilities that only handle pesticides or FCSs (21 USC §350f and 21 CFR §1.227(a)).
[g] If rule sets a specific limitation for substance in food, the limit is binding (21 CFR §170.30(i) & (j)).
[h] If dietary supplement, serious adverse events must be reported. Those events are those that result in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect; or requires, based on a reasonable medical judgment, a medical or surgical intervention to prevent an outcome described above (21 USC §379aa-1(a)(2)).

maximum concentration or tolerance limit of a substance in food, the manufacturer must comply with those restrictions. If a safety determination is incorporated into a CFR section, the manufacturer must comply with the specific conditions in that section (21 USC §342, §348, and §331). However, there are limitations to this general approach:

- For prior-sanctioned substances, if a manufacturer does not want to comply with the conditions in the document sanctioning the use, it has the option of making a GRAS self-determination of safety even if this new decision contradicts the limitations in the document. In this situation, the substance's use would no longer be prior-sanctioned (21 CFR §181.5).
- For FDA-affirmed GRAS substances, where the substances are affirmed as GRAS with specific limitations, any variation from those limitations requires the filing of a food additive petition by a manufacturer. However, for GRAS substances other than FDA-affirmed GRAS substances with specific limitations (21 CFR §170.30(i) and (j)), if a manufacturer intends to use a substance in a manner not covered by the previously established conditions used as the basis for an existing safety determination, it may make a self-determination of safety even if this new decision differs significantly from the original safety determination. It may do so even for FDA-listed GRAS substances codified in the CFR.
- For food additives covered by a FCS notification or a below the threshold of regulation notification, FDA maintains a manufacturer is bound by the terms of its notification and FDA's decision. Note that in a representative no objection letter provided to the authors FDA recommended but did not require that the manufacturer notify the agency of modifications to the limitations or specifications in the notification (FDA 2011f).

However, an important qualification is that a manufacturer's self-determination must be one accepted by experts in the field. If FDA learns of the decision and disagrees with it, the agency could take enforcement action claiming the firm violated the law by introducing into commerce an unapproved food additive.

B. Conduct hazard analysis for food facilities. The FDA Food Safety Modernization Act passed in 2011 (FSMA) required food facilities to conduct a hazard analysis to identify and evaluate known and reasonably foreseeable hazards that may be associated with a facility (Public Law 111-353 Sec 103, 21 USC §350g). Based on a hazard analysis, a facility must undertake risk-based preventive controls. The hazard analysis requirement applies to "biological, chemical, physical, and radiological hazards, natural toxins, pesticides, drug residues, decomposition, parasites, allergens, and unapproved food and color additives" (21 USC §350g(b)(1)(A)). While facilities have always been required to ensure compliance with the rules, FSMA creates a requirement for a written analysis. The application of the word "unapproved" to "food and color additives" in the statute suggests that facilities now must have written documentation confirming that all substances added to food are allowed by the food additive regulatory program. The law requires FDA to promulgate regulations implementing and clarifying the requirements by July 2012.

C. Report on new research on hazards. For pesticide chemicals or residues, manufacturers are required to monitor and

report new research on hazards if "at any time after the registration of a pesticide the registrant has additional factual information regarding unreasonable adverse effects on the environment of the pesticide . . ." (7 USC §136d(a)(2)). See also 40 CFR §159.152(a) and §159.155(a). There is no similar requirement for food additives, GRAS substances, prior-sanctioned substances, color additives, or drugs in animal feed even if new research casts doubt about the original "reasonable certainty of no harm" determination.

D. Report adverse health reactions to FDA. The U.S. Congress requires that a "responsible party" report an article of food when "there is a reasonable probability that the use of, or exposure to, such article of food will cause serious adverse consequences or death to humans or animals" (21 USC §350f(a)(2)). Reports must be made through FDA's reportable food registry within 24 h. A responsible party is a person required to register a food facility pursuant to 21 USC §350d and §350f(a)(1). The term food facility includes parties responsible for food facilities that manufacture, process, or handle foods and food ingredients but excludes facilities that only handle FCSs or pesticides (21 CFR §1.227(b)(4)). Specific additional requirements for some categories of substance uses are as follows:

- for pesticide chemicals or residues, all "unreasonable adverse effects" rather than only serious adverse health effects must be reported (40 CFR Part 159); and
- for drugs in animal feed, records and reports of clinical and other experiences with a new animal drug must be maintained and immediately reported to FDA for any significant chemical, physical, or other change or deterioration in the drug (21 CFR §510.301).

In summary, a manufacturer's postmarket responsibilities for food additives, GRAS substances, prior-sanctioned substances, and color additives are very limited. Manufacturers generally must report to FDA situations where there is a reasonable probability of serious adverse consequences to humans or animals resulting from use of the food and, when FDA promulgates the rules, confirm that the substances are used as approved pursuant to the food additive regulatory program. They must also comply with the conditions of the safety decision. However for prior-sanctioned substances and GRAS substances (other than FDA-affirmed GRAS substances with specific limitations), a manufacturer may make a self-determination which deviates from the conditions of the original safety decision as long as the self-determination meets the requirements for GRAS status.

Manufacturers of pesticide chemicals and drugs in animal feed have greater and more specific responsibilities for those substances than manufacturers have for other substances added to food. Both categories require reporting of all adverse reaction, not just those with a reasonable probability of serious adverse consequences to human or animals. Manufacturers are required to monitor and report new research on hazards only for pesticide chemicals or residues.

Contrast the postmarket responsibilities for manufacturers under the food additive regulatory program with the requirements of the Toxics Substances Control Act (TSCA) (Public Law 94-469, 15 USC §2601 et seq.) for industrial chemicals and chemicals used in consumer products other than pesticides, food, drugs, and cosmetics described below. While the food additive regulatory program emphasizes premarket review and approval, TSCA relies on premanufacturing notices (PMN) for new chemicals (but not new uses of existing chemicals) and stronger postmarket responsibilities (described below) (15 USC §2604 and §2607). The PMN is similar to the requirement for food contact substance notifications by giving the agency an opportunity to object. Note that TSCA has a less stringent safety standard of "will present an unreasonable risk" instead of the reasonable certainty of no harm safety standard used in the food additive regulatory program (15 USC §2605). In addition to relying on an unreasonable risk standard rather than a strict safety standard, TSCA has been construed in an important court decision to, in essence, put the burden on the government to prove unreasonable risk (Corrosion Proof Fittings v. EPA, 947 F.2d 1201 (5th Cir. 1991)), whereas for food additives, the manufacturer must prove a reasonable certainty of no harm. Note that substances used in food may be covered by TSCA if they are used in nonfood situations as is relatively common for FCSs.

- **Substantial Risk Reporting.**

  TSCA §8(e) requires that, "Any person who manufactures, processes, or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment shall immediately inform the Administrator of such information unless such person has actual knowledge that the Administrator has been adequately informed of such information." (15 USC §2607(e))

  EPA applies this requirement broadly and allows manufacturers to submit formal notices and "For Your Information" (FYI) submissions where there may be some doubt as to the potential risk of a substance. EPA had received 1500 FYI notices as of 2006 (EPA 2011b).

  In contrast, FDA established its Reportable Food Registry in 2009. The registry requires that responsible parties notify FDA if "a reasonable probability that the use of, or exposure to, such article of food will cause serious adverse health consequences or death to humans or animals" (21 USC §350f). This requirement applies to facilities where food, including food additives but not FCSs, is manufactured, processed, packed, or held and which have registered with FDA (21 USC §§350d and 350f). Both FDA and EPA accept direct reports of adverse events from consumers (FDA 2009d; EPA 2010).

  The FDA requirement is significantly narrower than EPA's requirement under TSCA.

- **Allegations of Significant Adverse Reactions Recordkeeping.**

  TSCA §8(c) requires that, "any person who manufactures, processes, or distributes in commerce any chemical substance or mixture shall maintain records of significant adverse reactions to health or the environment, as determined by the Administrator by rule, alleged to have been caused by the substance or mixture. Records of such adverse reactions to the health of employees shall be retained for a period of 30 years from the date such reactions were first reported to or known by the person maintaining such records. Any other record of such adverse reactions shall be retained for a period of 5 years from the date the information contained in the record was first reported to or known by the person maintaining the record. Records required to be maintained under this subsection shall include records of consumer allegations of personal injury or harm to health, reports of occupational disease or injury, and reports or complaints of injury to the environment submitted to the manufacturer, processor, or distributor in commerce from any source. Upon request of

any duly designated representative of the Administrator, each person who is required to maintain records under this subsection shall permit the inspection of such records and shall submit copies of such records." (15 USC §2607(c))

These records shall include records of consumer allegations of personal injury or harm to health, reports of occupational disease or injury, and reports or complaints of injury to the environment submitted to the manufacturer, processor, or distributor in commerce from any source.

The FFDCA requires drug, dietary supplement, and medical device companies to track adverse events and report serious adverse events. Food establishments are required to report to FDA at the Reportable Food Registry website any occurrences where there is a reasonable probability that an article of food will cause serious adverse health consequences or death.

- **Unpublished Health and Safety Studies.** TSCA §8(d) authorizes EPA to promulgate rules requiring any person who manufactures, processes, or distributes or proposes to manufacture, process, or distribute in commerce any chemical substance, or mixture to submit unpublished health and safety studies (15 USC §2607(d)). FDA has no similar authority.
- **Use Reporting.** Pursuant to TSCA §8(b), EPA adopted its Inventory Update Rule Program for chemical substances (15 USC §2607(b) and 40 CFR Part 710). Under this rule, chemical manufacturers and processors submit to EPA every 4-y extensive production and use information for thousands of substances used in significant amounts in commerce (EPA 2011c). FDA lacks similar authority and has no means to systematically collect such information on usage. However, according to FDA, the agency monitors usage through a variety of data on common substances.

To further understand the limits of a manufacturer's postmarket responsibilities, compare the food additive regulatory program's requirements to FEMA's expert panel requirements. According to FEMA, manufacturers voluntarily participating in its program must submit use reporting information every 5 y to maintain the panel's approval. The panel uses this information to estimate exposure and trigger a review of its decision when exposure doubles over the 5 y. In addition, FEMA periodically reassesses its decisions—usually every 12 y—to determine if any new studies warrant a more detailed reassessment. In contrast, FDA has no system to reassess its food additive reviews other than responding to petitions requesting a change.

Trends in FDA Reviews for Human Food Since 1990

Before 1990, manufacturers choosing to seek FDA's review and approval of a food additive or a GRAS substance needed to submit a petition to the agency. If it approved the petition, FDA promulgated a new section in the CFR or changed an existing one. While FDA's approval was mandatory for food additives, it was not required for GRAS substances; however, manufacturers generally preferred FDA's approval for a GRAS substance because they found it generally reduced liability and made it easier to market, especially in a global economy.

In response to congressional and industry pressure to be more timely in the agency's decision process, starting in 1990 FDA developed a new approach which relies on notifications submitted by manufacturers that the agency reviews instead of petitions it approves. Pursuant to this new approach, the manufacturer makes the safety determination instead of FDA. The agency issues a letter summarizing its review, instead of adopting a new or modified regulation, and posts its decision on its website. The manufacturer's goal is to receive a "no objection" or "no question" letter since that effectively means the manufacturer has *de facto* authorization from FDA to market and sell a substance for use as described in the notification. If FDA has concerns about a notification, it issues an "insufficient basis" letter—implicitly rejecting the manufacturer's safety decision (Kahl 2010). Because FDA generally signals its intent to issue an "insufficient basis" letter before finalizing it, and it allows manufacturers to withdraw the petition to avoid a negative decision, manufacturers have, in all cases since 2002 of which the authors are aware, taken advantage of that option. FDA has issued no "insufficient basis" letters since 2001 while allowing 31 withdrawals (Kahl 2010). After withdrawal, manufacturers may elect to drop the product, conduct additional investigations in order to resubmit to FDA later or make a manufacturer's self-determination that the substance is GRAS—effectively bypassing FDA's review. This latter option presents the risk that FDA would take enforcement action claiming the firm introduced into commerce an unapproved food additive although the authors are not aware of any situations where that has occurred.

FDA designed the notification approach to facilitate quicker and more efficient reviews. A significant outcome was that the agency reduced transparency by avoiding rule-making, public notices, and requests for public comments for each notice. Nonconfidential portions of the notifications, including toxicity and exposure data, are available from FDA through the Freedom of Information Act (5 USC §552). FDA began the shift in 1990 by accepting submissions (notifications) for voluntary post-consumer recycled plastic in food contact articles (FDA 2011g). In 1995, the agency accepted notifications for "FCSs below the threshold of regulation." In 1997, the U.S. Congress embraced this approach and allowed notifications rather than petitions for all FCSs. The same year, FDA launched its voluntary GRAS notification program. And in 2000, FDA began accepting Food Contact Substance Notifications (FCNs). Each change is described in more detail below.

1. **Voluntary Post-consumer Recycled Plastic Submissions.** Recycled plastic can be an indirect food additive if its components may migrate into food. Since 1990, FDA has accepted voluntary submissions (notifications) from manufacturers who have determined that specific post-consumer recycled plastic processed in a specific manner is essentially the same as the original plastic material already allowed for food as an indirect additive and does not contain additional contaminants. If FDA's review finds the recycling process to be acceptable, such that the recycling process renders recycled plastic suitably pure for contact with food, it posts on its website a brief description of the substances involved, use limitations, the manufacturer submitting it, and contents of the "no objection" letter (FDA 2011g, 2011h). According to a leading expert, support for the request for a "no objection letter" typically involves intentionally contaminating plastic with surrogate chemicals representing categories of substances which might come into contact with the plastic during use by consumers. The recycling process must be demonstrated to remove these surrogate chemicals to a level of no safety concern. The agency does not post the original submission for the post-consumer recycled plastic. The decision applies only to the plastic processed in the manner described in the submission.
2. **FCSs below Threshold of Regulation Notifications.** In 1995, FDA began accepting exemption requests from

manufacturers essentially establishing the "FCSs below threshold of regulation" subcategory discussed in Section "Categories and Subcategories of Substances Added to Food." FDA designed the program for manufacturers that have determined that substances in food contact articles they produce are highly unlikely to present any health or safety concerns (21 CFR §170.39). FDA posts affirmative decisions on its website providing the chemical identification, use limitations, and the name of the manufacturer (FDA 2011b). It does not post the manufacturer's notification or the contents of the agency's letter to the manufacturer.

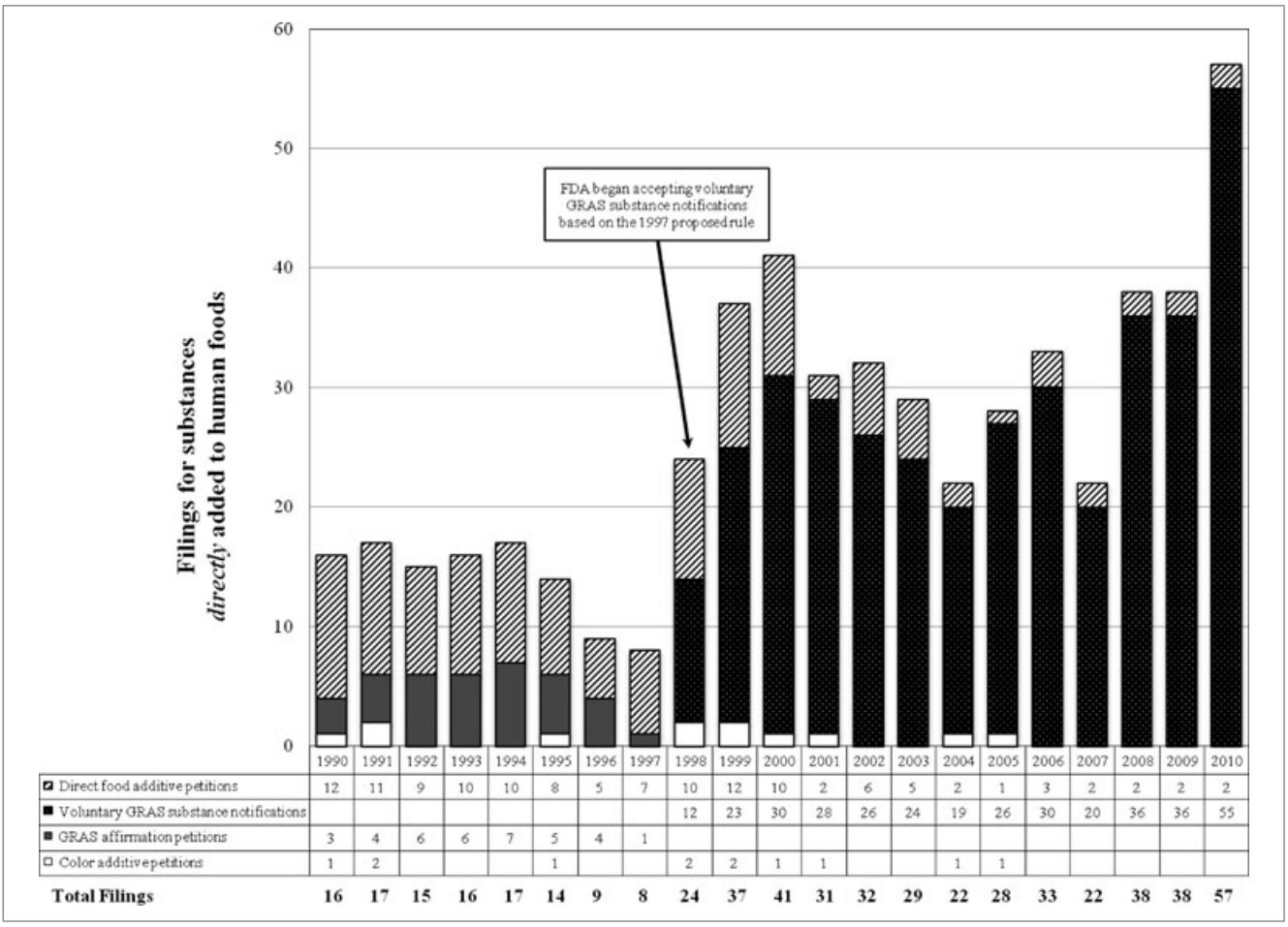
3. **FCNs.** Since 2000, FDA has been accepting FCNs pursuant to rules it proposed that year and essentially established the "substances covered by FCNs" subcategory discussed in Section "Categories and Subcategories of Substances Added to Food." The agency converted 120 previously submitted indirect food additive petitions and FCSs below the threshold of notification. In 2002, it finalized the rules at 21 CFR §§170.100-170.106 (FDA 2005). FDA has a strict 120-d period in which to actively object, otherwise a notification becomes effective and a manufacturer may market its product. This program effectively replaced the food additive petition for indirect additives and has helped reduce the need for GRAS affirmation petitions for indirect additives, as well. FDA posts affirmative decisions (and ones FDA has not objected to) on its website and describes the chemical, use limitations, and the name of the manufacturer (FDA 2011a). It does not post the manufacturer's notification or the contents of the agency's letter to the manufacturer. Congress prohibited FDA from posting information on the notice prior to making a decision (21 USC §348(h)(4)). The decision applies only to substances described in the notice from the manufacturer that submitted it. Competitors may not rely on the decision so there may be multiple notifications for similar substances and uses (21 USC §348 (h)(2)(C)).
4. **Voluntary GRAS Substance Notifications.** This voluntary notification program replaced the GRAS affirmation petition program (for FDA-affirmed GRAS substances) and essentially established the subcategory of FDA-reviewed GRAS substances discussed in Section "Categories and Subcategories of Substances Added to Food." The notification program is guided by a proposed rule from 1997 (62 Fed. Reg. 18938, April 17, 1997). In December 2010, FDA initiated the process to finalize the rule and anticipates that it will finalize the rule by 2012. FDA is no longer devoting resources to GRAS affirmation petitions (FDA 2004). As manufacturers voluntarily submit notifications of their GRAS determinations to FDA, the agency posts the notifications on its website and, when the agency makes its decisions, it posts the contents of its decision letters. FDA's decision applies to the substance's use described in the notification so competitors may rely on it (McQuate 2011). However, many of the substances are described in a manner that makes it difficult for a competitor to match, so there may be notifications for similar substances and uses.

FDA uses a similar approach to the notification process for 2 types of bioengineered substances, but labels them "consultations" instead of "notifications." First, since 1995, the agency requested manufacturers to submit biotechnology consultations to assess bioengineered foods. These consultations consider whether the bioengineered food in question "is not materially different" from the nonmodified food and therefore is not expected to raise issues that would require FDA premarket review or approval. If FDA finds material differences in a bioengineered food, the agency could require a food additive petition or impose other requirements, such as special labeling. FDA posts its decisions online including its response letter and note to the file but not the consultations it receives from the manufacturers. These are available through a request under the Freedom of Information Act (FDA 2011i and 2011j). Second, in 2009, FDA provided "New Protein Consultations" for bioengineered, nonpesticidal proteins produced by new plant varieties where the proteins would be added to food. For new protein consultations, both the manufacturer consultation and FDA's response letter are posted online (FDA 2006b).

To visualize the transition from the older petition programs to the newer notification programs and how the shift impacted the review and approval process for substances added to food, the authors conducted a novel analysis of the 1913 petitions and notifications (hereinafter referred to as "filings") submitted to FDA from 1990 to 2010. Figure 3 illustrates the trends for substances *directly* added to food. Figure 4 provides the same type of information for substances *indirectly* added to foods. Both charts stack the data so that the height of the bars represents the total number of petitions and notifications received that year for which FDA issued an affirmative safety decision or "no objection" letters. Note that filings involving nonhuman foods items and food irradiation were excluded to ensure consistency. With the exception of FCNs, all dates are based on the date the notification was submitted. FDA does not post the submission date for FCNs on its website so the effective date is used; since FDA must decide within 120 d of receiving a completed submission, these dates should be relatively close in time. Please note that there are a handful of GRAS notifications that might cover substances indirectly added to foods; for simplicity, those were kept on the chart for substances directly added to foods.

As illustrated in Figure 3, when FDA created the voluntary GRAS substance notification program in 1997, it quickly came to dominate the GRAS affirmation petition process. In 1999, there were more voluntary GRAS substance notifications than all other filings for substances directly added to foods in a single year from 1990 to 1997. This new program is the most likely cause of an overall 111% increase from an average of 14.9 direct filings annually from 1990 to 1996 to an average of 31.4 from 1997 to 2010. The new voluntary notification program effectively replaced GRAS-affirmation petitions with the last petition submitted in 1997. The decrease in total filings in 1996 and 1997 suggests that at least some manufacturers delayed filings in anticipation of the shift from petitions to notifications. The greatest number of total filings was 57 in 2010, only 2 of which were direct food additive petitions.

The voluntary GRAS substance notifications also appear to have reduced the number of direct food additive petitions filed annually from an average of 9.4 in the 1990s to average of 3.4 in the 2000s. This delayed reduction indicates that manufacturers needed several years to publish the pivotal studies and secure general recognition of safety for substances that would have otherwise been considered food additives. There is insufficient information to suggest that the increase in 2010 represents a trend. Overall, the trends indicate that manufacturers who had previously been making self-determinations of safety without FDA review transitioned to submitting notifications to FDA. In the voluntary GRAS notification system, the safety determination remains in the hands of the notifier. FDA's role seems to be to identify potential flaws in the safety assessments of those substance's uses for the voluntary



	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Direct food additive petitions	12	11	9	10	10	8	5	7	10	12	10	2	6	5	2	1	3	2	2	2	2
Voluntary GRAS substance notifications									12	23	30	28	26	24	19	26	30	20	36	36	55
GRAS affirmation petitions	3	4	6	6	7	5	4	1													
Color additive petitions	1	2				1			2	2	1	1			1	1					
Total Filings	**16**	**17**	**15**	**16**	**17**	**14**	**9**	**8**	**24**	**37**	**41**	**31**	**32**	**29**	**22**	**28**	**33**	**22**	**38**	**38**	**57**

Figure 3–Trends in filings (petitions and notifications) for food additives and GRAS substances directly added to human food submitted to FDA from 1990 to 2010.

notifications that the agency receives, not to make their own safety determination. FDA has no role in reviewing safety determinations of GRAS substances never submitted to the agency.

For substances indirectly added to food, Figure 4 shows a similar but more dramatic increase in filings with the total doubling from an annual average of 39.9 filings from 1990 to 1997 to 80.8 from 1998 to 2010. The FCSs below the threshold of regulation notifications grew quickly after being launched in 1995 but were largely replaced by the FCS notifications. The FCS notifications also almost entirely replaced the indirect food additive petitions. This shift was partially the result of FDA converting 120 indirect additive petitions and FCSs below threshold of regulation notifications into FCNs (FDA 2005). The 6 indirect food additive petitions submitted after the FCS notification program started appear to be the result of objections by FDA to FCS notifications. The post-consumer recycled plastic submissions averaged 7 filings annually from 1990 to 2010.

In summary, a dramatic shift in the filings that manufacturers submit to FDA occurred during the last 20 y. Before the mid-1990s, petitions were the dominant mechanism for FDA's review of substances directly and indirectly added to foods but from 2006 to 2010, more than 97% of all decisions were made through the notification program. On the one hand, the notification programs developed in the 1990s allowed manufacturers to bypass the traditional rulemaking process involving public notice and opportunity to comment and expedite a substance's time-to-market (Kahl 2010). As a result, FDA appears to have significantly increased the overall number of substances and decisions it reviews. On the other hand, the lack of public scrutiny resulted in a less transparent regulatory process.

Methodology

Methodology used to estimate number of current affirmative safety decisions and number of substances currently allowed to be used in human food

To assess how commonly used each category is, the authors considered several ways to provide context on the categories and subcategories of substances within the food additive regulatory program.

1. The Quantity-Used Metric would estimate the total quantity of the substances in each category and subcategory produced or used by food manufacturers or additive suppliers each year. This estimate would provide a good sense of how much consumers may consume of the different categories of substances added to food. Unfortunately, because FDA does not require periodic reporting of production or use information, therefore, this measurement could not be done. The authors considered 2 alternatives for estimating quantity used and found each to be insufficient as well:

a. The Economic Research Service of the U.S. Department of Agriculture annually estimates per capita food

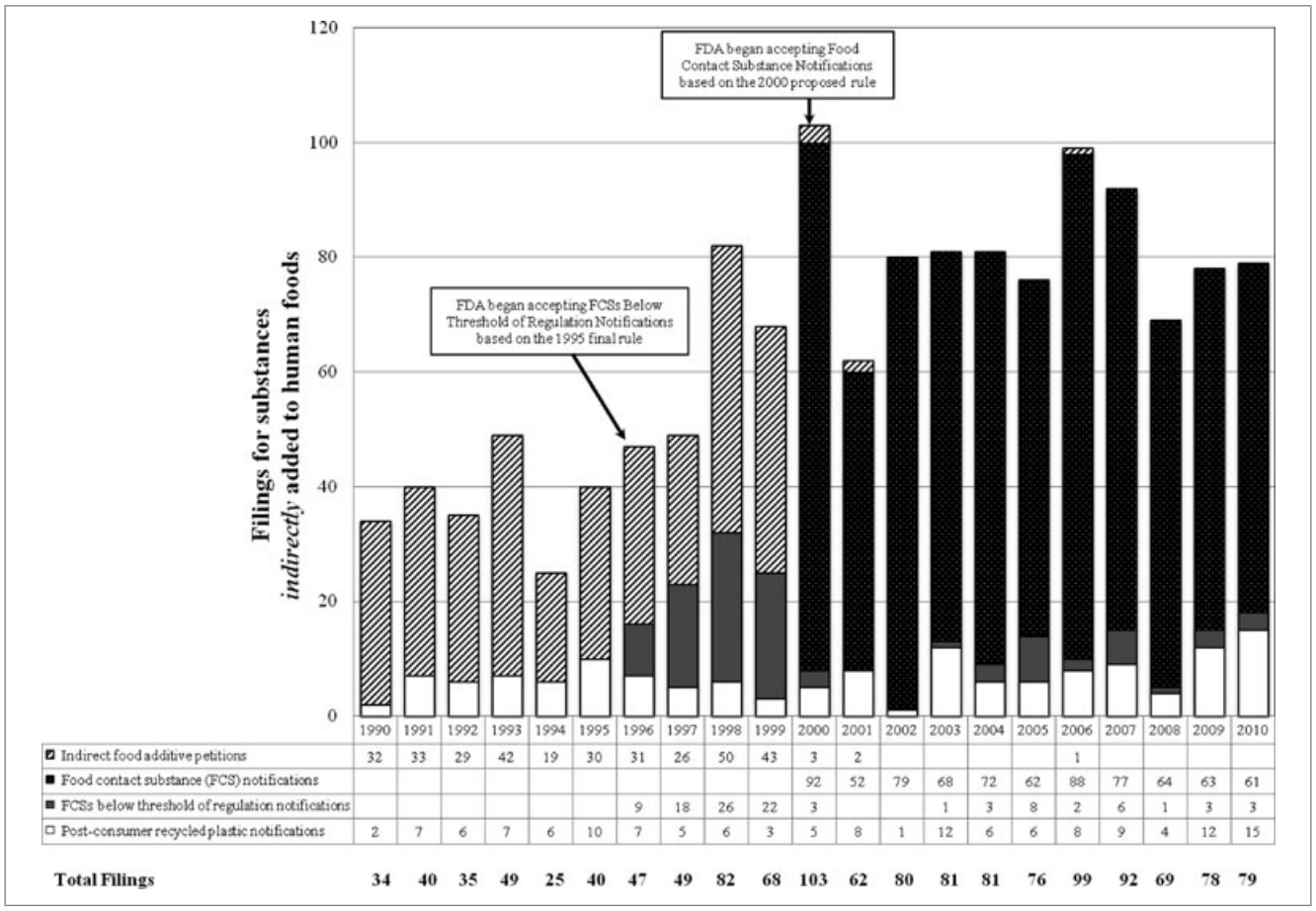


Figure 4–Trends in filings (petitions and notifications) for food additives and GRAS substances indirectly added to human food submitted to FDA from 1990 to 2010.

and commodity availability based on data provided by the U.S. Census Bureau and other sources such as manufacturers for major food products such as meat, produce, and dairy to provide estimated annual production amounts (USDA 2011). However, these food availability data are applied across the entire U.S. population and are not broken down by the relevant categories of substances used in food, so they are not particularly useful for estimating exposure to specific substances.

b. Pursuant to EPA's Inventory Update Reporting Rule for chemical substances (40 CFR Part 710), chemical manufacturers and processors report to EPA every 4-y extensive production and use information for thousands of substances pursuant to Section 8(a) of the Toxic Substances Control Act (TSCA) (15 USC §2602(2) and 15 USC §2607(a)). However, food and food additives are excluded from the scope of TSCA. Therefore, the amount of substances added to food is not required to be reported (EPA 2011c).

2. Number of Substances Allowed Metric would estimate the total number of unique substances in each category and subcategory currently allowed to be added to food. It does not estimate consumption.

Information on the current number of substances allowed in human food is generally available from FDA and EPA's regulations and FDA's website, as well as from the FEMA expert panel published reports. This metric could avoid duplicates by relying on a unique substance identifier called the Chemical Abstract Service (CAS) Registry Number (as maintained by the American Chemical Society). However, there are 2 subcategories that would be difficult to estimate: common food ingredients of natural biological origin such as flours, vinegar, fruits, vegetables, and meat that were commonly in use before 1958 and manufacturer self-determined GRAS substances of which there are no public records concerning safety decisions. When estimating the number of manufacturer self-determined GRAS substances, it is possible to draw upon food safety experts to make informed estimates.

3. Number of Affirmative Safety Decisions Metric would estimate the total number of current affirmative safety decisions made by FDA, EPA, association expert panels or manufacturers in each category and subcategory. Essentially, this metric would use regulatory activity as a useful complement to the number of substances allowed metric by providing insight into who makes the decision and how common those decisions are.

The number of current affirmative safety decisions in each category is generally available. However, as with estimating the number of substances measurement, the number of affirmative safety decisions is difficult to estimate because of FDA's generic approval of common food ingredients used before 1958 and because, in the manufacturer self-determined GRAS substances subcategory, manufacturers do not notify FDA of their decisions.

Note that this metric would only include affirmative safety decisions that are still in effect. It would not include decisions

finding that a substance's use is not safe or those affirming or modifying a previous decision. In the 50 y of the safety program's operation, too much of this information is both difficult to recover and would have little relevance to the current situation.

While measuring the amount of substances used (the first metric) may be the most useful for estimating prevalence, the information is not available. Therefore, the authors selected the number of substances allowed and number of affirmative safety decisions (the latter 2 metrics discussed above) to assess the prevalence of each category and subcategory of substances added to food and developed 4 methods for counting the number of substances allowed and affirmative safety decisions made. They also counted only decisions and substances associated with human food excluding those involving only animal feed or pet food from the calculations since it is difficult to ascertain a count of substances from AAFCO's ingredient lists. The authors developed 4 methods to determine the number of current affirmative safety decisions and the number of substances currently allowed to be added to human food in the United States (discussed in Section "Number of Affirmative Safety Decisions and Substances Allowed for Human Food"). The following is an explanation of each method and its application.

A. CFR Sections Method

The authors identified 7 distinct categories or subcategories of substances intended to be added to human food that FDA specifically authorized in the CFR. The authors used the following methods to evaluate these CFR sections:

1. **Counting Current Affirmative Safety Decisions.** The authors treated each section of the CFR as a distinct affirmative decision made by FDA (or in one case EPA) and counted the number of sections that fit in a specific category.
2. **Counting Substances Allowed.** The authors used various FDA databases such as EAFUS plus an analysis of individual CFR sections to count the number of unique substances allowed in each category. They put the information into a database and then removed duplicates. A duplicate had the same name and the same CAS number.

All counts, unless otherwise noted, are based on the CFR and databases as of January 11, 2011. The 7 categories or subcategories and the detailed description of each are as follows:

- **Direct Food Additives—230 CFR Sections/1483 Substances.** This subcategory of the food additives category includes substances intended to be directly added to human food. All direct food additives must be specifically identified in the CFR. The authors estimate that 230 CFR sections refer to specific substances:
  - 21 CFR Part 170—Food additives (3 sections)
  - 21 CFR Part 172—Food additives permitted for direct addition to food for human consumption (149 sections)
  - 21 CFR Part 173—Secondary direct food additives permitted in food for human consumption (55 sections)
  - 21 CFR Part 180—Food additives permitted in food or in contact with food on an interim basis pending additional study (3 sections involving direct additives)
  - 21 CFR Part 189—Substances prohibited from use in human food (20 sections involving direct additives)

  The authors used FDA's EAFUS database to generate the list of the 1483 substances in the CFR sections (FDA 2010c). They captured all 3911 records in the database on January 21, 2011. Note that many sections have multiple substances: one section (21 CFR §172.515 on synthetic flavoring substances and adjuvants) had 727 substances; 5 sections had more than 100 substances each; 16 sections had more than 10 substances each; and 42% of the sections had more than 1 substance. There were 1502 unique substances after eliminating duplicates. The authors then repeated the process keeping separate only those substances identified in only the animal feed or pet food sections and subtracted these 19 substances for a total of 1483 substances currently allowed to be added to human food as direct additives.
- **Indirect Food Additives—171 CFR Sections/3007 Substances.** This subcategory of the food additives category includes substances intended to be used indirectly on human food either in packaging or on production equipment. This subcategory excludes FCNs and FCS below Threshold of Regulation notifications since those decisions are published as decisions on FDA's website instead of as rules in the CFR. The indirect food additives category consists of the following 171 CFR sections that refer to specific substances:
  - 21 CFR Part 175—Indirect food additives: adhesives and components of coatings (14 sections)
  - 21 CFR Part 176—Indirect food additives: paper and paperboard components (15 sections)
  - 21 CFR Part 177—Indirect food additives: polymers (88 sections)
  - 21 CFR Part 178—Indirect food additives: adjuvants, production aids, and sanitizers (47 sections)
  - 21 CFR Part 180—Food additives permitted in food or in contact with food on an interim basis pending additional study (1 section involving indirect additives)
  - 21 CFR Part 189—Substances prohibited from use in human food (6 sections involving indirect additives).

  The authors used FDA's "List of Indirect Additives Used in FCSs" database to generate the list of the substances in each CFR section (FDA 2011k). They captured all of the 3237 records in the database on January 23, 2011. They attempted to use EAFUS but found serious problems matching the information in EAFUS against several key CFR sections. EAFUS only had 1494 unique substances. In contrast, the indirect additives database had 3007 unique substances. Most sections of the CFR covered more than one substance. For example, 1 section (21 CFR §175.105 on adhesives) had 1265 substances and 11 sections had more than 100 substances each. Overall, the authors found a total of 6838 substances but 3831 of these substances were duplicates: typically substances used in various adhesives, coatings, and types of packaging. There were 3007 unique substances after eliminating duplicates.
- **FDA-listed GRAS Substances—85 CFR Sections/437 Substances.** This subcategory of the GRAS substances category includes substances that FDA found were "generally recognized as safe" in human food as direct or indirect additives before 1973. The subcategory consists of 84 CFR sections in 21 CFR Part 182 that refer to specific substances.

  In addition, one section (21 CFR §182.1) does not refer to specific substances but includes most common food ingredients used before 1958 when the law establishing the GRAS program was adopted. In this CFR section FDA states that it regards "common food ingredients such as salt, pepper, vinegar, baking powder, and monosodium glutamate as safe for their intended use." The authors included this CFR section in this subcategory for completeness.

  The authors used EAFUS to generate the list of the substances in each CFR section. They considered using the

List of Indirect Additives database as well but found that the database had no references to the relevant CFR sections. The authors found a total of 488 substances; according to EAFUS, 1 CFR section (21 CFR §182.20) on essential oils, oleoresins (solvent-free), and natural extractives (including distillates) had 224 substances; 6 CFR sections had more than 10 substances; and 21% of the CFR sections had more than one substance. The authors then repeated the process keeping only those substances identified in only the animal feed or pet food sections and subtracted these 25 substances for a total of 437 substances currently allowed to be added to human food as indirect additives.

- **FDA-affirmed GRAS Substances—230 CFR Sections/270 Substances.** This subcategory of the GRAS substances category includes substances that FDA affirmed, as opposed to listed, as GRAS. FDA affirmed other substances based on its review of affirmation petitions. The subcategory consists of the following 230 CFR sections that refer to specific substances:
  - 21 CFR Part 184—Direct food substances affirmed as generally recognized as safe (214 sections)
  - 21 CFR Part 186—Indirect food substances affirmed as generally recognized as safe (16 sections).

  The authors used EAFUS to generate the list of the substances in each CFR section. They considered using the List of Indirect Additives database but found that it had no references to the relevant CFR sections. The authors found a total of 270 unique substances after eliminating duplicates.
- **Pesticide Chemicals or Residues—581 CFR Sections/581 Substances.** This category consists of substances allowed by EPA for use as pesticides in human food. EPA makes 2 types of decisions: setting tolerances or granting exemptions from tolerances. EPA grants an exemption when it determines that the total quantity of a pesticide chemical in or on all raw agricultural commodities under conditions of use currently prevailing or proposed will involve no hazard to the public health (40 CFR §180.900). FDA essentially adopts EPA's decisions for human food at 21 CFR 170.19. This category consists of the following 581 CFR sections that refer to specific substances.
  - 40 CFR Part 180—Tolerances and exemptions for pesticide chemical residues in food
    - Subpart C—Specific tolerances (385 sections)
    - Subpart D—Exemptions from tolerances (196 sections).

  Generally EPA established 1 CFR section for each pesticide used on raw agricultural commodities. A section typically covers use of only one pesticide on all raw agricultural commodities although there are exceptions such as 40 CFR 180.319 for interim tolerances which covers the use of 4 pesticides.
- **Color Additives—52 CFR Sections/148 Substances.** This category includes CFR sections where FDA approved a color additive for use in human food. The category consists of the following 54 CFR sections that refer to specific substances:
  - 21 CFR Part 73—Listing of color additives exempt from certification (36 sections)
  - 21 CFR Part 74—Listing of color additives subject to certification (9 sections)
  - 21 CFR Part 81—General specifications and general restrictions for provisional color additives for use in food (1 section)
  - 21 CFR Part 82—Listing of certified provisionally listed colors and specifications (6 sections).

  The authors used FDA's EAFUS database to generate the list of the substances in each CFR section. They considered using the List of Indirect Additives database but found that it had only a few references to the relevant CFR sections. The authors found a total of 148 unique substances.
- **Prior-Sanctioned Substances—12 CFR Sections/120 Substances.** This category consists of 12 sections in 21 CFR Part 181. The authors counted 122 substances and reduced the total to 120 by eliminating duplicates. The number of sections and substances is unlikely to grow since it is based on sanctions issued by FDA or USDA more than 50 y ago. The number could shrink if FDA revoked a prior sanction. The total does not include substances that were covered by FDA or USDA prior sanctions for which FDA does not have documentation and therefore are not in the CFR.

B. Notices to FDA Method

The authors identified 3 subcategories of substances intended to be added to human food that FDA reviews but which are not included in the CFR. Generally, FDA receives a notification from a manufacturer stating its determination that a substance's use is safe. FDA reviews the notification and issues a letter to the manufacturer with its assessment.

The authors used the following methods to evaluate the notification programs:

1. **Counting Current Affirmative Safety Decisions.** The authors counted decisions for which FDA reported it had "no questions" or "no objections." The authors did not count decisions where the notifier withdrew the notification or FDA found an insufficient basis for an affirmative safety decision.
2. **Counting Substances Allowed.** Each notice typically covers a single substance or a class of similar substances. Sometimes a notice addresses a substance covered by a previous notice but the new notice addresses a different use or a different producer. Except as noted below for the GRAS Notification Program, a manufacturer could not rely on another manufacturer's notices. It would need to submit a separate notice, even for the same substance and use. To avoid double counting of substances, the authors reviewed FDA's summary of a substance and eliminated duplicates for affirmative safety decisions where the substance description was exactly the same as another.

All counts are based on what was contained on the FDA website as of January 11, 2011. A detailed description of each subcategory follows:

- **Substances Covered by FCNs—773 Decisions/701 Substances.** Pursuant to a law enacted in 1997 and 21 CFR 170.100–170.106 (promulgated in 2002), FDA began accepting notifications for FCS in 2000. FCSs are substances intended for use as a component of materials that make contact with food but are not intended to have a technical effect in such food.

  As of January 11, 2011, FDA reported receiving 784 notices. It issued "no-objection" letters in whole or in part on 773 notices. See www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=fcsListing. The authors removed duplicates for a total of 701 substances.
- **FCSs below the Threshold of Regulation Notifications—101 Decisions/101 Substances.** FDA

reported issuing 101 "exempt from regulation" letters in response to FCS below the Threshold of Regulation Notifications as of January 11, 2011. See www.fda.gov/Food/FoodIngredientsPackaging/FoodContactSubstancesFCS/ucm093685.htm. While it posts withdrawn notices, FDA does not appear to post notices where it objects or has questions. There do not appear to be any duplicates. Withdrawn notices were not counted.

- **Substances Covered by FDA-reviewed GRAS Notifications—267 Decisions/237 Substances.** As of January 11, 2011, FDA CFSAN reported receiving 361 notices. See www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS. At the time, FDA had issued "no-question" letters on 267 notices and was still reviewing 23 notices. It had ceased to evaluate 56 notices at the notifiers' request and found that 15 notices did not provide a basis for a GRAS determination. The authors found that 33 notices were for different uses of substances covered by prior notices. They removed these duplicates resulting in a total of 237 substances.

C. FEMA Reports Method

The authors are only aware of one organization, the FEMA that has an established program to systematically review candidates for GRAS and make decisions regarding human food. FEMA established an expert panel in the early 1960s and has been routinely making decisions since then. FEMA also submits its decisions and supporting documentation to FDA, but FDA does not conduct a formal evaluation. The decisions are not included in the GRAS Substance Notifications Category above. See http://www.femaflavor.org/gras for more information about the program.

On January 11, 2010, FEMA reported to the authors that it had made affirmative decisions on 2702 GRAS substances. FEMA confirmed that there is only one substance for each determination.

D. Authors' Estimate Method

The authors estimated that, as of January 11, 2010, manufacturers had independently made 1000 decisions finding a substance is a GRAS substance. Since manufacturers are not required to publish their decisions, the authors relied on their discussions with industry consultants and representatives to make this estimate. The actual number is unlikely to be less than 500 but could be several times larger than 1000.

The authors estimate that there are 5 types of decisions:

1. **Vertically integrated manufacturers.** A manufacturer may wish to keep a substance and its uses confidential to protect a trade secret. Therefore, it will not voluntarily submit a GRAS notification to FDA. Under normal circumstances, downstream human food processors will insist that a supplier document a GRAS decision preferring to see an FDA "no-question" letter in response to a GRAS substance notification. However, a vertically integrated manufacturer with control of human food processing and the final product and the production of a GRAS substance may feel comfortable keeping knowledge of its decision internal. Such a manufacturer has no downstream supplier to satisfy. Several large manufacturers informed the authors that they have used this approach. Note that the common name for a substance must be listed on a label unless the substance is a spice or flavor. Spices and flavors may be identified without identifying their chemical name or their common name.
2. **One-off manufacturers.** A manufacturer may rely on another manufacturer's GRAS notification that FDA has no question with or might choose to rely on FDA's GRAS lists or affirmations in the CFR. This practice is likely to be common.
3. **One-off uses.** FDA's evaluation of a GRAS notification is limited to the specific use described in the notice. In practice, manufacturers seeking other uses, such as in a different type of human food, for a substance are likely to rely heavily but not entirely on FDA's "no question" decision as the basis for a safety determination.
4. **Naive supplier.** A manufacturer may not fully understand the requirements for GRAS substances and may make a decision to add a substance to human food by relying on the assurances of a supplier or by simply making an assumption.
5. **Withdrawn GRAS notification.** If FDA has questions about a GRAS notification, a manufacturer submitting the notice may withdraw the notice and ask FDA to cease its review. FDA routinely complies with this request. FDA's questions may involve concerns over whether the studies used as the basis of the decision have been published or whether there is actually general recognition of safety. In this situation, the manufacturer is free to make a self-determination despite FDA's questions.

Methodology for developing 20-y trends

The authors developed a counting methodology to track filing trends for substances added to human foods over the 20 y spanning 1990 to 2010. Two distinct categories are represented in Figure 3 and 4, substances directly added to human food and substances indirectly added to human food. A filing was categorized as a direct additive if it involved a direct food additive, color additive, FDA-affirmed GRAS substance or a substance covered by a FDA-reviewed GRAS notification. A filing was categorized as an indirect additive if it involved an indirect food additive, substances covered by a FCN, FCSs below threshold of regulation, or post-consumer recycled plastic notification.

The focus of the analysis was on methods that are used to notify or petition FDA regarding a substance added to human food. The result of the filing was not considered. There is at least one instance where a substance was submitted as a voluntary GRAS notification twice, in sequential years, and FDA deemed that the notices did not provide a sufficient basis for a GRAS determination; this compound was then submitted for review in a Food Additive Petition in 2002 (67 FR 30716, May 7, 2002) and 2006 (71 FR 62475, October 25, 2006). In this example, individual filings were counted, independent of the outcome, because the authors were analyzing trends in manufacturer's submissions to the agency that the agency published on its website or in the *Federal Register* as of June 30, 2011.

A. Food Additives and GRAS Substances Directly Added to Human Food (Figure 3). In counting trends in Direct Additives, 4 categories of filing options were identified during the 20-y period covered: Direct Food Additive Petitions, Voluntary GRAS Substance Notifications, GRAS Affirmation Petitions and Color Additive Petitions.

1. **Direct Food Additive Petitions.** Direct Food Additives were identified using the search terms "Filing of Food Additive Petition" in the Federal Register at HeinOnline Legal

Research Database. As mentioned above, substances that are intended to have a technical effect on human food were included as direct additives. To ensure accuracy in counting, each year was queried individually and each "Matching Text Page" hit was reviewed for "Action: Notice" and the substance and use for categorization. A single page of the Federal Register can contain up to 3 individual notices of a filing of a food additive petition; reviewing each notice individually allowed categorization of the substance according to intended use (to prevent miscategorization) and prevented underestimation by counting individual filings that were on the same Federal Register page. Filing Amendments were also excluded from the counting, to reduce over-estimation.

2. **Voluntary GRAS Substance Notifications.** The voluntary GRAS Substance Notification database (http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=grasListing) lists all voluntary GRAS notifications submitted to FDA since the beginning of the program which was first proposed in 1997 (62 FR 18938, April 17, 1997). Substances and their uses in this category were counted by filing date of the notification. This counting does not include GRAS determinations that were not filed with FDA for the following reasons: (1) this analysis was dedicated to the number of filings of substance/uses with FDA, and (2) as mentioned previously, there is no reasonable mechanism for estimating the number of self-determinations conducted annually. The total number of GRAS determinations per year could be substantially higher than is presented in this figure.
3. **GRAS Affirmation Petitions.** Similar to Food Additive Petitions, the number of GRAS Affirmation Petitions filed per year was counted by searching HeinOnline's Federal Register Library with the search terms "Filing of Petition for Affirmation of GRAS status." Citing Agency resource limitations, the GRAS Affirmation process was replaced with the voluntary GRAS notification proposed rule in 1997. To be thorough in counting, the years after 1997 were still searched individually for GRAS Affirmations, though none were filed because of the proposed rule.
4. **Color Additive Petitions.** HeinOnline's Federal Register Library was queried with the search terms "Filing of Color Additive Petition" for notices submitted to FDA from 1990 to 2010. Similar to Direct Additives and GRAS Affirmation Petitions, each notice was reviewed individually to prevent miscategorizing.

B. Food Additives and GRAS Substances Indirectly Added to Human Food (Figure 4). Indirect Additives, substances that are not considered to impart a technical effect on human food, were counted in 4 individual categories: Indirect Food Additive Petitions, FCNs, FCSs below Threshold of Regulation Notifications and Voluntary Post-consumer Recycled Plastic Notifications. FDA's website contains a database that lists Indirect Additives Used in FCSs (http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=iaListing).

1. **Indirect Food Additive Petitions.** Indirect food additive petitions were counted using the same method and search terms as described in Direct Food Additive Petitions above. The "technical effect on food" guideline described above was used to distinguish indirect food additives, including components of plastic polymers and adhesives from direct food additives.
2. **Food Contact Substance Notifications.** Similar to the voluntary GRAS notification system, the FCN Program was developed to replace an existing mandatory petition process. Premarket notifications of substances/uses were counted by the effective date, which is no later than 120 d after the submission date in the Inventory of Effective FCNs database (http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?filter=&sortColumn=%263\%3C3K%24Y%3D&rpt=fcsListing). Unlike voluntary GRAS notifications, the submission itself and, therefore, the date of submission is not publicly available, and so the effective date provides a best estimate used for consistency in counting.
3. **FCSs below Threshold of Regulation Notifications.** FCSs below threshold of regulation are listed on FDA's website (http://www.fda.gov/Food/FoodIngredientsPackaging/FoodContactSubstancesFCS/ucm093685.htm) and were counted according to the file name, the first 2 digits of which represent the year.
4. **Voluntary Post-consumer Recycled Plastic Notifications.** Submissions on Voluntary Post-consumer Recycled Plastics are listed in a database on FDA's website (http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?filter=&sortColumn=%263\%2C3K%24Y%3D&rpt=recyListing&displayAll=true). These submissions are listed by date of No-Objection Letter.

Note that the 2 methodologies discussed above (number of affirmative safety decisions and number of filings) will result in different numbers because:

- The first deals with affirmative safety decisions and the later deals with filings submitted to the agency whether affirmed, rejected or withdrawn.
- For several types of filings, FDA does not post them on its website until it has made a final decision. Therefore, FDA may have received the filings but not made them available on its website as of June 30, 2011. In addition, the authors used an estimate of affirmative safety decisions posted on FDA's website (January 11, 2011). In order to include all relevant data, the trends for filing were counted in June of 2011, when it was assumed that all notifications would be publicly available. As a result, there are minor discrepancies in the total numbers of filings listed.

Conclusions

The complexity of food production has increased substantially since the U.S. Congress enacted the Food Additives Amendment of 1958. Food has gone from being produced locally out of fairly basic ingredients to being produced worldwide, often containing a large and diverse array of substances ranging from food and color additives to pesticides to drugs in animal feed. These substances serve a crucial role in meeting consumers' expectations and needs. Their many uses are highlighted by the microwave-ready frozen children's meal referenced throughout this document. Its ingredient list identifies 68 items which range from whole grain flour to microcrystalline and carboxymethyl cellulose; however, the meal contains many additional substances not listed such as FCSs and processing aids.

Like food production, the food additive regulatory program has grown complex. At the center of the complexity is the original framework the U.S. Congress laid out in 1958. To implement the law, FDA created a detailed, layered program designed to encourage manufacturers to submit their safety decisions for agency review; to set minimum expectations for the scientific basis of a

decision; and to address consumers' and manufacturers' demands for safety and efficiency. As a result, FDA's current regulatory program allows manufacturers to select from multiple pathways to bring many types of new substances to market, balancing many factors including timeliness, the level of FDA and public scrutiny, the ability to claim FDA's "approval," and the opportunity to make a later self-determination if FDA raises questions or if a previous approval no longer fits a manufacturer's current needs.

Most substances used in food, such as the whey protein and citric acid in the children's meal, must meet a "reasonable certainty of no harm" safety standard. The exceptions are prior-sanctioned substances and dietary supplements. While the safety standard itself is important, who makes the safety decision and whether that decision is subject to FDA and public scrutiny can significantly influence the outcome. The choice of how to bring a substance to market is, therefore, especially significant in the case of manufacturers that might put their short-term financial interests—getting their product to market—over the long-term interests in protecting the American consumers' health.

A robust initial safety decision of a substance is also crucial since the food additive regulatory program relies heavily on premarket review. Except for pesticide chemicals or residues and, to some extent, drugs in animal feed, once the decision has been made that a substance is safe and the product is on the market, a manufacturer does not have an obligation to regularly reassess its safety decision or notify FDA of new science or increased consumption of a substance. Under the current federal regulations, only pesticide chemicals or residues are required to undergo periodic reassessment of safety decisions to respond to new research and exposure trends. Recognizing the importance of such a reassessment, one association's expert panel (FEMA) also requires review of the science and estimated exposure of the GRAS substances it finds safe in order to maintain its approval. FDA has no similar system.

In the past 10 y, Congress has increased a manufacturer's postmarket responsibilities as part of broader revisions to the Federal Food Drug and Cosmetic Act to make food safer. Manufacturers are now obligated to report when there is a reasonable possibility that exposure to a food or a substance in food will cause serious adverse consequences to human or animal health. FDA will be promulgating rules requiring food facilities to conduct a hazard analysis and write risk-based preventive control plans pursuant to the FDA Food Safety Modernization Act. These plans are expected to require most manufacturers to confirm that their products continue to comply with the food additive regulatory program.

Over the last 20 y FDA has shifted from promulgating rules for its safety decisions for FCSs and GRAS substances to reviewing a manufacturer's safety decision and choosing whether or not to object. As a result, FDA's process is faster and, therefore, appears to have encouraged manufacturers to seek the agency's review rather than make a self-determination without notifying the agency of the decision. Although the notification programs have been successful in reducing the need for rulemaking, by eliminating the requirement for public notices and comments, these programs effectively made it more difficult for the public to access the information necessary to understand the basis for safety decisions and provide comments on those decisions before FDA acts. Overall, FDA's changes have moved away from public scrutiny and, in the case of its voluntary GRAS notification program, away from independent safety review by the agency.

The cumulative result is that there are an estimated 6204 current affirmative safety decisions which allow for more than an estimated 10000 substances to be used in food. More than half of the safety decisions are not made by FDA or EPA. Overall, federal agencies made approximately 40% of the more than 6,000 safety decisions allowing substances in human food. These decisions allowed an estimated 66% of the substances currently believed to be used in food. FEMA has made more affirmative food safety decisions than FDA. In addition, an estimated 1000 manufacturer safety decisions are never reported to FDA or the public.

In summary, navigating this system is a challenge for both food safety professionals and policy makers. Despite vast scientific advancement and changes in how food is made, food production is heavily shaped by the decisions made by Congress more than 5 decades ago. FDA has worked to adapt to changes in the system while conforming to the limits of Congress' original framework. The result is a complex system with multiple categories and subcategories covering thousands of safety decisions and substances. Manufacturers have increased their submissions to FDA, but public input has become increasingly limited and the requirements governing postmarket responsibilities are minimal and vary depending on the substance in question.

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