Original Investigation

Conflicts of Interest in Approvals of Additives to Food Determined to Be Generally Recognized as Safe
Out of Balance

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IMPORTANCE Food and Drug Administration (FDA) guidance allows food manufacturers to determine whether additives to food are "generally recognized as safe" (GRAS). Manufacturers are not required to notify the FDA of a GRAS determination, although in some instances they notify the agency. The individuals that companies select to make these determinations may have financial conflicts of interest.

OBJECTIVE To determine the extent to which individuals selected by manufacturers to make GRAS determinations have conflicts of interest between their obligations to ensure that the use of the additive is safe and their financial relationships to the company.

DESIGN Using conflict of interest criteria developed by a committee of the Institute of Medicine, we analyzed 451 GRAS notifications that were voluntarily submitted to the FDA between 1997 and 2012.

MAIN OUTCOMES AND MEASURES Number of GRAS notices submitted to the FDA; frequency of various types of relationships between decision maker and additive manufacturer; frequency of participation on GRAS panels by individuals; and number of GRAS safety determinations identified by the FDA that were not submitted to the agency.

RESULTS For the 451 GRAS notifications, 22.4% of the safety assessments were made by an employee of an additive manufacturer, 13.3% by an employee of a consulting firm selected by the manufacturer, and 64.3% by an expert panel selected by either a consulting firm or the manufacturer. A standing expert panel selected by a third party made none of these safety assessments. The 290 panels that made GRAS determinations had an average of 3.5 members, with a maximum of 7. Ten individuals served on 27 or more panels; 1 individual served on 128 panels (44.1%). At least 1 of the 10 individuals with the most frequent service was a member of 225 panels (77.6%).

CONCLUSIONS AND RELEVANCE Between 1997 and 2012, financial conflicts of interest were ubiquitous in determinations that an additive to food was GRAS. The lack of independent review in GRAS determinations raises concerns about the integrity of the process and whether it ensures the safety of the food supply, particularly in instances where the manufacturer does not notify the FDA of the determination. The FDA should address these concerns.

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Additives to food are a fundamental part of the food supply, providing flavor; enhancing taste, appearance, and nutrient value; and preventing spoilage, as well as serving as components of food packaging.[1] The term *food additive* has a specific legal meaning, that is a substance whose use "results or may reasonably be expected to result, directly or indirectly, in its becoming" part of food or affecting the characteristics of food.[2] Congress excluded from the legal definition those additives whose use is designated as "generally recognized as safe" (GRAS). In common parlance, however, the term is used to refer to food additives in general.

According to the US Food and Drug Administration (FDA), the Food Additives Amendment of 1958[3] allows manufacturers to determine when an additive is GRAS.[4] Such a review is known as a GRAS determination. Common GRAS additives include *trans* fat, caffeine, salt, and sweeteners derived from the stevia plant (*Stevia rebaudiana*), such as the sweetener known as Truvía (The Truvía Company, LLC). In past decades, the FDA made many formal GRAS determinations, but the agency has made very few such determinations recently.

After a GRAS determination is made, manufacturers are not required to notify the FDA, although in some instances the agency is notified. When the agency has agreed with the determination, it has responded by formally approving the manufacturer's decision in its regulations or by informing the company in writing that it has "no questions" about the chemical's safety (referred to as a GRAS "no questions" letter).[5] After 1997, the agency phased out the first option, replacing it with the second option. When the agency has disagreed, it has sent a letter to the manufacturer stating that there is an insufficient basis for the GRAS determination. The company then decides how to proceed. Notices to the FDA either involve new GRAS additives (not previously reviewed or approved by the FDA) or additives that have already been reviewed or approved, with expanded uses, differing purities, or increased concentrations.[6]

A standing expert panel sponsored by the Flavor and Extract Manufacturers Association (FEMA) also makes GRAS determinations about additives that are flavors and informs the FDA in writing of its decisions. However, these written communications are not considered formal notifications to the agency and are not publicly available. Also, these communications are unrelated to the GRAS notifications to the agency from companies.[6] Decisions by the FEMA panel, but not their rationale or the safety assessment data, are periodically published in *Food Technology*, a trade magazine. Food manufacturers generally accept the decisions of the FEMA panel as confirmation that a flavor additive is GRAS. Since 1963, the FDA has monitored the panel's decisions on more than 2700 additives that are flavors; the agency, however, does not review the decisions.

In 2011, Neltner et al[6] estimated that more than 10 000 additives are allowed in food, 43% of which are GRAS additives. Manufacturers have made GRAS determinations that allow the use of an estimated 1000 of these additives, without notifying the FDA.[6] The manufacturers or FEMA notified the agency of the remaining GRAS additives.

To qualify for a GRAS determination, manufacturers of additives must conclude that the use of the additive is safe.[7] Safe is defined to mean "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use."[8] The safety of the GRAS additive must be generally recognized, which "requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food."[9] Congress recognized that the potential health effects of additives are often difficult to identify and may take years to recognize.[10,11]

In 2010, the US Government Accountability Office (GAO) scrutinized the GRAS program, concluding that the FDA should strengthen its oversight.[4] Among other recommendations, the GAO said the FDA should "minimize the potential for conflicts of interest in companies' GRAS determinations" and "require any company that conducts a GRAS determination to provide FDA with basic information—as defined by the agency to allow for adequate oversight—about this determination."[4(p34)]

Given this background, we used criteria developed by an Institute of Medicine (IOM) committee for medical research, education, and practice to evaluate the conflicts of interest of the individuals who make GRAS determinations.[11]

Methods

Assessment of Severity of Conflicts of Interest

The IOM committee[11(p46)] defined conflict of interest as follows:

a set of circumstances that creates a risk that the professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest.

We assessed the severity of a conflict based on the likelihood that a decision could be unduly influenced by a financial interest, and the seriousness of possible harm if the decision was influenced.[11]

For purposes of our study, we considered the primary interest as ensuring that a use of an additive was GRAS, consistent with federal law. The secondary interest was the potential for financial gain from a determination that enabled a manufacturer to sell a new additive, to expand the use of an existing additive to new foods, or to increase the amount of an additive in food. We did not evaluate the nonfinancial professional interests of the individuals; this could not be done with the available information.

We identified the possible categories of individuals making GRAS determinations based on their relation to manufacturers of additives. **Table 1** gives these categories and the criteria we used to assess the likelihood that a determination by an individual would be unduly influenced by the financial interests of a manufacturer. **Table 2** gives the criteria we used to assess the seriousness of possible harm if a GRAS determination was unduly influenced by the financial interests of a manufacturer of an additive, based on whether there was an FDA review and whether the notification to the agency was made public. Federal ethics laws and regulations prohibit FDA employees from having financial conflicts of interest.[12]

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Table 1. Likelihood That a Decision by an Individual Making a "Generally Recognized as Safe" Determination Would Be Unduly Influenced by the Financial Interests of a Manufacturer of an Additive

Category of Decision Makers	Value of the Secondary Interest[a]	Scope of the Relationship[b]	Extent of the Discretion[c]
Employee of manufacturer of additive	Job security/stock ownership	Long-term and deep	Significant especially if safety data are limited
Employee of consulting firm selected by manufacturer of additive	Secure more work from maker and others	Duration and depth varies significantly	Significant especially if safety data are limited
Expert panel selected by consulting firm or manufacturer of additive	Being selected for more panels	Typically short and shallow, unless regular panelist	Varies with panel
Standing expert panel selected by third party	Continuing to serve on panel	Short and shallow, unless third party is close to additive manufacturer	Limited depth and duration
Employee of the FDA	None	Financial interests prohibited	Limited especially with external peer reviews

Abbreviation: FDA, US Food and Drug Administration.

[a] Secondary interest is the potential financial gain from a decision that enables a manufacturer of an additive to sell the new chemical or more of a previously allowed chemical.

[b] Scope refers to the duration and depth of the relationship. According to the Institute of Medicine, "Longer and closer associations increase the scope and therefore the risk."[11(p54)]

[c] Discretion is a factor in search of published literature, evaluation of toxicological data, assessment of cumulative exposure from all dietary sources including pharmacologically similar chemicals, and extent to which there is a genuine dispute whether there is reasonable certainty that the substance is not harmful under the intended conditions of use.

Table 2. Seriousness of Possible Harm If a "Generally Recognized as Safe" (GRAS) Determination Is Unduly Influenced by the Financial Interests of Manufacturer of an Additive

Type of FDA Review	Value of the Primary Interest[a]	Scope of the Consequences	Extent of Accountability
No FDA review	Significant value in consumer health and confidence in safety of food supply	Significant since additive may be used in a wide range of foods	Limited especially if additive is not on ingredient list
FDA review but does not make notice publicly available[b]	Same as above	Same as above	Moderate if FDA has resources to review information
FDA review and makes notice publicly available[c]	Same as above	Same as above	Significant if information posted and additive on ingredient list

Abbreviation: FDA, US Food and Drug Administration.

[a] Primary interest is ensuring a chemical's use is generally recognized as safe consistent with federal law.

[b] Such as the biotechnology review or food contact substance notification.

[c] Such as through GRAS notifications.

Assessment of GRAS Notices Voluntarily Submitted to the FDA

With a small number of GRAS notices, we conducted a pilot analysis. The author who performed the evaluation (H.M.A.) shared the results with coauthors and a third-party contractor specializing in checking facts. The authors discussed disagreements and, with feedback from the contractor, reached consensus on the categorization of the notices. After further refinement of the methodology, one author (H.M.A.) then reviewed the 451 GRAS notices posted on FDA's website[13] that were submitted to the agency between 1997 and 2012; the contractor randomly selected and evaluated 15% of the notices for quality control.

The criteria to classify who made the GRAS determinations included the following: (1) standing expert panel if the notice referred to an ongoing panel similar to FEMA's that considered additives from many manufacturers; (2) expert panel if such a panel was named in the notice and selected by the manufacturer or a consulting firm hired by the manufacturer; (3) manufacturer's employee if a panel was not identified and an individual signed the notice on behalf of the firm; or (4) employee of consulting firm if an employee of the firm signed the notice and there was no expert panel. We excluded FDA employees because the agency only reviews the notices; it does not make the determinations. We also calculated the frequency of the service of individuals on expert panels and noted the affiliations of those most commonly selected.

We considered only the likelihood of undue influence of GRAS determinations and the seriousness of possible harm. We did not evaluate specific decisions to determine if there was actual undue influence or harm because the available documentation was insufficient. Finally, we reviewed instances since 1997 when the FDA sought to obtain a GRAS safety determination that it had not received a notification for.

Results

Assessment of GRAS Notices Submitted to the FDA

Of the 451 GRAS notices voluntarily submitted to the FDA between 1997 and 2012, 22.4% were made by an employee of an additive manufacturer, 13.3% were made by an employee of a consulting firm selected by a manufacturer, and 64.3% were made by an expert panel selected by the manufacturer or a firm that was a consultant to the manufacturer (**Table 3**). A determination by a panel reflected the view of the entire panel, not an individual member or a subset of members.

We found no instances where a manufacturer who submitted a GRAS notice to the FDA used a standing expert panel selected by a third party—the method least likely to involve a conflict of interest (Table 2)—to establish whether an additive met the GRAS criteria.

Assessment of Frequency of Participation on GRAS Panels by Individuals

The 290 panels that made GRAS determinations averaged 3.5 members, with a maximum of 7. In total, 216 individuals served on at least 1 panel. Most were consultants, and almost all of them had doctor of philosophy degrees; some were physicians or held

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Table 3. Type of Individuals Making "Generally Recognized as Safe" Determinations Submitted to the US Food and Drug Administration

Decision Maker	Notices, No. (%) (n = 451)
Employee of manufacturer of additive	101 (22.4)
Employee of consulting firm selected by manufacturer of additive	60 (13.3)
Expert panel selected by consulting firm or manufacturer of additive	290 (64.3)
Standing expert panel selected by third party	0

Table 4. Profession and Frequency of Service of 10 Individuals Who Served on 27 or More of the 290 Panels That Made "Generally Recognized as Safe" Determinations

Individual	Profession	Panels Served on, No. (%)
1	Consultant and emeritus professor	128 (44.1)
2	Consultant	41 (14.1)
3	Consultant and professor	40 (13.8)
4	Consultant and emeritus professor	38 (13.1)
5	Consultant	35 (12.1)
6	Consultant	34 (11.7)
7	Consultant and emeritus professor	34 (11.7)
8	Consultant	28 (9.7)
9	Consultant and emeritus professor[a]	28 (9.7)
10	Consultant	27 (9.3)

[a] Deceased.

other advanced degrees. However, 10 individuals served on 27 or more panels; 1 person served on 128 panels (**Table 4**). Over the 15-year period, at least 1 of these 10 individuals participated in 225 panels (77.6%), accounting for 43.1% (433 of 1004) of the total number of seats on all 290 panels. Thus, only 65 panels (22.4%) did not include 1 of these 10 individuals. All 10 identified themselves as consultants; 5 cited academic positions.

Assessment of GRAS Safety Determinations Not Submitted to the FDA

From 1997 to 2012, we found only 1 instance when the agency sought to obtain a GRAS safety determination that it had not received a notification for. In 2010, the FDA sent letters to 4 companies inquiring whether they had determined that the use of caffeine in alcoholic beverages was GRAS.[14] The FDA has affirmed caffeine as GRAS in cola-type drinks. The agency was reacting to reports of serious injuries or deaths among young people consuming the beverages. In fact, none of the 4 companies had made GRAS determinations. A year later, in 2011, 1 company submitted a GRAS notice that the agency found insufficient. Subsequently, the FDA issued warning letters to all 4 firms directing them to stop the use of caffeine in alcoholic beverages until the agency formally approved it. All companies appear to have removed caffeine from such products.[14]

Discussion

Between 1997 and 2012, we found that financial conflicts of interest were ubiquitous in determinations that an additive to food was GRAS. The lack of independent review in GRAS determinations raises concerns about the integrity of the process and whether it ensures the safety of the food supply, particularly in instances when the manufacturer does not notify the FDA of the determination. When manufacturers or their consultants convene an expert panel to make GRAS determinations, they often pick one of a small number of individuals to serve on the panel.

Our study has limitations. First, although we analyzed the 451 publicly available GRAS notices submitted to the FDA, we lacked comparable data on the many GRAS determinations, without notifications to the FDA.[6] Second, we did not evaluate GRAS determinations by the FEMA panel. These determinations are limited to additives that are flavors and are not formally submitted to the agency; the publicly available information is incomplete. Third, our analysis of conflicts of interest was limited to the employment of individuals who served on panels because the FDA does not request information on other financial and nonfinancial conflicts of interest. Fourth, our results do not prove that the conflicts of interest that we identified actually compromise the GRAS decision process, although they raise such concerns. As the IOM committee noted, the existence of a conflict of interest does not mean that a decision itself will be biased.[11] The individuals making these safety decisions may (1) act with great integrity and completely ignore their employer's business interests; (2) work in organizations that take strong measures to protect employees from conflicts of interest; or (3) see no conflicts because they believe a company takes seriously its legal obligation to produce safe products and would not jeopardize its reputation for short-term gain.

Despite the limited number of GRAS determinations that we evaluated, it is concerning that at least one of 10 individuals served on more than three-quarters of the 290 panels. First, is there a limited pool of experts? This is unlikely. There are multiple schools offering food science, toxicology and risk assessment degrees, and the Institute of Food Technologists has certified 1200 food scientists.[15] Second, is it beneficial to draw from a limited number of experts? Possibly. Certain experts may know the GRAS review criteria and procedures well, and because of the experience gained over many years their decisions may be less likely to be questioned by the FDA. However, repeated use of the same experts would limit the range of knowledge and experience on the panels. Third, does the concentration of expertise compromise the quality of decisions? Our study cannot answer this question.

Congress gave the FDA the responsibility to ensure that the manufacturers of additives to food properly make GRAS determinations. As recommended by the GAO, minimizing conflicts of interest in these determinations should be an essential part of that effort. The FDA's actions should be informed by its own drug development regulations[16] and policies on conflict of interest for its advisory committee members,[17] the policies of FEMA's expert panel,[18] and guidance from the European Food Safety Authority's advisory panels.[19,20] To minimize and manage conflicts of interest, an essential first step is for

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the FDA to require that it be notified of all GRAS determinations and the financial conflicts of interest of those who make these determinations. The agency should routinely make public all notifications of GRAS determinations, including those made by the FEMA panel, and all the information that it receives about conflicts of interest in these determinations.

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Invited Commentary

Conflicts of Interest in the Regulation of Food Safety
A Threat to Scientific Integrity

Marion Nestle, PhD, MPH

Conflicts of interest in medical research, education, and practice are well known to increase the risk of undue influence by corporate sponsors. Because conflicts of interest are so prevalent and troublesome, the Institute of Medicine (IOM) was asked to develop guidelines for dealing with them. An IOM committee reviewed the substantial body of evidence demonstrating that financial ties with pharmaceutical and medical device companies influence prescribing practices; the opinions of experts; and the design, conduct, and interpretation of research studies. The guidelines produced by the IOM focus on financial connections with industry, largely because such connections are easier to monitor than other conflicting interests, such as career advancement or personal favors.[1]

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Although conflicts created by financial relationships with drug and device companies have been a source of concern for decades, concerns about the effects of food company sponsorship on nutrition research, practice, and policy are more recent. Nevertheless, financial ties with food and beverage companies are now recognized as influences on federal dietary guidelines, opinions of nutrition professionals, and the inter-

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