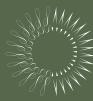


A report from



THE PEW CHARITABLE TRUSTS

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# Fixing the Oversight of Chemicals Added to Our Food

Findings and Recommendations of Pew's Assessment of the U.S. Food Additives Program



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## Overview

The American diet is dramatically different today compared with what it was when Congress enacted the Food Additives Amendment of 1958. Our food supply is more diverse and more processed and tends to be produced farther from where it is consumed. Chemicals used to process, package, store, and transport food more easily, as well as the compounds used to flavor, color or preserve it, are consumed by hundreds of millions of people every day. Ensuring that these additives are safe is a core function of the U.S. Food and Drug Administration under a law that, despite these tremendous changes to our diet, has remained largely unchanged for more than five decades.

From 2010 to 2013, The Pew Charitable Trusts conducted a comprehensive assessment of FDA's food additives regulatory program. Our analysis focused on how the program functions rather than weighing in on the ongoing controversies over the safety of specific chemicals. Relying on a transparent process that engaged stakeholders, we examined food additive issues in partnership with the food industry, the public interest community, and government. We held five expert workshops and published six reports in peer-reviewed journals. This report summarizes our findings and provides recommendations to address the problems we identified.

With more than 10,000 additives allowed in food, our research found the FDA regulatory system is plagued with systemic problems that prevent the agency from ensuring their use is safe. If one of these chemicals was causing health problems short of immediate serious injury, it is unlikely that FDA would detect the problem unless the food industry alerted the agency. When new research raises doubts about the safety of an additive that is already on the market, FDA's limited resources and authorities leave the agency heavily dependent on industry's voluntary cooperation with its requests and on public education. In practice, FDA may have to prove actual harm before it can restrict use of an additive in the food supply—even though Congress mandated that no additive is allowed in food unless there is a reasonable certainty that the intended use would not result in harm to consumers.

The cause of this breakdown in our food safety regulatory process is an outdated law with two significant problems. First, the law contains an exemption intended for common food ingredients that manufacturers have used to go to market without agency review if they determine that the additive use is "generally recognized as safe," or GRAS, in regulatory parlance. FDA has interpreted the law as imposing no obligation on firms to tell the agency of any GRAS decisions. As a result, companies have determined that an estimated 1,000 chemicals are generally recognized as safe and used them without notifying the agency. The firms usually use their own employees, consultants or experts that they select and pay to make the safety decision with no disclosure or apparent efforts to minimize the inherent conflicts of interest.

Voluntary GRAS notifications submitted by the food industry to the agency for review indicate that over the past decade, almost all new chemicals added directly to food have gone through this GRAS exemption rather than the formal approval process intended by Congress. The loophole essentially swallowed the law, hindering the agency's efforts to upgrade its science, because if FDA asks tougher questions, then firms may be less likely to voluntarily inform it of their GRAS decisions. In an increasingly global marketplace where additives and food are imported into the United States, the exemption presents a situation that undermines public confidence in the safety of food and raises significant questions about whether FDA has the ability to fulfill its statutory mission to protect public health by ensuring that all food additives are safe.

Secondly, the law does not give FDA the authority it needs to efficiently obtain the information necessary to identify chemicals of concern that are already on the market; set priorities to reassess these chemicals; and then complete a review of their safety. Moreover, the agency has not been given the resources it needs to effectively implement the original 1958 law. As a result, FDA has not reevaluated the safety of many chemicals originally

approved decades ago, generally rechecking safety only when requested by a company to do so, or when presented with allegations of serious adverse health effects.

One recent congressional remedy for food safety problems, the FDA Food Safety Modernization Act of 2011, required food manufacturers to produce a written plan to minimize hazards in food, including those created by additives, and have it in place by July 2012. The agency is behind schedule implementing this rule. In any case, the law falls short of what is needed, especially compared with modern tools that other agencies use to address problems with chemicals in consumer products.

## What FDA says today about the safety of additives

**“** It's perhaps a time to look at what the legal framework looks like and what opportunities there are now to ask and answer questions in new ways because of advances in science and technology.

—FDA Commissioner Margaret Hamburg, (Reuters, May 2013)

**“** We're not driven by a sense that there is a pressing public health emergency. But there are decisions being made based on data that we don't have access to, and that creates a question about the basis on which those decisions are made.

—FDA Deputy Commissioner for Foods Michael Taylor, (Associated Press, March 2013)

**“** FDA plans to issue guidance to industry on meeting the GRAS criteria established under the Act.

—FDA spokeswoman Theresa Eisenman, (USA Today, August 2013)

Our evaluation confirms the 2010 findings of the U.S. Government Accountability Office that FDA cannot ensure the safety of new and existing GRAS additives. But our report also identifies additional problems plaguing the disjointed food safety regulatory system, in which outdated science generally continues to be the basis of the assessment and decision-making process. To remedy the problems, we recommend that Congress update the Food Additives Amendment of 1958 to ensure that FDA:

- Approves the first use of all new chemicals added to food.
- Reviews new uses or changes to existing uses of previously approved additives.
- Streamlines its decision-making process so it is timely and efficient.
- Upgrades its science to determine safety.
- Uses the scientific tools and has access to the data it needs to set priorities to reassess the safety of chemicals already allowed in food and take action.

In the meantime, the agency should use its existing authority to limit the GRAS exemption, modernize its science, and review the safety of older chemicals. Until it does, the safety of additives to food largely depends on the motivation and competence of food manufacturers, rather than on the agency with the responsibility—but not the authority or resources—to protect the food supply from chemical additives.

## About the U.S. food additive regulatory program

Chemical additives are a fundamental part of our modern food supply. They provide flavor, enhance taste, appearance, and nutrient value, and prevent spoilage.<sup>1</sup> They are also used in food preparation and packaging materials. Their use enables consumers to have access to the food they want when they want it. But additives can also be controversial.<sup>2</sup>

The Food Additives Amendment of 1958,<sup>3</sup> passed by Congress and signed by President Dwight D. Eisenhower, designed a system to handle 800 additives<sup>4</sup>—far fewer than the 10,000 allowed today.<sup>5</sup> Most new chemical additives were supposed to go through a formal process of agency review that would be triggered when a company submitted a food additive petition.<sup>6</sup> The petition process requires FDA to notify the public; provide an opportunity for comment; and, if the agency deems the chemical's intended use to be safe, issue a regulation allowing the use.<sup>7</sup> The law provided an exemption for common food ingredients, such as oil and vinegar,<sup>8</sup> when their use is “generally recognized as safe,” or GRAS. When a chemical’s use is designated as GRAS, the formal public notice and comment rulemaking process is not required.<sup>9</sup>

### Meaning of “safe”

“Safe” for food additives 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.”<sup>10</sup> Congress set this high standard in 1958 because it wanted to encourage innovation while ensuring public confidence that the chemicals added to food would not have harmful effects years later.<sup>11</sup> The benefits of an additive are not a factor in determining whether it is safe.<sup>12</sup>

The GRAS exemption on its face sounds very straightforward. For an additive to qualify, its use must be safe, and that safety must be generally recognized by scientists knowledgeable about the safety of substances added to food.<sup>13</sup> But the food industry and FDA over the years have come to interpret the law as allowing additive manufacturers to determine that a chemical’s use is safe without notifying the agency.<sup>14</sup>

Initially, the GRAS exemption was used by the flavor industry for its products<sup>15</sup> and by manufacturers of additives that were in common use before 1958.<sup>16</sup> Many of the 10,000 additives were authorized by FDA or the food industry by the end of the 1960s.<sup>17</sup>

In 1969, because of safety concerns, President Richard M. Nixon ordered the agency to reassess the safety of additives and review all its prior decisions.<sup>18</sup> In 1982, an FDA-convened expert panel called the Select Committee on GRAS Substances completed its review of approximately 400 GRAS substances. The panel also laid out a rigorous approach to evaluating a chemical’s safety and suggested improvements to the agency’s process.<sup>19</sup> (See Box on page 4 for a timeline of food safety policies related to FDA.)

In the 1980s, the agency laid out a comprehensive Priority-Based Assessment of Food Additives program to reevaluate its previous decisions.<sup>20</sup> This program set priorities but did not simplify the process the agency followed to reverse additive decisions due to new science or other concerns. This formal rulemaking process provided manufacturers with a right to an administrative hearing in most circumstances. As a result, only a handful of additives were ever reassessed, and citizen petitions calling for restriction have often not been resolved.<sup>21</sup>

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## Food additives safety timeline

1938	Congress passes Federal Food Drug and Cosmetic Act of 1938. <sup>22</sup>
1958	Congress passes the Food Additives Amendment of 1958. <sup>23</sup>
1969	President Nixon orders a review of FDA's additive decisions. <sup>24</sup>
1973	FDA revises food additive and GRAS regulations. <sup>25</sup>
1982	Select Committee on GRAS Substances completes its review. <sup>26</sup>
1982	FDA issues guidance (known as Redbook) based on comprehensive assessment of program. <sup>27</sup>
1982	FDA launches its Priority-Based Assessment of Food Additives program. <sup>28</sup>
1997	FDA launches voluntary GRAS notification program. <sup>29</sup>
2000	FDA launches food contact substance notification program. <sup>30</sup>
2010	Government Accountability Office issues report finding flaws with GRAS program. <sup>31</sup>
2011	Congress passes the FDA Food Safety Modernization Act of 2011. <sup>32</sup>

With limited resources and an increasingly complicated rulemaking process, FDA had an overwhelming backlog of unresolved reviews by the early 1990s.<sup>33</sup> In response, in 1997 it began accepting voluntary notifications from additive manufacturers claiming that their chemicals are GRAS, which the agency would informally review.<sup>34</sup> The goal of companies submitting these notices is to persuade the agency to issue "no question letters."<sup>35</sup> In some cases, these are subsequently cited as evidence of FDA clearance, although the agency maintains that the letters are informal and do not constitute approval.<sup>36</sup> Today, virtually all new chemical additives added directly to food go through the GRAS exemption: This loophole has effectively swallowed the law.<sup>37</sup>

In 2010, the chairs of two congressional panels with jurisdiction over food safety, Senator Tom Harkin (D-IA) and Representative Rosa DeLauro (D-CT), asked the Government Accountability Office to scrutinize FDA's GRAS program. Later that year, the nonpartisan investigative arm of Congress concluded that:

- "FDA's oversight process does not help ensure the safety of all new GRAS determinations."
- "FDA is not systematically ensuring the continued safety of current GRAS substances."<sup>38</sup>

GAO made a series of six recommendations,<sup>39</sup> but FDA has made significant progress on only one of them, by issuing draft guidance on nanoengineered particles in 2012.<sup>40</sup> As of October 2013, the agency has made little progress on the others except to request comment on several in 2010.<sup>41</sup>

In 2011, Congress passed the FDA Food Safety Modernization Act to address long-standing concerns, primarily involving pathogens.<sup>42</sup> The law directs the agency to promulgate a series of regulations to prevent unsafe food from entering the market and gives it more authority to act if problems are found. One of these regulations, requiring food manufacturers to conduct a formal hazards analysis and have written risk-based preventive controls to minimize these hazards, was supposed to be finalized by July 2012. These rules have yet to be finalized, however, with only a proposal issued for comment in January 2013. When the regulations are completed and in effect, industry will have to evaluate in accordance with the rules its processes to ensure that no unapproved food additives are used in its products.<sup>43</sup>

Overall, Pew estimates that more than 10,000 chemicals are permitted to be used in human food, about half

as direct additives and the balance in packaging or other food contact materials.<sup>44</sup> The number is not in itself a problem. Rather, it is a reflection of the diversity of the food supply and the ingenuity of industry. It also hints at the challenges facing FDA in ensuring that these chemical additives are safe.

Pew determined that FDA has not reviewed the safety of about 3,000 of the 10,000 additives allowed in food.<sup>45</sup> An estimated 1,000 of these 3,000 are self-affirmed as GRAS by additive manufacturers without notice to or review by the agency, with the balance affirmed as GRAS flavors by an expert panel convened by the flavor industry trade association.<sup>46</sup> FDA monitors but does not review these flavor industry decisions.

## Pew's approach

In 2010, Pew launched its food additives project to:

- Evaluate the federal regulatory program designed to ensure that chemicals added to food are safe, including an examination of how it responds to advances in scientific understanding of chemical safety and changing uses of chemicals in food.
- Identify and assess viable, evidence-based, expert-vetted policy solutions if flaws are found in the regulatory program.
- Educate policymakers and key stakeholders, including industry, public interest groups, and medical associations, about the project's findings.<sup>47</sup>

To accomplish these objectives, Pew hired a team of scientists and lawyers to conduct the review, assembled expert advisers to guide our work, arranged for the American Academy of Pediatrics to provide critical review, and committed to a transparent process that engaged stakeholders and published our findings in peer-reviewed scientific journals.

Pew spent more than two years conducting research. As part of this research, we wrote an article that provided a comprehensive analysis of the U.S. food additive regulatory program, including its history and recent trends, which was published in a peer-reviewed journal of the Institute of Food Technologists, the professional society of food scientists.<sup>48</sup> Recognizing the global marketplace for additives, we commissioned an industry consulting firm and a professor of international food science to compare food additive laws in other developed countries. We also held two workshops focused on the science used to make safety decisions. These workshops were and co-sponsored by the journal Nature and the Institute of Food Technologists, with FDA participating in them and assisting in their design. More than 70 experts from industry, academia, government agencies, and public interest organizations participated in each event.<sup>49</sup> We published the proceedings of each of these workshops in the Institute of Food Technologists' journal.<sup>50</sup>

In 2012, Pew shifted from research to analysis of policy options. We held a workshop with multiple stakeholders, again in collaboration with Nature and the Institute of Food Technologists and with continued participation from FDA, to develop and critique potential recommendations proposed by participants. We also supported further research into three critical issues: nanoparticles, endocrine disruptors (substances that impair our hormones), and use of cell-based tests to identify chemical hazards (known as Tox21). To support this research, we held an additional workshop, supported three others, and funded an industry-affiliated think tank that convened a multidisciplinary team to evaluate methods of measuring exposure to nanoengineered particles in food.

With this foundation in place, in 2013 we identified three core issues and published our analysis in three peer-review journal articles. These issues are:

- Conflicts of interest that arise when an additive's manufacturer selects the scientist who makes the GRAS safety decision.
- Data gaps in toxicity testing for additives that have been previously approved by FDA.
- FDA's reliance on outdated science to assess the safety of chemical additives.

Finally, we hosted a fifth workshop to address potential conflicts of interest in more depth and submitted proposed guidance to FDA to help it resolve the issue and implement one of the Government Accountability Office's recommendations on this problem. (See Appendix 1 for a list of expert advisers, Appendix 2 for a list

of the peer-reviewed journal articles, and Appendix 3 for brief descriptions of each workshop that Pew's food additive project organized or supported.)

## Pew's findings

Our analysis focused on the overall regulatory system that is expected to ensure the safety of more than 10,000 chemical additives,<sup>51</sup> rather than on concerns raised about specific substances. We evaluated FDA's ability to fulfill the mission of its food additive regulatory program to protect public health from chemicals intentionally added to food or food packaging. We did not evaluate whether specific chemicals or groups of substances, such as salt, trans fat, caffeine, bisphenol A (which is used to line the inside of cans), or artificial colors or flavorings, cause actual harm to the public. We also did not consider contaminants found in food from natural sources or because of pollution, because those are not intentionally added and are regulated under a different set of health and safety standards.

Our research found that the FDA regulatory system is plagued with systemic problems that prevent the agency from ensuring the use of food additives is safe. If one of these chemicals were causing health problems short of immediate serious injury it is unlikely that FDA would detect the problems unless the food industry alerted it. This is particularly true if the health consequences of ingesting the additive take years or decades to become manifest after the food is eaten.<sup>52</sup> If the agency did identify a problem, it would still face challenges proving harm. Proof of harm was not the safety standard laid out by Congress in 1958. Under the law, a chemical may be used in food if competent scientists are reasonably certain that the use will cause no harm over a lifetime. In short, the question is whether it will cause no harm, rather than whether harm can be proven.

Under the law, FDA is supposed to make a determination only after it has considered the cumulative effects from similar chemicals and has information ensuring an adequate margin of safety.<sup>53</sup> But it is essentially impossible for the agency to connect an additive to a health problem when it has:

- Not been notified about an estimated 1,000 chemicals<sup>54</sup> currently allowed in food.
- Not been informed of actual usage for all chemicals.<sup>55</sup>
- Not been alerted to studies that suggest previously unknown potential health effects.<sup>56</sup>

In contrast, Congress in 1976 gave the U.S. Environmental Protection Agency greater, albeit still limited, authority to get more of the information it needed to make safety decisions for virtually all chemicals that are used in consumer products not regulated by FDA. In 1996, Congress gave EPA additional authority to protect the public from pesticide residues that may be in food.<sup>57</sup> (See Box 4.)

Despite these fundamental limitations and ongoing resource challenges, FDA has:

- Pursued implementation of its many responsibilities under the FDA Food Safety Modernization Act, especially the hazard analysis and preventive control requirements that should improve food additive safety.<sup>65</sup>
- Partnered with EPA and the National Institutes of Health on the federal Tox21 project, which set the stage to move chemical safety work into the 21st century.
- Launched the Advancing Regulatory Science Initiative,<sup>66</sup> in response to concerns raised by its Science Board, to help FDA develop tools, standards, and approaches to assess the products it regulates.
- Secured voluntary industry commitments to restrict use of existing additives when concerns have arisen.<sup>67</sup>
- Developed methods to estimate exposure to chemicals that are proposed for use in food.<sup>68</sup>

- Supported its food additive scientists, helping some of them to become recognized experts among their peers in the international community.<sup>69</sup>

## EPA v. FDA authority for chemical health and safety

Almost 20 years after Congress set up the regulatory program for food additives, it enacted the Toxic Substances Control Act of 1976 for use of nearly all chemical substances not regulated by FDA, whether toxic or not.<sup>58</sup> Although experts from Environmental Protection Agency,<sup>59</sup> the chemical industry,<sup>60</sup> and non-profit organizations<sup>61</sup> have called for strengthening this law, it does give EPA significantly more authority than FDA to obtain certain information needed to assess the safety of chemicals. About half of the additives to food (more than 4,500) are also regulated by EPA under this law. Specifically:

- EPA must be notified at least 90 days before the manufacture of a chemical and be given an opportunity to veto it. In contrast, according to the agency's interpretation of the law, manufacturers are not required to notify FDA when a chemical's use is determined to be GRAS.
- Manufacturers, importers, and processors must notify EPA every five years about the uses of chemicals and their amounts. In contrast, FDA lacks clear authority to gather this information, which is critical to estimating exposure.
- EPA must be notified of unpublished health and safety studies (including sampling results) indicating a substantial risk. There is no similar requirement for FDA.
- EPA can require testing by rule for new and existing chemicals. FDA's authority to require such testing has been questioned.<sup>62</sup>

In 1996, Congress went further, setting up a truly modern system to ensure the safety of pesticides used on food.<sup>63</sup> Manufacturers must report more information more often to EPA, and the pesticide's safety must be periodically reviewed by the agency under safety standards that are generally more rigorous than those for additives. Moreover, EPA has long had the authority to issue a "data call-in," requiring pesticide makers to test and provide other data for their products, through issuance of a simple order.<sup>64</sup>

In summary, Pew's analysis documented that while the FDA has made efforts to improve oversight a number of serious problems with the food additive regulatory system that have led us to conclude that the Food Additives Amendment of 1958 is not working as Congress intended. Specifically, we found:

- **Conflicts of interest.** Food manufacturers make GRAS safety decisions without FDA's knowledge despite conflicts of interest among those making the determinations. The GRAS loophole as currently used is inconsistent with Congress' plan and the practices of other developed countries.
- **Lack of information.** FDA lacks even basic information needed to assess the safety of thousands of chemicals that have been cleared for use in food. As a result, the agency reevaluates the safety of only a relative handful of existing additives.
- **Outdated science.** FDA uses outdated science to evaluate additive safety. It relies on a process that does not ensure independent scientific input and is often not transparent, particularly for food contact substances.
- **Missed safety deadlines.** The agency has fallen behind the FDA Food Safety Modernization Act rulemaking deadlines. Until those rules are in place, the agency has limited means to identify compliance problems.

Each of these findings is explored in more detail below.

## Conflicts of interest

Pew estimates that food manufacturers have designated 1,000 chemicals as “Generally Recognized as Safe” without FDA’s knowledge. This total does not include more than 100 chemicals that were reviewed by the agency for the first time through its voluntary GRAS notification program. It also does not include industry GRAS safety decisions involving existing additives that expand the allowed uses to different foods, allow increased concentrations in food, or accommodate different manufacturing processes or purities.

As noted above, Congress required the food industry to use a petition process to obtain FDA review and approval for safety decisions on additives. Only if there was “consensus” among scientists that the use was generally recognized as safe could a chemical avoid the petition route and be declared GRAS. From 2003 to 2012, however, only 23 food additive petitions were submitted. A handful of these were for changes to existing agency approvals, not new chemicals. In contrast, during this same time, food manufacturers submitted 332 GRAS notifications for more than 100 chemicals to FDA seeking letters from the agency saying it had “no questions” about the safety decision. This total does not include the safety decisions made by manufacturers that they chose not to provide to the agency.

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The GRAS exemption has become the loophole that has swallowed the law. It is an anomaly: No other developed country allows new chemicals to be added to a food product without government approval.

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Of the 451 GRAS notifications voluntarily submitted to FDA for review from 1997 to 2012, Pew found that financial conflicts of interest in these decisions are ubiquitous. Our findings relied on a conflict-of-interest framework developed by the Institute of Medicine in 2009. There is no basis to assume that the decisions withheld from agency review are any better. This lack of independent review raises concerns about the integrity of the process and the safety of the food supply, particularly when the manufacturer does not notify FDA.

The GRAS exemption has implications beyond the safety of a specific additive. It hinders the agency’s efforts to modernize its science, because if FDA asks tougher questions, then firms may be less likely to voluntarily inform it.<sup>70</sup> It also raises the issue of whether an additive can be recognized as safe while its identity and uses are kept secret.

Our analysis confirms the GAO’s conclusion that “FDA’s oversight process does not help ensure the safety of all new GRAS determinations.”<sup>71</sup> In an increasingly global marketplace where additives and food are imported into the United States, this loophole presents a situation that undermines public confidence in the safety of food and raises questions about FDA’s ability to ensure the protection of public health. Until conflicts of interest are minimized and safety decisions are subject to FDA review, the safety of food additives will largely depend on the integrity and competence of food manufacturers.

## Lack of information

Our investigation found that most additives are not tested for safety in accordance with FDA’s limited testing recommendations.<sup>72</sup> Agency guidelines, for example, say that chemicals intentionally added to food should be fed to laboratory animals to identify potential harmful effects, but we found that in the majority of cases,

chemicals directly added to food did not undergo this very basic test. The data gaps are not significantly better for the chemicals reviewed by the agency under its voluntary notification program, even when the agency had no questions.

In instances where FDA has recommended reproductive toxicity tests on additives, such studies do not appear to have been done in the vast majority of cases.<sup>73</sup> And when health and safety studies indicate possible problems, food companies are not obligated to notify the agency except in very limited circumstances.<sup>74</sup>

FDA also lacks clear authority to order companies to test the safety of chemicals they add to food. So even if the agency wanted to require additional testing, it is not clear that companies would be required to comply with such requests.<sup>75</sup> Further, companies are not required to regularly report the amount of a chemical added to food, making it difficult for FDA to assess exposure or identify troubling use trends.<sup>76</sup>

FDA's lack of authority to get the information it needs stands in stark contrast to the Environmental Protection Agency. Although its authority is still limited, EPA has access to more information on pesticides and on chemicals that go into consumer products not regulated by FDA than that agency has on chemicals used in food. Congress gave EPA the ability to get information on pesticides and to make decisions on individual chemicals in a streamlined fashion that reduces the administrative burden without limiting transparency. This differential treatment of chemicals, which often are regulated simultaneously by both agencies, makes little sense.

As a result of these limits, thousands of chemical additives approved before 1980 have not been reassessed for safety.<sup>77</sup> With a lack of resources, no mandate from Congress, and an unusually difficult rulemaking process, FDA takes a passive approach to reviewing the safety of existing chemicals. Its failure to set science-based priorities for reassessment wastes resources, leads to litigation, undermines public confidence, and may result in firms selling unsafe food.<sup>78</sup> Our analysis confirms the GAO's conclusion that "FDA is not systematically ensuring the continued safety of current GRAS substances"<sup>79</sup> but also finds that it applies to most additives other than GRAS substances as well.

## Outdated science

Much of the science that FDA uses to review the safety of chemicals added to food has not been significantly updated for decades.<sup>80</sup> Using the 1982 report by its Select Committee on GRAS Substances as a baseline, we identified areas of concern where the issues raised more than 30 years ago remain unresolved and relevant today. They include:

- **Behavioral effects.** FDA has not aggressively pursued the development of test methodologies for the impact of additives on behavior. It has not incorporated into its guidance methods that EPA and other developed country members of the Organization for Economic Cooperation and Development adopted years ago.
- **Endocrine systems.** FDA has not taken a leadership role in the development and validation of new technologies to identify and evaluate additives for potential endocrine disruption to hormones. Unlike EPA, it has not adopted or made use of validated screening tests and predictive models.
- **Subpopulations.** FDA has not systematically considered exposures of additives to sensitive populations except for infants. For hypersensitivity, it has not developed guidelines to screen or test for potential dangers or offered an effective system for consumers to report health problems.
- **Thresholds of alleged toxicological insignificance.** FDA has adopted inadequate thresholds of exposure in rules and guidance below which industry is not expected to develop toxicity data when evaluating the safety of a chemical.

- **Absorption, distribution, metabolism, and excretion data.** FDA's guidance allows industry to make safety decisions without the detailed data necessary to understand how the human body handles and eliminates chemicals that may be in food.
- **Reassessment and consistency across substances.** FDA has not developed a system to prioritize its review of previous safety decisions. Instead, it relies on a case-by-case approach. In addition, it does not appear to closely coordinate its hazard or exposure assessment with EPA when a chemical is regulated by both agencies.
- **Weight of evidence.** FDA maintains that it closely scrutinizes all available studies. But its analysis is often based on professional judgment without using the available methods to compare various studies in a more rigorous, transparent, and reproducible manner.<sup>81</sup>

In addition, the program Congress imposed on FDA in 1997 to review voluntary notifications for food contact substances lacks transparency. Until the agency takes final action on a notice, the public is unaware of the decision, and the notices are not publicly available. This process limits participation by academics, competitors, public interest organizations, and the public in additive safety reviews.<sup>82</sup> As a result, the agency's decisions generally do not benefit from outside expertise.<sup>83</sup>

## Missing safety deadlines

As noted, under a provision in the FDA Food Safety Modernization Act of 2011, industry will have to evaluate its processes to ensure that no unapproved food additives are used in its products. Yet FDA has fallen behind in finalizing those rules, which were supposed to take effect by July 2012 but were not even issued in draft form until January 2013. Until the law's regulations are in place, FDA lacks an effective system to ensure compliance with food additive regulations, and food firms do not feel obligated to have internal management standards in place to prevent violations.<sup>84</sup> In the meantime, FDA relies on tips and complaints from competitors, voluntary reports from manufacturers, or the infrequent inspections it conducts to identify compliance problems with its regulations for additives to food.<sup>85</sup>

## Pew's recommendations

The systemic problems plaguing the food additive regulatory program prevent FDA from ensuring the safety of all chemicals added to our food as Congress has intended, but there is no need to start over. Rather, it is better to adopt administrative and legislative solutions so that the Food and Drug Administration can more effectively ensure that new and existing uses of chemical additives in food are safe.

We recommend that FDA take immediate action on its own to narrow the “generally recognized as safe” exemption to what Congress originally intended so that it is no longer a loophole and that it modernize its food additive science. We believe Congress should provide FDA with the funding and authority it needs and ensure that the agency takes these actions. Legislative oversight and direction are essential to build and maintain stakeholder support.

For additives already on the market, the situation is different. FDA lacks the clear authority to get the information it needs to identify problems, set priorities, and, when necessary, efficiently restrict the use of these additives to ensure safety. With about half of the additives already regulated by the Environmental Protection Agency under the Toxic Substances Control Act, and with many additives also regulated as pesticides, Congress needs to look at what is working at both agencies and devise an integrated chemical safety program that allows each agency to fulfill its essential responsibilities in a coordinated manner to minimize duplication of effort, recordkeeping, and the regulatory reporting burden on industry.

To accomplish these objectives, we make the following recommendations:

- Close the GRAS loophole.
- Modernize FDA’s food additive science.
- Ensure that existing chemical additives are safe.
- Establish a fee-based funding program to pay for the review process.

Each recommendation is examined in more detail below.

### Close the GRAS loophole

Congress should amend the Food Additives Amendment of 1958 so that FDA approves the use of all new chemicals added to food and reviews significant changes to the use of previously approved additives by implementing a more streamlined and efficient decision-making process.

The food industry (and, to some extent, the agency itself) relies on the GRAS exemption because it believes that the food additive petition process that Congress adopted in 1958 is too burdensome and time-consuming, requiring that FDA use extensive formal rulemaking procedures. It prefers the GRAS notification program because it is informal and, as currently constructed, is voluntary. Manufacturers have the flexibility to seek FDA review when they want the legitimacy provided by that review and have the option to keep their innovations secret from competitors, even if the FDA and the public are excluded.

Yet as discussed above in our findings section and documented in our paper in the Journal of the American Medical Association-Internal Medicine,<sup>86</sup> the GRAS program has serious problems, especially with regard to conflicts of interest, that must be addressed in order for the public to have confidence in the safety of foods. We recommend that Congress require FDA to review and, if appropriate, approve the first food use of a new

chemical. The GRAS notification and the food contact substance notification program should be limited to changes in existing uses or to additional uses only after FDA has approved the chemical's use in food.

We recognize that concerns have been raised about the burden of the current food additive petition process. This is why we recommend that Congress establish a modernized, streamlined FDA approval process that the agency can effectively and efficiently administer; allows meaningful public input; meets industry's legitimate needs for timeliness and predictability; and, most importantly, restores public confidence that chemical additives are safe. Congress should consider as potential models existing programs that review and approve medical devices, drugs, and pesticides used on food.

To ensure that the notification programs are transparent and credible, Congress should allow FDA to revise the food contact substance notification program so it is more transparent. The notices, with confidential business information removed, should be publicly available on its website before the agency takes final action. Its decision letter to the company should also be posted on its website. This approach would be similar to what is done for GRAS notifications. In both programs, the public and stakeholders should have an opportunity to comment in an informal process before the agency takes final action.

Until Congress changes the law, FDA should revise how it implements the GRAS program to minimize conflicts of interest and to ensure that an additive's use is truly generally recognized as safe by the scientific community

General recognition of additive safety requires consensus in the scientific community. There can be no such consensus if the chemical's use is unknown to the scientific community and to FDA. The experts charged with assessing whether a scientific consensus exists should not have a relationship with the company that makes and sells the chemical additive. In addition, the experts must fairly represent the diversity of the scientific community.

Congress made clear that, in cases where there is no general recognition of safety, FDA should make the decision through the food additive petition process, which requires public notice and comment followed by an FDA rule. As an interim step, FDA should use its existing authority to establish clear guidance that an evaluation by an expert with a conflict of interest will not be effective:

- Until the agency has reviewed it and agreed upon its safety.
- Unless the expert making the decision would be eligible to serve on an agency advisory committee considering the issue.

## Modernize FDA's food additive science

Congress should ensure that FDA uses the latest scientific methods to assess additive safety

Consistency is important in science, but FDA's approach to safety assessment is significantly different from those used by EPA and other agencies. FDA has the authority to upgrade its regulatory science and is committed to doing that through its Advancing Regulatory Science Initiative, but that initiative primarily focuses on areas other than chemical additives to food. Some of the differences in the way EPA and FDA assess additive safety stem from FDA's being subject to an outdated law while the laws for other chemicals regulated by EPA are more recent.

To overcome these safety assessment problems, Congress should provide FDA with directions to modernize its program so that it evaluates a wider array of important health effects and improves its ability to ensure that public health is protected. It should consider the standards used in the Food Quality Protection Act of 1996,

especially the margins of safety needed for vulnerable populations such as children and pregnant women and the evaluation of chemicals for potential endocrine disruption.

FDA should modernize the regulatory science it uses to evaluate the safety of chemical additives

FDA should upgrade the science used to evaluate the safety of additives through its ongoing Advancing Regulatory Science Initiative. As a critical first step, the agency should seek advice from an independent scientific advisory body to guide its modernization efforts. It should also continue and enhance its evaluation of the Tox21 program, which shows significant promise in setting priorities. The evaluation should consider two aspects:

- **Upgrade the science:** FDA should define what constitutes harm and test for potential endocrine disruption, behavior effects, and developmental neurotoxicity at all life stages, including, when appropriate, additional safety factors for children and pregnant women.
- **Improve the process:** FDA should more clearly separate the evaluation of science from management decisions, minimize conflicts of interest and bias from industry evaluations, provide a clear process to assemble and evaluate the evidence, and harmonize its analysis to be consistent with other agencies, especially EPA.

The FDA should adopt and implement a science-based program to systematically review existing chemicals

FDA's current approach of reacting to citizen petitions, industry notifications, and media reports regarding additives already on the market is ineffective. Citizen petitions languish, and the agency stretches its limited resources, shifting from one additive to another without necessarily resolving the underlying scientific challenges.

The agency needs to rejuvenate its system to set priorities using modern scientific tools. We recognize that its Chemical Evaluation and Risk Estimation System is designed to accomplish this goal, but the details are unclear. Specifically, it is not clear that the system incorporates the information developed from Tox21 or that it will be rigorously validated through a transparent process that engages stakeholders. Both are essential.

The agency's top priorities should be widely used additives, those for which it lacks data, and those that are the source of public health concerns. Additives that do not merit immediate review include those recently reviewed and accepted by the European Union or other international organizations, or those that FDA moves to a lower priority based on the available evidence after some form of public input. Based on these priorities, the agency should establish a schedule to reassess chemicals in light of its resources. Additives that are designated as low-priority could be moved up based on new science or changing uses.

Although FDA may not immediately have the resources or tools to fully implement the plan, Congress is unlikely to give it what it needs without a plan in place. Industry and the public may withhold support if they lack confidence in its likelihood of success.

## Ensure that existing chemical additives are safe

Congress should update the law to give the agency the ability to obtain the information it needs to set priorities and reassess the safety of existing additives

To effectively manage 10,000 additives, FDA needs to efficiently estimate consumer exposure, be alerted by industry to health and safety studies, and require testing. With about half the additives already regulated by EPA, we recommend that Congress strengthen and amend the Toxic Substances Control Act so food manufacturing

companies routinely report to EPA via existing programs the information about the use of those additives also regulated by that law and notify FDA through EPA when it believes there is a substantial risk posed by an additive that was previously unknown.

In addition, Congress should provide clear authority for FDA to issue orders requiring the food industry to conduct testing and submit safety and use data to the agency, as EPA is authorized to do for pesticides used on food.

The law should be updated to require FDA to conduct a retrospective assessment of previously cleared chemicals through a transparent public process that sets priorities based upon available information

Because 10,000 chemicals are already allowed in food, we acknowledge that it is not practical to conduct a thorough safety evaluation of all of them under current constraints. If FDA had the authority to get the information it needs and coupled it with modern scientific tools to set priorities, then reviews could be done more quickly and efficiently—especially if food manufacturers cooperated in the analysis.

The task is daunting and would take time, but the increasing complexity of our food supply chain makes it necessary so that consumers can have confidence in it. We recommend that Congress and the agency set a specific timetable for designing and completing a review cycle, as was done for pesticide food tolerances under the Food Quality Protection Act of 1996.

Until Congress updates the law, FDA needs to request missing information from other agencies and industry

Until Congress gives FDA the additional data collection authority and streamlined decision-making process it needs, we recommend that the agency obtain data from EPA and from the European Commission, which has undertaken a similar effort for chemicals added to food and other consumer products. The agency should also request that industry provide it with all relevant health and safety studies and exposure information.

## Establish a fee-based funding program

Congress needs to establish a fee-based program similar to that used for the pharmaceutical and pesticide industries to pay for FDA's review and implementation of the food additives program. Although fees are not popular with manufacturers, FDA otherwise will not be able to make the investment it needs to ensure that food additives are safe and to restore public confidence in the safety of these additives. The agency has sufficient experience with fees to make independent science-based decisions in a timely and effective manner.

## Endnotes

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## **Appendix 1**

### Expert academic advisers

The following individuals served as expert academic advisers. They provided guidance to Pew throughout the project, often commenting on drafts of articles and moderating sessions of workshops. While invaluable to this report, these advisers are not responsible for our analysis, findings, or recommendations.

**P. Vincent Hegarty, Ph.D.**, *Founding Director and Professor Emeritus, Institute for Food Laws and Regulations, Michigan State University*

**Joseph Hotchkiss, Ph.D.**, *Director and Professor, School of Packaging, Michigan State University*

**D. Gail McCarver, M.D.**, *Professor, Pediatrics and Pharmacology, Co-director, Clinical Pharmacology, Pharmacogenetics and Teratology, Children's Hospital of Wisconsin, Medical College of Wisconsin*

**J. Routt Reigart, M.D.**, *Professor Emeritus, Department of Pediatrics, Medical University of South Carolina*

**Stephen M. Roberts, Ph.D.**, *Director, Center for Environmental & Human Toxicology, University of Florida*

**I. Glenn Sipes, Ph.D.**, *Professor of Pharmacology, Chair, Department of Pharmacology, University of Arizona*

**John G. Vandenbergh, Ph.D.**, *Professor Emeritus, Department of Biology, North Carolina State University*

**Tracey J. Woodruff, Ph.D., MPH**, *Professor and Director, Program on Reproductive Health and the Environment, Institute for Health Policy Studies, University of California, San Francisco*

**R. Thomas Zoeller, Ph.D.**, *Professor, Biology Department, University of Massachusetts Amherst*

## **Appendix 2**

### Peer-reviewed articles published by Pew staff on food additives

(in reverse chronological order)

Neltner, T. G., N. R. Kulkarni, H. M. Alger, M. V. Maffini, E. D. Bongard, N. D. Fortin, and E. D. Olson, "Navigating the U.S. Food Additive Regulatory Program," *Comprehensive Reviews in Food Science and Food Safety* (2011)10:342-368, <http://onlinelibrary.wiley.com/doi/10.1111/j.1541-4337.2011.00166.x/abstract>.

Maffini, M. V., H. M. Alger, E. D. Bongard, and T. G. Neltner, "Enhancing FDA's Evaluation of Science to Ensure Chemicals Added to Human Food Are Safe: Workshop Proceedings," *Comprehensive Reviews in Food Science and Food Safety* (2011)10: 321-341, <http://onlinelibrary.wiley.com/doi/10.1111/j.1541-4337.2011.00165.x/abstract>.

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Magnuson, B., I. Munro, P. Abbot, N. Baldwin, R. Lopez-Garcia, K. Ly, L. McGirr, A. Roberts, and S. Socolovsky "Review of the regulation and safety assessment of food substances in various countries and jurisdictions," *Food Additives & Contaminants: Part A.*, published online June 20, 2013, <http://dx.doi.org/10.1080/19440049.2013.795293>.

Beausoleil, C., J.-N. Ormsby, A. Gies, U. Hass, J. J. Heindel, M. L. Holmer, P. J. Nielsen, S. Munn, G. Schoenfelder "Low Dose Effects and Non-monotonic Dose Responses for Endocrine Active Chemicals: Science to Practice Workshop: Workshop Summary, *Chemosphere*, accepted June 13, 2013.)

A series of articles developed by the "NanoRelease Food Additive" project lead by the International Life Sciences Institute Research Foundation will publish a series of five articles and a State of the Science report on methods to measure the release of nanoengineered particles from food. A summary of these articles will be submitted to one or more of the following peer-reviewed journals in 2013 and 2014: *Nanotoxicology; Regulatory Toxicology and Pharmacology; Comprehensive Reviews in Food Science and Food Safety; and Nature Nanotechnology*.

## **Appendix 3**

### Stakeholder events

Pew-led with co-sponsorship of the journal *Nature* and the Institute of Food Technologists

(in reverse chronological order)

*"Enhancing FDA's Evaluation of Science to Ensure Chemicals Added to Human Food are Safe,"* April 5-6, 2011, at Pew's Washington, DC, conference center

- Pre-workshop webinar on March 29, 2011
- Report for participants distributed on March 29, 2011
- Proceedings published in Oct. 2011

*"Perspectives on FDA's Exposure Assessment to Ensure Substances Added to Human Food are Safe,"* Nov. 17-18, 2011, at Pew's conference center

- Pre-workshop webinar on Oct. 19, 2011
- Report for participants distributed on Nov. 10, 2011
- Proceedings published in Dec. 2012

*"Workshop on Enhancing FDA's Food Additives Program to Ensure the Safety of Substances Added to Food,"* April 19, 2012 at Pew's conference center

- Policy suggestions distributed to participants on April 12, 2012

*"Workshop on Non-Monotonic Dose Responses: Relevance and Implications for Food,"* April 20, 2012, at Pew's conference center

*"Workshop on Potential Conflicts of Interest in GRAS Additive Decisions,"* August 7, 2013, at Pew's conference center

- Draft guidance distributed to participants on July 23, 2013

Other significant food additive-related workshops organized or supported by Pew

*"Food Additives Workshop,"* Dec. 13, 2010, in Washington, DC, convened by the Grocery Manufacturers Association to learn about Pew's project.

*"International Law for Chemicals Added to Food: Different Approaches to Protecting Public Health,"* June 13, 2011, in New Orleans, LA, convened by Pew as a session at the annual meeting of the Institute of Food Technologists.

*"Navigating the U.S. Food Additives Regulatory Program,"* May 22, 2012, as a webinar convened by Pew for the Institute of Food Technologists.

*"Low Dose Effects and Non-monotonic Dose Responses for Endocrine Active Chemicals: Science to Practice Workshop,"* Sept. 12-14, 2012, in Berlin, convened by the European Commission and National Institute of Environmental Health Sciences with facilitation and technical support provided by Pew.

*"Workshop on Measurement Methods for the Release of Engineered Nanomaterials from Food and Absorption by the Body,"* Dec. 11-12, 2012, at Pew's conference center convened by the International Life Sciences Institute Research Foundation as part of the Pew co-funded NanoRelease Food Additive Project.

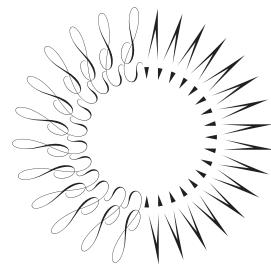
*"Chemical Testing in the 21st Century: Opportunities and Challenges,"* Jan. 23-24, 2013, at Pew's conference center convened by the Environmental Defense Fund.

*"Environmental Health and Food,"* May 6, 2013, at a session of the annual meeting of Academic Pediatrics Association.

*"The Whole Package: Regulating Chemicals in the Food Supply,"* May 21, 2013, as a webinar for the Sustainable Agriculture & Food Systems Funders Network.

Pew's food additive staff also delivered at least a dozen additional presentations as part of other events for industry, scientific, or public interest organizations.





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