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Strengths and Weaknesses of the Current Regulatory Framework

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1 OVERVIEW OF THE REGULATION OF PLANT PRODUCTS UNDER THE COORDINATED FRAMEWORK

The executive branch formally announced its biotechnology policy on June 26, 1986, in the form of the Coordinated Framework for Regulation of Biotechnology (OSTP 1986), as reviewed previously and described in more detail in this article. The three lead agencies with responsibility for implementation of the policy were the US Department of Agriculture (USDA), the Department of Health and Human Services (DHHS), and the Environmental Protection Agency (EPA). Since announcement of the coordinated framework, federal regulators have cleared the way for hundreds of new agricultural, health care, and industrial products, including dozens of plants modified through modern biotechnology.

The coordinated framework established the basis for regulation of new plant varieties produced by rDNA techniques. Although the term genetically modified is commonly used to describe these transgenic plants, it could just as easily be applied to products and plants that result from conventional plant breeding techniques because these techniques also result in the modification of the plant's genetic makeup. The coordinated framework successfully resolved early disputes among the agencies concerning products that fall within the jurisdiction of more than one agency. For example, USDA would regulate plants grown to produce food or feed, and the Food and Drug Administration (FDA) within DHHS would have jurisdiction over the food or feed itself.

What the framework left unresolved were jurisdictional issues that would have to be addressed before commercial introduction of a number of products, including transgenic plants that were modified to resist disease and ward off insect pests. In fact, plants modified to exhibit pesticidal traits were not specifically addressed by the coordinated framework. Although it contained an extensive discussion of EPA's authority to regulate pesticides, the framework concentrated almost exclusively on microorganisms that were produced with pesticidal intent (OSTP 1986, p. 23319); this was undoubtedly because research involving transgenic pest-protected plants was at a relatively early stage.

In the 14 years since introduction of the coordinated framework, the lead agencies have worked to coordinate their oversight responsibilities and have resolved many of the issues that

were either unforeseen or unaddressed in 1986. Hundreds of new plant varieties have been the subject of federally approved field tests, and dozens of new plant products are on the market today (section 1.5.5). These commercially available transgenic crops include corn, cotton, potato, squash, and papaya that are protected against harmful insects or viruses; and corn, cotton, canola, soybeans, and sugar beet that are modified to tolerate the application of herbicides. Determining which agencies have responsibility for a particular plant-related product depends on two factors: the traits that have been engineered into the plant and the use of the crops that will be harvested. A summary of the key regulatory schemes will help to put this in perspective. In general, the committee found that

Under the coordinated framework, transgenic products are subject to regulation under existing statutory authorities and USDA, FDA, and EPA are exercising regulatory oversight on that basis.

1.1 US Department of Agriculture and the Regulation of Plants

USDA has responsibility for protecting plants and for safeguarding American agriculture. The Federal Plant Pest Act (FPPA) provides USDA with the authority to regulate the movement into or within the United States of organisms that may pose a threat to agriculture and to prevent the introduction, dissemination, or establishment of such organisms (US Congress 1957).[1] The plant pest definition under FPPA is listed in a previous article (US Congress 1957, section 150 aa(c)). The FPPA establishes a permit system that has been expanded by USDA into a comprehensive prerelease review system for potential plant pests. Building on that system, which has been in effect for many years, USDA issued rules in 1987 designed specifically to regulate genetically modified organisms before their release into the environment or movement in commerce (USDA 1987). Those rules prohibited the introduction of so-called regulated articles without a permit from the USDA Animal and Plant Health Inspection Service (APHIS). The process typically has been used to address small-scale field testing of genetically modified plants before commercialization, and it now requires either a permit for or advance notification of the test.

Under the USDA rules, a permit is required for (1) any organism altered or produced through genetic engineering if the donor or recipient organism either (a) belongs to a group of plant pests listed in 7 C.F.R. § 340.2 or (b) is an unclassified organism and/or an organism whose classification is unknown, (2) any product that contains a listed plant pest or unknown/unclassified organism, or (3) any other organism or product altered or produced through genetic engineering that USDA determines to be or has reason to believe is a plant pest (as defined by 7 C.F.R. § 340.1). The rules define genetic engineering as genetic modification of organisms by rDNA techniques. The rules do not regulate research with genetically modified organisms in a laboratory or contained greenhouse but come into play only when a person seeks to introduce genetically modified organisms into the environment or interstate commerce.

USDA has issued some 887 permits for genetically modified organisms since the program began in 1987, primarily for limited field tests involving crop plants (USDA 1999f).[2] On the basis of its experience with the permit program, USDA has provided a number of exemptions for articles that it has determined do not pose a plant pest risk. One of the more important exemptions authorizes the introduction of certain regulated articles without a permit provided that USDA is notified in advance. To qualify for the notification process, a regulated article must be one of the plant species identified in the rule and must meet six eligibility criteria (for example, introduced genetic material must not cause the introduction of an infectious entity) and six performance

standards (for example, field trials must be conducted so that regulated articles will not persist in the environment) (USDA 1987, section 3b). In the notification process, USDA must either acknowledge that notification is appropriate for the designated introduction activity (import, interstate movement, or environmental release) or deny permission for introduction and require a permit (USDA 1987, section 3e). USDA has acknowledged approximately 4,400 notifications for field tests to date; another 260 have been denied, withdrawn or otherwise voided. As noted previously, about 40% of permits and notifications involve transgenic pest-protected plants.

Another important exemption allows researchers to petition USDA for a determination that an article should not be regulated as a plant pest. The rules contain detailed requirements for the data and information to be included in a petition for determination of "nonregulated status". USDA will publish a notice in the *Federal Register* and provide for a 60-day public-comment period for each petition that meets the rules' eligibility criteria. USDA has approved 50 of 69 petitions submitted for nonregulated status; the other 19 were withdrawn or found to be incomplete or void.

Before issuing a permit for the release of a regulated article into the environment, USDA must follow the requirements of the National Environmental Policy Act (NEPA; US Congress 1969) by preparing a publicly available environmental assessment and if necessary, an environmental impact statement (USDA 1995b). Before acknowledging the appropriateness of a notification or issuing a permit for an environmental release, USDA must coordinate with the state where the release is planned, submitting a copy of the application or notification to the state department of agriculture for review (USDA 1987, sections 3e and 4b).

1.2 The Food and Drug Administration and the Regulation of Food

The Federal Food, Drug and Cosmetic Act (FFDCA) provides FDA with broad regulatory authority over foods and food ingredients (US Congress 1958). No particular statutory provision or regulation deals expressly with food produced by biotechnology. FDA's formal position concerning such foods, as expressed in the coordinated framework, is that the statute provides ample tools for the agency to apply to meet the challenges of novel foods and biotechnology (OSTP 1986, p. 23309). That position was confirmed in 1992 on publication of a comprehensive policy statement for foods derived from new plant varieties (FDA 1992). [3]

The 1992 policy provides that foods developed through genetic modification are not inherently dangerous and, except in rare cases, should not require extraordinary premarket testing and regulation. The policy holds that genetically modified foods should be regulated as ordinary foods are unless they contain substances or demonstrate attributes that are not usual for the product. According to FDA, most food-related issues concerning products of biotechnology will involve the application of sections 402(a)(1) or 409 of FFDCA (see US Congress 1958, sections 342(a)(1) and 348, respectively).

Section 402(a)(1) does not subject new food products to premarket approval but does establish a safety standard that can come into play depending on the circumstances presented by a given food or food constituent. The section is FDA's primary enforcement tool for regulating the safety of whole foods, including foods derived from genetically modified plants. Any person who introduces food into interstate commerce is responsible for ensuring that the food does not run afoul of the provisions of section 402(a)(1). Under FFDCA, FDA is authorized to seize adulterated food, enjoin its distribution, and prosecute persons responsible for its distribution (US Congress 1958, sections 332-334).

Under the safety standard of section 402(a)(1), food is considered to be adulterated if it contains any substance that occurs unexpectedly in food at a level that may be "injurious to health".

Those substances include naturally occurring toxicants whose levels are unintentionally increased by genetic modification and unexpected toxicants that appear in the food for the first time. The policy provides guidance to the food industry in the form of flowcharts and other instructions regarding scientific approaches to evaluating the safety of foods derived from new plant varieties, including the safety of added substances that are subject to section 402(a)(1). Perhaps most important, FDA encourages voluntary consultations between producers and agency scientists to discuss relevant safety concerns.

Section 409 of FFDCA provides for the regulation of "food additives", defined broadly as including any substance "the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component of food…and which is not generally recognized as safe" for such use (US Congress 1958, section 321(s)). A food additive must be approved by FDA before being used in food. The statutory mechanism for securing agency approval is the submission of a food additive petition, which must contain data and information that show a reasonable certainty that the additive will be safe for its intended use. The petition is subject to public notice and comment.

The 1992 policy acknowledges that, in some cases, whole foods derived from new plant varieties, including plants developed by new genetic techniques, might fall within the scope of section 409. It is the transferred genetic material and the intended expression product of that material in the plant that could be subject to food additive regulation if such material or expression product is not generally recognized as safe (GRAS). FDA has rarely had occasion to review the GRAS status of foods derived from conventionally bred plants, because these foods have been widely recognized and accepted as safe. The policy is clear, however, that in regulating foods and their byproducts derived from new plant varieties, FDA will use section 409 to require food additive petitions whenever safety questions are sufficient to warrant formal premarket review to ensure public health protection.

FDA does not generally expect that transferred genetic material itself to be subject to food additive regulation. In regulatory terms, such material is presumed to be GRAS. Substances present in food as a result of the presence of transferred genetic material, referred to as "expression products," will typically be proteins or substances produced by the action of protein enzymes, such as carbohydrates, fats, and oils. If the intended expression product differs significantly in structure, function, or composition from substances found ordinarily in food or if it has no history of safe use in food, it might not be GRAS and might require food additive regulation. Again, the 1992 policy provides guidance to producers in evaluating the safety of food that they intend to market, including criteria and analytic steps for determining whether a product is a candidate for food additive regulation and whether consultation with FDA is appropriate. Ultimately, food producers are held accountable for the safety of their products.

As of July 1999, FDA has conducted 45 final consultations under its 1992 policy, of which 16 concerned transgenic pest-protected plants (FDA 1999b). A final consultation is evidenced by a letter from FDA acknowledging completion of the consultation process. The agency likely has had many more preliminary consultations with researchers and producers during the same period, although no public record is kept of such meetings.

1.3 The Environmental Protection Agency and the Regulation of Pesticides

The Federal Insecticide, Fungicide, and Rodenticide Act

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) is a licensing statute under which EPA regulates the sale, distribution and use of pesticides (US Congress 1947). Pesticide is defined broadly as including any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating a pest (US Congress 1947, section 136(u)). The concept of pesticidal intent is critical to the definition pesticides under federal law. Pest means: 1) any insect, rodent, nematode, fungus, weed, or 2) any other form of terrestrial or aquatic plant or animal life, or virus, bacterium, or other microorganism (except viruses, bacteria, or other microorganisms on or in living humans or other living animals) that the EPA declares to be a "pest" (US Congress 1947, section 136(t)).

The statute authorizes EPA to exempt a pesticide from the requirements that would ordinarily apply if the agency determines that the substance is either adequately regulated by another federal agency or of a character that is unnecessary to regulate under FIFRA to carry out the purposes of that statute (US Congress 1947, section 136 w(b)). Examples of exemptions issued by EPA are shampoo products designed to kill head lice and subject to FDA regulation as human drugs; articles treated with pesticides, such as insect-protected lumber and mildew-resistant paints, in which the pesticides are already registered for such use; and natural and synthetic pheromones when used in traps (EPA 1988a, sections 152.20b, 152.25a, and 152.25b). EPA has also issued regulations identifying substances that are not considered pesticides at all because they are not for use against pests or not used for a pesticidal effect (EPA 1988a, sections 152.8 and 152.10). Such substances include fertilizers, plant nutrients, deodorizers, and products that exclude pests by providing a physical barrier and that contain no toxicants, such as pruning paints for trees. In sharp contrast with pesticides exempted from FIFRA regulation, substances that EPA deems to fall outside the definition of a pesticide are subject to regulation under other federal statutes, such as section 409 of FFDCA (US Congress 1958) for food additives, the Toxic Substances Control Act (US Congress 1976b) for industrial and consumer chemicals, and the Consumer Product Safety Act (US Congress 1976a).

Modern genetic techniques permit the development of plants that produce their own pesticides or are otherwise resistant to insects, viruses, and other plant pests. That capability is in some respects an extension of conventional plant breeding techniques that attempt to select the heartiest and most disease-resistant strains for use in producing hybrid seeds and plants for commercial agriculture and home gardens. Plants and other macroorganisms with pesticidal properties have been exempted from the requirements of FIFRA for many years (EPA 1988a, section 152.20a). The exemption was established before any consideration of modern biotechnology to exempt the many plant species that are naturally pest-protected (such as chrysanthemums) and insects and other macroorganisms (such as lady bugs and praying mantises) that act as natural pest control agents (OSTP 1986, p. 23320). EPA refers to this entire category of products as "biological control agents."

To be registered under FIFRA, a pesticide must not cause "unreasonable adverse effects on the environment". This phrase is defined as including both ecological concerns and risks to human health. Traditionally, that criterion required EPA to balance the potential adverse effects associated with the use of compounds that are often inherently toxic against their social, economic, and environmental benefits (US Congress 1947, section 136bb(1)). Since 1996, EPA has been required to apply a safety-only standard when examining the potential dietary risks that may be posed by

residues of a pesticide that might be found in food (US Congress 1947, section 136bb(2)). Registration is conditioned on the submission and review of test data regarding the health and ecological effects of the pesticidal substance.

Section 408 of the Federal Food, Drug, and Cosmetic Act

Any substance deemed to be a pesticide under FIFRA is automatically subject to regulation under FFDCA section 408 if used on a food or feed crop or if residues of it are otherwise expected to occur on food or feed (US Congress 1958). EPA's jurisdiction under FFDCA applies even if the pesticide has been exempted from regulation under FIFRA. Section 408 provides authority for EPA to issue regulations that permit pesticide residues in or on food. Maximum permissible residue levels for pesticides are referred to as tolerances and are set by rule for raw agricultural commodities and for processed food and animal feed under the same "reasonable certainty of no harm" standard that FDA applies to food additives under section 409 of FFDCA. Section 408 also authorizes EPA to issue exemptions from the requirement of a tolerance where a pesticide poses no toxicological concerns and/or dietary exposure is negligible. By definition, a pesticide cannot be a food additive.

Additional data related to dietary exposure must be submitted to EPA to support issuance of a tolerance in conjunction with the registration of a food-use pesticide. As with unapproved food additives, in the absence of a duly promulgated tolerance or exemption, or if a residue level exceeds the tolerance, the food is deemed to be adulterated and subject to enforcement action under section 402 of the FFDCA (US Congress 1958, section 342(a)). Although EPA is responsible for setting pesticide tolerances, foods are subject to inspection and enforcement action by FDA.

2 EVALUATION OF THE ENVIRONMENTAL PROTECTION AGENCY'S REGULATION OF PESTICIDAL SUBSTANCES IN PLANTS UNDER THE 1994 PROPOSED RULE

In 1994, after a long review of regulatory options and having gained valuable experience in the evaluation of proposals for field tests of several transgenic pest-protected plants, EPA announced its intention to regulate the pesticidal substances produced in such plants, but not the plants themselves, under the provisions of FIFRA and FFDCA (EPA 1994a, c). The committee found that

Consistent with the coordinated framework and EPA's statutory mandates, EPA has determined that pesticidal substances expressed in plants meet the statutory definition of a pesticide and has asserted jurisdiction over pesticidal substances in transgenic pest-protected plants. If such substances were not considered pesticides, they would be subject to regulation under other federal statutes.

In effect, under the 1994 proposed rule, EPA would regulate pest-protected plants in the same way that it had traditionally regulated treated articles (EPA 1988a, section 152.25a). As long as a pesticidal substance is approved, or "registered", for a given use, the treated article itself (in this case, the plant) is not subject to regulation under FIFRA. EPA's original proposal referred to these products as plant-pesticides, creating considerable confusion and controversy (Hart 1999a, b, c): some thought, and apparently still believe, that EPA was regulating the plants themselves as

pesticides. The agency has recently sought public comments on the adoption of an alternative term (EPA 1999c). In summary, the committee found that

There is a misunderstanding on the part of many parties that plants themselves are being regulated by EPA as pesticides.

The committee recommends that

EPA's rule and preamble should clearly restate the agency's position that genetically modified pest-protected plants (that is, plants modified by either transgenic or conventional techniques) are not subject to regulation as pesticides. EPA must remain sensitive to the erroneous perception that plants are being regulated as pesticides.

As discussed in previous sections, EPA's proposal included a policy statement, regulations, and a number of specific exemptions from the tolerance requirements that would ordinarily apply under FFDCA. EPA would capture pesticidal substances produced in plants by amending the long-standing FIFRA exemption for biological control agents and then exempting pesticidal substances that did not warrant review, with separate exemptions required under FFDCA. Although the proposal has not been finalized, the agency has been implementing its essential elements in registration actions taken since 1995. Field testing of plants modified to express pesticidal traits has been sanctioned by EPA case by case since as early as 1992.

EPA regulation typically proceeds in two or three distinct stages, depending on the product involved. First, researchers interested in conducting large-scale field tests (10 acres or more) apply for an experimental use permit under section 5 of FIFRA (US Congress 1947, section 136c). Generally, at this point small-scale field tests (under 10 acres) would have already been conducted pursuant to a permit or notification under USDA's plant pest program. EPA does not require permits for field tests of under 10 acres unless the crop is to be used for food or animal feed or unless the small-scale testing is not conducted pursuant to a USDA permit, notification, or deregulation determination. The next stage, which applies to most products, involves an application to EPA for a registration that is limited to the production of propagative plant products, such as seeds, tubers, corms and cuttings (EPA 1995d). The production of these plant reproductive materials is an integral step in the development of commercial plant varieties. Finally, an application for full commercialization of the plant-expressed pesticidal substance is submitted for agency review under section 3 of FIFRA. If the plant will be used for food or feed, the applicant must also petition for establishment of a tolerance or an exemption from tolerance requirements under section 408 of FFDCA. Under EPA's proposed policy, both the registration and the tolerance action apply to the pesticidal substance and the genetic material necessary for its production in the plant.

The proposed rule includes several exemptions from regulation as plant-pesticides (section 1.5.3 and section 3.2). However, it does not explicitly address the need, on the basis of new information or improved understanding of the science, to create exemptions for additional categories of pesticidal substances under FIFRA, FFDCA, or both. It also does not discuss the need to revisit existing exemptions to assess whether they should be revoked or restricted on the basis of new information or changed circumstances. The committee found that

Current law provides sufficient flexibility for agencies to regulate products on the basis of risk and/or uncertainty and to exempt from regulation products believed to pose negligible risk.

Therefore, the committee recommends that

Regulations should be considered flexible and open to change so that agencies can adapt readily to new information and improved understanding of the science that underlies regulatory decisions.
EPA should make explicit a process for the periodic review of its regulations on the basis of new information or changed circumstances to identify additional categories of pesticidal substances expressed in plants that should be exempt from regulatory requirements and existing exemptions that should be revoked or restricted.

Finally, the proposed rule would establish several exemption categories, but does not offer any opportunity for an applicant to seek an exemption for an individual product. Given the dynamic nature of the technology, products with unique characteristics and use patterns that might warrant specific exemptions probably will be developed within the next 5 to 10 years. Without a mechanism to address these individual products case by case, a time-consuming rule-making process would be required to establish one or more new exemption categories. The committee also recommends that

EPA's rule should establish a process for applicants that do not qualify for an existing exemption to consult with the agency and seek an administrative exemption on a product-by-product basis when the pesticidal substance in the plant does not warrant registration. The process should be transparent, with sufficient information made available to allow subsequent applicants to benefit.

For a substance to qualify for exemption from FIFRA requirements in the proposed rule, EPA would require any person who sells or distributes it to notify the agency of any new information concerning potential adverse effects on human health or the environment associated with the product (EPA 1994a). That provision would, for the first time, require nonregistrants to comply with a reporting obligation imposed by statute on registrants (FIFRA § 6(a)(2); US Congress 1947, section 136d(a)(2)). Although little attention has been directed to the impact of this proposal, it would probably apply to many plant breeders, researchers and seed distributors that work with conventional pest-protected plants and have never been subject to FIFRA or EPA jurisdiction. The proposed rule does not assess the potential for taking advantage of monitoring systems that use federally funded insect surveys, independent crop consultants, and USDA extension agents to identify potential adverse effects associated with conventional pest-protected plants and other crops. The committee recommends that

EPA should publicly reexamine the extent to which FIFRA adverse effects reporting is intended to apply to plant breeders, researchers, and seed distributors of conventional pest-protected plants who have never been subject to FIFRA or EPA jurisdiction. For products that meet the definition of a pesticide but are exempt from registration under FIFRA, EPA

should review the extent to which existing field monitoring systems could substitute for traditional FIFRA reporting requirements.

3 EVALUATION OF THE REGULATION OF TRANSGENIC PEST-PROTECTED PLANTS UNDER THE MULTIAGENCY APPROACH OF THE COORDINATED FRAMEWORK

3.1 Overview

The US regulatory scheme for biotechnology products relies on multiple agencies to implement a mosaic of existing federal statutes. Each statute has a specific goal, for example to protect public health and the environment or to ensure food safety. The mosaic approach was deemed appropriate by the coordinated framework to regulate the diverse new biotechnology products and to provide credible assessments that would form the basis of sound regulatory determinations without unduly hindering the development of the technology.

The success of the multiagency approach can be assessed relative to three objectives:

- Sound science
- Effective coordination
- Transparency and public trust.

Scientific issues were addressed primarily in previous sections, but their relevance to coordination, transparency, and public trust will be addressed in the discussion that follows. Only through effective coordination can the three lead agencies—EPA, USDA, and FDA—minimize duplication, avoid inconsistent regulatory decisions, address potential gaps in oversight, ensure that regulations evolve with experience and scientific advances, and effectively review the human health and environmental safety of products. Ultimately, the credibility of the regulatory process will depend heavily on the public's ability to understand the process and the key scientific principles on which it is based.

The coordinated framework addresses several elements that contribute to a sound regulatory process. The committee has considered those elements and identified five that are most relevant to the immediate task (Box 1).

3.2 Coordination Under Existing Policy Statements and Proposals

The coordinated framework established several guiding principles to help the federal agencies coordinate their regulatory responsibilities. It states (OSTP 1986) that

The agencies will seek to operate their programs in an integrated and coordinated fashion and together should cover the full range of plants, animals and microorganisms derived by the new genetic engineering techniques. Agencies have agreed to have scientists from each other's staff participate in reviews.

Consistent with regulatory practice regarding traditional products, the 1986 framework called for jurisdiction over biotechnology products to be determined by their use. It identified the lead agency and supporting agencies that would be responsible for the oversight of various classes of products (Table 1). The approach was explained as follows:

Where regulatory oversight or review for a particular product is to be performed by more than one agency, the policy establishes a lead agency, and consolidated or coordinated reviews.

Table 1: Regulatory Scheme for Coordinating Reviews of Commercial Biotechnology Products

Product Class	Lead Agency (Other Participating Agencies)	Federal Statutes
Plants and animals	USDA-APHIS (USDA-FSIS[a], FDA)	FPPA, PQA[b], NEPA, FFDCA
Pesticide microorganisms	EPA (USDA-APHIS)	FIFRA, FFDCA, FPPA, PQA[b], NEPA
Food and additives	FDA (USDA-FSIS[a])	FFDCA

[a]Food Saftey Inspection Service
[b]Plant Quarantine Act

Box 1: Elements that Support the Objectives of the Coordinated Framework

- Consistency of definitions and regulatory scope.
- Clear establishment of lead and supporting agencies with a mechanism for effective interagency communication.
- Consistency of statements of information to support reviews.
- Comparably rigorous reviews.
- Transparency of review process.

Two other principles enunciated in the framework to promote coordination are that agencies should adopt, to the extent permitted by their statutory authorities, consistent definitions of the organisms subject to review; and that agencies should use reviews of comparable rigor. The authors of the policy also recognized that future scientific developments should lead to further refinements in the coordinated framework. They expected regulations to evolve as scientists and regulators gained experience in predicting which products required more or less controls.

EPA's 1994 proposed policy on pesticides subject to FIFRA and FFDCA discusses interactions with other agencies The policy makes EPA the federal agency primarily responsible for the regulation of pesticides and states that EPA works closely with USDA and FDA in fulfilling this mission. On the matter of coordination with USDA, EPA's proposed policy states (EPA 1994a, p. 60513) that

EPA and USDA-APHIS have consulted and exchanged information on plants and plant-pesticides and intend to continue to do so in the coordination of their regulatory activities. The two Agencies also have and intend to continue to consult closely on scientific issues related to the safety considerations associated with the environmental impact of field tests of plant-pesticides.

A similar statement of commitment to coordination is made with respect to EPA-FDA interactions on jurisdictional questions and scientific matters. To minimize potential overlap, the proposed policy states that EPA will address food safety issues associated with plant-pesticides. Any food safety questions beyond those associated with plant-pesticides are under FDA's jurisdiction.

EPA has registered 10 pesticidal substances expressed in transgenic potato, cotton, or corn plants and has established corresponding exemptions from the requirement of a tolerance for these pesticidal substances under the agency's proposed regulations (see section 1.5.3 and section 3.2).

Seven additional pesticidal products, also considered by EPA to be subject to its jurisdiction, are exempt from FIFRA registration because they consist of coat proteins of plant viruses. The transgenic pest-protected plants that express the exempt pesticides include potato, watermelon, zuchini, papaya, and cucumber. Indicating the shared responsibility for oversight of these products, USDA has made a determination of non-regulated status for each of the transgenic pest-protected plants. Those plants were formerly considered "regulated articles" under the FPPA. The producers of the products also voluntarily engaged in consultations with FDA pertaining to the safety of the foods derived from the plants.

There are opportunities for interagency coordination during at least two stages of the regulatory process for transgenic pest-protected plant products. The first comes early in the process, when the developer is discussing the prospective product with the regulatory agencies to determine the kinds of data and information that will be necessary to support the regulatory review. These discussions are referred to as presubmission consultations and are encouraged by all three agencies. This is often the time when unique aspects of the product are discussed. A new product could raise jurisdictional questions or a need for new or different approaches to product testing or risk assessment.

Issues associated with new transgenic pest-protected plants might be of interest to more than a single agency. For example, a product consisting of a crop-gene combination that could result in gene flow and pose a potential human or environmental impact might raise legitimate issues for EPA or USDA and possibly for FDA as well. Interagency discussions at this early stage could help to avoid problems and delays later. To the committee's knowledge, the agencies have not yet interacted with one another on product-specific issues at this stage of the regulatory process.

Although such interaction would appear to benefit all parties, there could be several reasons for the apparent lack of activity. One reason might be that the product is highly confidential at this early stage of development and the producer prefers to work with each agency separately before submission. If that is the case, agencies might be unable to interact without the producer's permission because of legal constraints on the sharing of trade secrets and other confidential business information (CBI).

A second opportunity for interagency coordination is the period during formal product review, when the agencies are formulating their regulatory decisions on a product. Successful coordination during this period requires an effective infrastructure within and between agencies that promotes and rewards cooperative interaction. In being consistent with CBI requirements, all agencies attempt to provide each other with as much information as possible to facilitate communication on issues of mutual concern. EPA has taken steps to clear representatives of other agencies for access to CBI in submissions made to EPA. The ability of agencies to communicate unencumbered by CBI constraints can only enhance the credibility and public acceptance of the regulatory process.

Effective interagency coordination relies on a high degree of consistency in definitions, regulatory scope, and technical guidance of applicants, as well as effective communication and transparent review processes of comparable rigor (Box 1). Several of those elements are highlighted in the coordinated framework (OSTP 1986), and the committee has considered each of them in its evaluation of the current status of interagency coordination in regulating transgenic pest-protected plant products. Although all the elements are desirable for promoting coordination, the committee recognizes that they might not all be relevant for every product. The committee also understands that the degree to which some of the elements are achievable is limited by the requirements of the statutes that the agencies administer. The following sections of this chapter discuss those elements outlined in Box 1.

3.3 Consistency of Definitions and Regulatory Scope

To facilitate consistent and efficient regulation, the coordinated framework established the principle that agencies should adopt consistent definitions of regulated products "to the extent permitted by their respective statutory authorities." An important implication of this principle is that definitions affect the scope of products subject to regulation. Each agency must be cognizant of the scope of products delineated for regulation by its fellow agencies to ensure that regulatory coverage is coordinated and complete, but not unnecessarily duplicative. The committee found that

Although statutory constraints prevent agencies from adopting uniform definitions for certain regulatory terms, this does not appear to have unduly hindered their ability to implement meaningful regulations.

Each agency defines transgenic pest-protected plant products in terms consistent with its regulatory authority: pesticides for EPA, plant pests for USDA, and foods for FDA (Table 2). The result is that there is no uniform interagency definition of these products. EPA focuses regulatory attention on pesticidal substances produced in plants rather than the plants themselves. These substances and the genetic material leading to their production are referred to in the 1994 proposed rule as plant-pesticides. USDA has declared some genetically engineered plants to be "regulated articles" because of potential plant pest risk. FDA regulates foods derived from new plant varieties. The lack of consistent product definitions appears to be an unavoidable outcome of regulating under existing statutes. Agencies can minimize the confusion that results from this situation by aggressively communicating how their regulations link to cover the full range of potential concerns (for example, food safety, environmental protection, and plant pest risk) for a single transgenic pest-protected plant product such as corn modified to express the *Bacillus thuringiensis* insect-control protein.

Table 2: EPA, USDA, and FDA Definitions of Regulated Products and Substances

	EPA	USDA	FDA
Regulated Product	Plant-pesticide (plant-expressed protectant)	Plant pest, regulated article	Food, feed, food additive
Regulated Substance	Pesticidal substance and genetic material necessary for its production	Organism engineered to contain sequences from plant pests	Human food (whole or processed), animal feed

There is a more urgent need concerning consistency in the scope of transgenic pest-protected products regulated by EPA, USDA, and FDA. The scope of products covered needs to be consistent across agencies to the greatest extent possible to ensure that all products receive the appropriate oversight, and that human health and the environment are thus protected appropriately. EPA articulates a broad scope of coverage that appears to include all plant-expressed substances that meet the FIFRA definition of "pesticide," including some plant regulators (EPA 1994a). Several categories of plant-expressed pesticidal substances are then proposed to be exempt from

regulation because the agency believes that they are of a type that does not require regulation under FIFRA or that they are adequately regulated by other federal agencies (section 1.5.3 and section 3.2).

FDA's regulatory coverage is similarly broad. It covers all food and feed, irrespective of how they were developed. There are no explicit exemptions from coverage, but premarket approval is not required unless a food or feed contains substances or demonstrates attributes that are not usual for the product. USDA exercises explicit regulatory authority over transgenic pest-protected plants that have been genetically engineered to contain inserted genetic material believed to have plant pest potential. All other transgenic pest-protected plants are implicitly exempt from USDA regulation unless the agency has a "reason to believe" that they could pose a plant pest risk.

Thus, all three agencies appear to have broad regulatory authority to cover transgenic pest-protected plants, but USDA and EPA have elected to narrow their effective scope of coverage by exempting particular products. The committee identified situations in which such exemptions warrant further scrutiny: the current limitation of USDA's explicit scope of oversight and EPA's proposed broad exemption of virus coat proteins under FIFRA (section 3.2.2). Both situations have the potential to result in gaps in regulatory coverage that could lead to instances where public health or environmental issues might not be adequately addressed. In general the committee found that

The scope of product reviews, as delineated by USDA and EPA, has the potential to result in gaps in regulatory coverage.

Concerning USDA's scope, USDA-APHIS oversees field tests of genetically modified crops, including transgenic pest-protected plants. It is the only agency that reviews the environmental and agricultural effects of transgenic pest-protected plants whose pesticidal substances EPA has has proposed to exempt from regulation under FIFRA. The scope of USDA's oversight includes "any organism which has been altered or produced through genetic engineering, if the donor organism, recipient organism, or vector or vector agent belongs to the genera or taxa designated in Section 340.2 and meets the definition of a plant pest" (USDA 1987, section 340.1). Many plants do not automatically meet the definition of a "plant pest." Thus, the upshot of this language is that, without a specific determination to the contrary, USDA regulations cover only genetically modified plants that have inserted genetic material from plant pests. In practice, USDA regulates genetically engineered plants with insertion vectors and promoters from plant pathogens, such as *Agrobacterium tumefaciens* and cauliflower mosaic virus. The agency also reviews voluntary submissions from those whose plants are not expressly covered.

Use of a small amount of genetic material from a plant pathogen as a vector or promoter, however, does not result in plants that pose greater plant pest risks than other types of genetically modified plants. The small amount of genetic material from plant pathogens that is inserted into plants does not result in diseased plants (Center for Science Information 1987; Goldburg 1989).

The development of new techniques for genetically engineering crops means that the scope of USDA's regulations might now fail to encompass some genetically engineered crops that the agency wishes to regulate. A number of techniques, such as the use of microprojectile guns, can now be used to insert DNA into plants without the use of the *Agrobacterium* vector. Genetic engineers can now make genetic constructs with promoters that are no longer automatically subject to USDA oversight, not because they pose any more or less plant pest risk than plants now being regulated by USDA, but simply because of the techniques used to modify them. Although

companies developing such plants may voluntarily notify USDA of field tests, it remains to be seen how USDA will regulate (or deregulate) such crops when they are commercialized. Moreover, companies and researchers obviously have considerable discretion whether they continue to notify USDA of field tests without a legal requirement to do so. Therefore, the committee recommends that

USDA should clarify the scope of its coverage as there are some transgenic pest-protected plants that do not automatically meet its current definition of a plant pest

3.4 Clear Establishment of Lead and Supporting Agencies With a Mechanism for Effective Interagency Communication

The coordinated framework does not identify lead and supporting agencies for oversight of transgenic pest-protected plants. That is probably because research with this category of plants was relatively new when the framework was created and field testing had not yet been conducted. Instead, the coordinated framework indicates that USDA is the designated lead agency for plants and reiterates that EPA has exempted from registration, under FIFRA, plants that are biological control agents.

Although EPA's 1994 proposed policy (EPA 1994a) reiterates the exemption of plants as biological control agents, it points out that EPA will regulate pesticidal substances expressed in the plants and the genetic material necessary for the production of the substances. The policy also clearly articulates the division of jurisdiction over the substances between EPA and FDA. The policy states that EPA will address food safety issues associated with pesticidal substances, including selectable markers; FDA will be responsible for any food safety issues separate from pesticidal substances such as changes in food quality and unintended compositional changes. That clear delineation of responsibility has resulted in product reviews that avoided duplication and achieved consistency. The committee found that

The delineation of EPA and FDA jurisdiction over transgenic pest-protected plant products is generally well defined. Agency reviews generally lack duplication and achieve consistency. The agencies are working together in an effort to potentially modify jurisdiction over selectable markers in the future to reduce ambiguity and minimize the potential for duplication.

Since publication of the 1994 policy, EPA and FDA have identified selectable markers as an area where a shift in lead agency may be appropriate. Having reviewed numerous products that contain selectable markers and having received public comments on this issue, EPA published a request for comments on excluding selectable markers as pesticide inert ingredients. EPA proposed that FDA rather than EPA, have direct jurisdiction over those substances in food products. Among the reasons given for the proposed change were statutory ambiguity pertaining to EPA oversight of selectable markers and public comments asserting the poten tial for duplication of reviews with FDA. The committee believes that EPA's request for comments on this topic shows how regulation under the coordinated framework is continuing to evolve with experience and public input.

Although not identified as such in EPA's 1994 policy statement, responsibility for allergenicity is shared by EPA and FDA. Both agencies are responsible for addressing public health issues associated with pesticidal substances in crops that are potential food allergens. If EPA

registers and establishes a tolerance for a pesticidal substance that is a potential food allergen, FDA has the authority to ensure that resulting food products carry appropriate precautionary labeling. The committee was encouraged to learn that EPA initiates consultations with FDA when issues of potential food allergenicity arise in connection with a product under review. FDA has shared with EPA its expertise on the assessment of food-allergenicity issues and has provided access to its database that is used to screen products for potential allergenic components. Therefore, the committee concludes that

EPA and FDA appropriately share responsibility for regulation of plant-expressed pesticidal substances that are potential food allergens. However, although there appears to be a high level of communication between the agencies when a potential food allergen is identified, there is no formal mechanism to ensure appropriate communication in the future as more products come under review.

Therefore, the committee recommends that

EPA and FDA develop a memorandum of understanding (MOU) that establishes a process to ensure a timely exchange of information on plant-expressed pesticidal substances that are potential food allergens. The MOU should articulate a process under which the agencies can regulate potential food allergens in a consistent fashionæby EPA through tolerance setting and by FDA through food labeling.

Neither the EPA proposed rule nor USDA's regulations provide a clear statement on the division of jurisdiction or shared responsibility between EPA and USDA for transgenic pest-protected plant products. In practice, because EPA has lead responsibility for pesticides, it has assumed the lead-agency role for those products. There is implicit recognition that EPA is the lead agency on human-health issues and most environmental issues, whereas USDA is responsible for assessing the potential for plant pest risk. The committee's discussions with EPA and USDA identified several subjects on which they request nearly identical information; in some instances, they appear to assess the same issues. That raises the question of regulatory overlap, which could lead to duplicative reviews and conflicting regulatory determinations.

The information that EPA and USDA require to support their FIFRA and FPPA risk assessments and USDA's NEPA environmental assessments are summarized in Table 3. A comparison of EPA and USDA requirements suggests a substantial level of duplication. The committee's review of several EPA fact sheets for registered transgenic pest-protected plant products indicates that the agency requires companies to submit the results of specific laboratory studies to assess mammalian toxicology, protein digestibility, and effects on potentially exposed nontarget organisms. EPA uses this information to determine whether there is a reasonable certainty of no harm to humans consuming the plant-pesticide, as required under FFDCA; and that the product will not cause unreasonable adverse effects to human health or the environment, as required under FIFRA. For the most part, companies appear to provide summaries of these data to satisfy USDA's information needs in case of overlap. Companies might also submit the human health data on a transgenic pest-protected plant product to FDA, although FDA review is directed at the nutritional and compositional characteristics of the food and the potential for unintended alterations in food constituents.

Table 3: USDA and EPA Data Requirements for Assessing Effects of Transgenic Pest-Protected Plant Products

USDA [a]	EPA [b]	
Information for review as regulated article		
Objective: Assess potential plant pest risk	**Objective: Assess potential for health and ecological effects**	
Genetic analysis	Product identity (construct, characterization, markers, vectors)	
Molecular biology of transfer		
Phenotype of article		
Environmental consequences	Protein digestibility	
Description of mode of action	Mammalian toxicology (acute oral)	
Current uses		
Effect on weediness	Allergenicity potential	
Gene transfer	Gene expression	
Potential for adverse effects	Environmental fate of protein	
Toxicology data on nontarget organisms and threatened and endangered species	Gene transfer potential	
	Nontarget organism toxicity (avian, fish, terrestrial and aquatic invertebrates)	
	Endangered species considerations	
Information for environmental assessment		**Objective: Assess potential for environmental impact**
Effect on agricultural practices		
Potential impact of pollen escape		
Effect on susceptibility of pathogens or insect pests		
Effect on resistance of pests		
Toxicology data on nontarget organisms (beneficial insects, animals, and humans)		
Potential change in virulence (viruses)		
Cumulative environmental effects		

[a]USDA 1996a.
[b]CFR 158.9(d); EPA (1999a,b,1998a,b, and 1999f).

USDA also requests applicants to provide human-health and ecological information; this suggests an unnecessary overlap in regulatory oversight. However, except for information pertaining to USDA's assessment of plant pest risk, the human health and ecological information

that it receives is used to support its environmental assessment under NEPA, not to support its granting or denial of a permit or determination of nonregulated status under FPPA. USDA does not typically ask applicants to generate human health or environmental data de novo to support its NEPA findings. Instead, companies are asked to submit the available information to support the environmental assessment. Therefore, the duplication in requested information stems largely from USDA's statutory obligations under NEPA. For the most part, the duplication has allowed health and ecological issues to receive a broader assessment and has not generally led to conflicting regulatory decisions. In summary the committee concludes that

There is significant overlap in the human health and environmental information that EPA and USDA receive and evaluate in their assessment of transgenic pest-protected plant products. The duplication appears to result from NEPA requirements that apply to USDA and has not generally led to confusion or serious incidents of conflicting regulatory decisions.

However, where EPA and USDA assert regulatory authority over the same endpoint, the lack of clarity as to the lead agency and the differing bases for decision-making can, on occasion, lead to confusion both in the agencies and in the regulated community. For example, the record indicates potential confusion in instances where gene transfer is analyzed by EPA and USDA. In the case of Bt cotton USDA and EPA asked for much of the same information to assess gene-flow issues. USDA concluded that gene transfer prompted no concerns and granted deregulated status to Bt cotton without restrictions. In contrast, EPA placed geographic restrictions on the planting of Bt cotton until additional information could be provided to adequately assess the potential for and consequences of transfer of the Bt gene to related species. EPA was focusing on overall environmental impact, whereas the USDA conclusions were related to plant pest issues.

The agencies indicated that they did not communicate with one another on this issue before making their regulatory determinations. However, USDA issued its determination of nonregulated status in June 1995 and EPA registered Bt cotton four months later in October 1995. It appears that the agencies were reviewing Bt cotton during a similar period, so interagency discussions presumably could have been held. The committee recognizes that science-based decisions can depend on an agencies regulatory perspective and that decisions based on the same information can differ. For example, USDA's FPPA determinations are driven by concern about plant pest risk and crop protection, whereas EPA's FIFRA determinations hinge on the potential for adverse impacts on nontarget species and environmental protection in a general sense. In the case of Bt cotton, different determinations concerning the need for geographic limits appear to have been based on somewhat different regulatory end points and levels of comfort with the available information. This may have resulted in stakeholder confusion and raised questions about the credibility of assessments.

The foregoing example emphasizes the need for agencies to avoid inadvertent duplication or the appearance of inconsistency in decisions by increasing their coordination in developing guidance in subjects of common interest and maintaining communication on data needs that are believed to be mutually exclusive. To enhance coordination , the committee recommends that

EPA, USDA, and FDA should develop a memorandum of understanding for transgenic pest-protected plant products that provides guidance to identify the regulatory issues that are the purview of each respective agency (for example, ecological risks and tolerance assessment for EPA, plant pest risks for USDA, and dietary safety of whole foods for FDA); identifies

the regulatory issues for which more than one agency has responsibility (for example, gene transfer for EPA and USDA and food allergens for EPA and FDA); and establishes a process to ensure appropriate and timely exchange of information between agencies.

If differences in regulatory findings remain after agency consultations, they should be adequately explained to ensure that regulatory decisions are not in conflict and do not have the appearance of conflict. Agencies should consider using *Federal Register* notices, EPA pesticide fact sheets, press releases, and their own websites and databases to provide such explanations.

Having been commercialized only within the last 5 years, transgenic pest-protected plant products have a relatively new regulatory framework. As more and more-diverse products approach the market, new issues and issues that might be less important for conventional products might warrant attention. For example, the development of Bt transgenic plant products has brought to light issues concerning insect resistance management (section 2.9). One specific concern is the potential effect of these products on the utility of Bt foliar spray products if widespread resistance to Bt insect control proteins evolves in pest populations. Resistance management is not a new issue and is not unique to Bt crops, but it has been left largely to industry and USDA to address through research, development of best practices, educational programs for growers, and other nonregulatory mechanisms. However, EPA has taken a regulatory approach to Bt crops. It has required research and monitoring, limited geographic use of some products, imposed agricultural practices for some products, and required the development and implementation of resistance management plans that rely on high Bt dose and the establishment of refugia to minimize the onset of resistant pest populations. This new role for EPA constitutes a broad set of regulatory initiatives that will probably require substantial resources to maintain, and represents a departure from, for example, the EPA initiative under the North American Free Trade Agreement that proposes voluntary labeling for resistance management related to conventional pesticides (EPA 1999e).

In contrast with EPA's approach, USDA appears to have determined that resistance management, at least as related to Bt crops, is not a plant pest risk issue that would be appropriately addressed through regulation under FPPA. But some USDA offices are working cooperatively with EPA to establish pest management centers that would foster research, education, and nonregulatory approaches to resistance management. These pest management centers are in their infancy, and it is unclear how successful they will be. One example of an activity proposed for these centers is to develop insect resistance management strategies to pesticides expressed in transgenic pest-protected plants.

In summary, the committee found that

As more transgenic pest-protected plant products reach the market additional issues concerning their safety and effective deployment will probably come to light. Not all of them will rise to a level that warrants regulation, nor will they all be amenable to traditional regulatory solutions.

Bt crops raise an important question with regard to resistance man agement and the potential to affect the use of Bt foliar spray products adversely. EPA–USDA collaborative efforts to develop pest management centers offer a nonregulatory approach that could serve as a model for handling other issues that might arise in the future. EPA should continue to deal seriously with Bt resistance management and any other transgenic pest-protected plants that present similar concerns, but,

Where regulation is not warranted, agencies should look for appropriate opportunities to promote nonregulatory mechanisms to address issues associated with transgenic pest-protected plant products, including encouraging development of voluntary industry consensus standards and product stewardship programs.

3.5 Consistency of Statements of Information to Support Reviews

As new transgenic pest-protected plant products are developed, the kinds of information necessary to support the agencies' risk assessments and regulatory determinations continue to evolve. Although agency reviews are risk based, there are differences in data requirements and in the emphasis placed on different kinds of data. Relatively little formal, detailed guidance to applicants is available. Each agency has taken a somewhat different approach in developing and providing guidance.

EPA included in its 1994 proposed policy a section on information needs and general considerations for product development and commercialization. It provides points to consider in the development of data on product identity and characterization, human health effects, ecological effects, fate of plant-pesticides in the environment, and movement via gene flow. The committee found that

In part because EPA does not have final regulations indicating the scope of products subject to FIFRA registration, relatively little formal guidance is available to companies seeking to determine the kinds of data and information that must be developed to support EPA registration of the pesticidal substances expressed by these plants.

Nevertheless, EPA is imposing data requirements and registering products case by case, creating an urgent need for companies to know to the fullest extent possible what the requirements are. Applicants can now review the existing EPA and other guidance documents, examine what previous applicants have done, and then have a presubmission consultation to seek clarification from EPA on information needs.

FDA's guidance includes its 1992 policy statement regarding the development of foods derived from new plant varieties. That document reviews the issues to be considered in the development of a food from new plant varieties, including the consideration of issues that can prompt a need for testing or consultation with FDA. In 1997, FDA issued *Guidance on Consultation Procedures for Foods Derived from New Plant Varieties* (FDA 1997c), which summarizes nine general points the FDA recommends be addressed in the development of a safety and nutritional assessment for such products as bioengineered foods.

FDA has not, however, issued guidance on the evaluation of the potential allergenicity of proteins added to foods via genetic engineering, despite assurances that it intends to. FDA coconvened a meeting on food allergy in 1994 with EPA and USDA that brought together leaders in the field to advise the agency on evaluating the allergenicity of proteins (FDA 1994b). FDA should use the results of that meeting, other scientifically relevant reports, and later research findings to develop guidance on allergenicity. The committee recommends that

FDA should put a high priority on finalizing and releasing preliminary guidance on the assessment of potential food allergens, while cautioning that further research is needed in this area.

Publication of such guidance by FDA would be helpful both to companies consulting with FDA and to companies seeking approvals from EPA, inasmuch as EPA staff depend heavily on the expertise of FDA staff on allergenicity. For example, the committee learned of one transgenic pest-protected plant that contains an insecticidal protein that has a key biochemical characteristic of food allergens: stability in simulated gastric juices (EPA 1998c). Crops containing this protein are currently restricted to use as animal feed. Tests that the manufacturer should conduct to evaluate the potential allergenicity of this protein are not well defined, and both EPA staff and the manufacturer would benefit from guidance from FDA.

USDA has guidance documents and model submissions to help applicants determine what information is needed and how to complete a submission (USDA 1996a). The application forms provide guidance as to specific information needs, but they do not discuss the depth of information required or specifically define the methods to be used.

The committee developed a comprehensive list of data needs based on guidance documents and summaries of regulatory determinations made available by the agencies. The committee provided the agencies with a detailed consolidated list and asked them to indicate the items of most importance for their regulatory review. Individual meetings were conducted with each agency to discuss the responses.

The agency responses reveal four areas where the regulatory authorities have similar information needs (Box 2): biology of recipient; molecular biology; products of inserted material; and selectable markers. These common needs might be a useful starting point for a harmonized list of data requirements. Although the agencies appear to prefer different levels of detail on these four subjects, the overall scope of information is virtually identical—an observation that the committee confirmed in meetings with EPA and USDA. Each agency needs this basic information to understand a product and conduct its assessment. The committee found that

Appropriately, EPA, USDA, and FDA request that applicants submit similar information concerning the recipient plant, molecular methods, characterization of gene products, and selectable markers.

The committee recommends that

EPA, USDA, and FDA should develop a joint guidance document for applicants that identifies the common data and information the three agencies need to characterize products (for example, biology of the recipient plant, molecular biological methods used to develop the product, identification and characterization of inserted genetic material and their product(s), and identity and characterization of selectable markers).

Box 2: Information Requirements Common to all Agencies

- *Biology of recipient:*
  —information on taxonomy, habitat, and growth characteristics.
- *Molecular biology:*
  —description of source and identity of transforming material and mode of transformation.
- *Products of inserted material:*
  —identity, characterization, purpose, and mode of action.
- *Selectable markers:*
  —identification and characterization.

3.6 Comparably Rigorous Reviews

Agency decisions concerning transgenic pest-protected plants should be based on scientific information. The information may come from the existing scientific literature. Depending on the relevance and completeness of the existing literature, agencies may require companies to generate original data to address environmental and food safety questions. USDA and EPA do not appear to be comparably inclined to require original data to support decision-making, and therefore might not always review products with comparable rigor.

At least two published studies have analyzed the use of scientific data by USDA in making regulatory decisions about transgenic crops (Wrubel *et al*. 1992; Purrington and Bergelson 1995). Both studies conclude that the agency relies heavily on existing scientific literature, rather than requiring that applicants and petitioners develop new experimental data directly relevant to risks that may be posed by individual transgenic plants. Purrington and Bergelson (1995) argue that there are "serious shortcomings in the content of the petitions" approved by USDA. Another analysis (Mellon and Rissler 1995) concludes that field trials conducted under USDA's oversight produce little information of value to risk assessment when it is time to commercialize transgenic crops.

USDA's approval in 1994 of a petition to deregulate transgenic squash that contained viral coat protein genes illustrates well the agency's reliance on existing information as the basis of agency determinations. Commercialization of the squash was controversial because some believed that it would probably transfer its acquired virus-resistance genes via pollination to wild squash, which is an agricultural weed in some parts of the southern United States. An analysis commissioned by USDA strongly recommended that new data be gathered for assessment of the risks that may be posed by commercialization of the squash (Wilson 1993), but USDA largely disregarded the recommendation. The agency deregulated the squash, relying almost entirely on existing information to find that commercialization of the squash would have no significant environmental impact (section 3.1.4). As the committee recommended in chapter 3, when published data are insufficient, USDA should require original data to support agency decision-making concerning transgenic crops.

In contrast, EPA generally requires that developers of transgenic pest-protected plants provide more scientific evidence, often including new data, before it makes regulatory decisions. The squash with viral coat proteins cannot be examined for comparison, because EPA was not required to review it before it was commercialized. However, the difference between the agencies' reviews can be illustrated by examining their use of data in their decisions concerning commercialization

of Bt cotton discussed above: USDA deregulated the cotton on the basis of existing information about gene flow to wild cotton, and EPA placed geographic restrictions on the planting of Bt cotton until additional data could be provided.

3.7 Transparency of Review Process

Background

The degree to which regulatory agencies make their regulatory processes transparent influences the acceptance of a regulatory program. Transparent regulatory processes provide a clear basis for regulatory coverage, provide clear direction to those who must comply with regulations, and assist the public in understanding how the process is intended to work. Public trust in the regulatory process is gained through transparency. When the regulatory process is applied to situations where the scientific underpinnings of the technology and its impacts are continuing to evolve, transparency is crucial to identifying how scientific knowledge is being applied in the regulatory process. One of the challenges to transparency in a regulatory process is identifying the degree to which a regulatory agency needs to protect the legitimate trade secrets of the regulated community.

From a general perspective, the coordinated framework, as implemented by the various federal agencies, has elements of transparency, but there is considerable variability among the agencies. Under the programs administered by the federal agencies implementing the framework, products of biotechnology have been commercialized in diverse sectors of the economy, and there has been reasonable public acceptance of the technology. This level of acceptance suggests public trust in the American regulatory system generally and other factors such as confidence in American agriculture to produce a safe food supply. That confidence contrasts with the skepticism concerning genetic engineering in general in Europe and other parts of the world (Layman 1999; Prakash 1999). Where public trust in the current framework appears to be fragile, lack of transparency in the process can be an exacerbating factor.

The strengths and weaknesses of the framework for regulation of transgenic pest-protected plant products can be examined in the context of a transparent regulatory process. The following analysis examines the transparency of the regulatory approaches taken by the three lead federal agencies from the standpoint of the regulated community, the state-level coregulator, and the public at large. The committee found that in general,

Ready access to information on product reviews and approvals and a meaningful opportunity for stakeholder participation are critical to the credibility of the regulatory process.

Transparency at the Animal and Plant Health Inspection Service

USDA has successfully used electronically accessible databases to improve the transparency of its regulatory process and to keep the public and the regulated community informed about changes in regulation. The APHIS Biotechnology Index, on the USDA website (USDA 1999b), provides timely access to a number of databases and other information that assist researchers, companies, and the public in working with and understanding the USDA regulatory program. For example, the Biotechnology Permits Database (USDA 1999c) is updated daily and provides detail on and the current status of recent applications for movement permits, notifications of intended release, and release permits. Other accessible databases linked to the Biotechnology Index include

historical environmental releases back to 1987, decision documents (environmental assessments and determinations on nonregulated status), public notices (proposed rules and links to the *Federal Register*), and summaries of field releases by type of crop, phenotype, and location. Other website resources listed in this index include guidance on applying for permits, making notifications, and petitioning for determination of nonregulated status and a variety of biosafety resource materials. The more traditional method of *Federal Register* notices to present regulations and convey regulatory decisions is also used. Those around the world who are interested in agricultural biotechnology use the databases maintained by USDA to track applications. Resource limitations, such as funding, can hamper the agency's ability to maintain the databases on those various aspects of the regulatory process. The committee finds the

USDA database on FPPA decisions to be particularly useful and user-friendly. It should serve as a model for the other agencies; the committee recommends full funding for the maintenance of the existing USDA databases.

USDA has identified aspects of data submissions that applicants may declare as CBI. In the preamble to the initial regulations, the agency directed that applicants provide a detailed statement regarding why submitted information should be treated as confidential because of the competitive harm that might result from disclosure (USDA 1987). The agency requests two copies of applications and notifications, one with CBI deleted so that the document can be shared with state coregulators. State regulators have the opportunity to assess the plant-pest risk issues for their state for permits, notifications, and determinations for deregulated status and provide comment to USDA. In response to states' concerns that applicants were designating most submitted information CBI, the agency has provided clarification on kinds of submissions that may not be so designated (USDA 1999c).

Transparency at the Environmental Protection Agency

Before EPA's Office of Pesticide Programs (OPP) issued its proposed rule in November 1994 (EPA 1994a), the agency discussed its regulatory direction with the Scientific Advisory Panel (SAP), an external scientific advisory body for OPP on matters related to FIFRA and pesticide tolerance issues under FFDCA (SAP 1994). The proposal included a policy statement that generally laid out the basis for the rule and aspects of EPA's regulatory approach to this wholly new kind of pesticide regulation. The agency began providing regulatory coverage to some plant-pesticides before the publication of the proposed rule (EPA 1994a, b). The availability of information on the regulatory program is discussed below from the standpoint of the interested public and the affected regulatory community.

Beyond the traditional means of communicating its regulatory decisions on new plant-pesticides through the *Federal Register*, EPA has used its website to improve the transparency of its regulatory program. The website provides access to pesticide fact sheets, which summarize the kinds of data and risk issues evaluated by the agency for individual active ingredients in making regulatory determinations, and it links to *Federal Register* notices of regulatory determinations under FIFRA and FFDCA (EPA 1999b). More-detailed evaluations of submitted data are not available on the website but can be requested under the Freedom of Information Act. EPA is not always able to respond to such requests in a timely manner, however, and the committee recommends that

EPA make data evaluations readily available on its website or in response to written requests.

The website provides text of presentations by EPA officials, which contain details of current regulatory approaches to plant-pesticides. (EPA 1999b). This latter resource, along with EPA fact sheets, is currently the best source of information on the kinds of data that the agency is asking for to address the array of substantive risk issues posed by plant-pesticides. EPA has also posted information and papers regarding issues on resistance management related to Bt crops (EPA 1998d and 1999b); this information is an extension of discussions between EPA and the SAP.

With respect to public communication of the health-testing results, the committee found that

The EPA pesticide fact sheets are the most readily available sources of information on human health effects, but they are not transparent with respect to either the tests performed or the results of the tests.

As these documents may be drafted to be accessible to nonexperts, sometimes they give the impression that the studies were not rigorous. For example, the fact sheet on the Bt *tolworthi* protein expressed in corn (EPA 1998c) describes toxic endpoints in one male and eight female mice in the acute-toxicity test and then states "CLASSIFICATION: Acceptable." The basis for that classification with some details of the design of the tests, the number of animals involved, and other testing methods should have been presented so that the public could appropriately evaluate the scientific rigor of the test. Another fact sheet, on Bt Cry3A in potato (EPA 1995a), fails to state the number of animals tested; however, details provided by the registrant (Lavrik *et al*. 1993) make it clear that the tests, although minimal, included an adequate number of animals. Synopses of the methods and data from which the information is obtained would be valuable to the readers. Therefore, the committee recommends that

EPA pesticide fact sheets should be prepared with greater clarity and with more factual information to clearly and quantitatively present the results of safety testing.

EPA addressed the issue of CBI in its proposed rule, and proposes to require substantiation at the time a claim is made (EPA 1994a). In the proposed rule, EPA actively admonished applicants to minimize the amount of data and other information claimed as CBI. Because of inherent differences in their regulatory systems, EPA does not share applications for pesticides with state coregulators as does USDA, so a comparison of treatments of CBI claims is not possible from that perspective. However, EPA does discuss some risk issues related to plant-pesticides with the SAP in public fora (for example, SAP 1994); through that venue, it is possible to assess that the agency has not allowed broad CBI claims. EPA staff report that some registrants' attempts to make broad CBI claims have been rebuffed by the agency (EPA 1999g).

Because EPA's proposed rule is not yet final, the agency has not provided specific guidance to the regulated community on the various aspects of the regulatory approach (Andersen and Milewski 1999). The regulated community under the proposed rule includes academic re searchers, plant breeders, and seed companies and is substantially more diverse than registrants of traditional pesticides. The agency has endeavored to communicate with the broader group through presentations at national meetings and has tried to work closely with groups or individuals seeking clarification of proposed exemptions and guidance on making an application (Milewski 1997; Andersen and Milewski 1999). Registrants of traditional pesticides that have expanded their scope

of business to include transgenic pest-protected plant products are better prepared to respond to the new regulatory coverage because of their familiarity with the existing system. More specificity on the regulatory process is available through individual staff identified on the website. The division managing the registration of plant-pesticides would benefit from having an ombudsperson to advise potential registrants, modeled after similar positions in other OPP divisions that register chemical pesticides.

The absence of clear guidance beyond the proposed rule itself on the following three subjects detracts from the transparency of EPA's regulatory programs: how to determine more definitively whether a plant-pesticide qualifies for the proposed exemptions, how to seek exemptions under FIFRA or FFDCA, and what specific kinds of data or rationale are needed by the agency to execute its regulatory program. This lack of transparency affects not only potential registrants or others affected by the proposed rule, but also affects state pesticide co-regulators and the public in understanding how the regulatory coverage is intended to work. Generally, it appears that OPP is handicapped in its efforts to make a transparent regulatory process by lack of a final rule on plant-pesticides.

The committee recommends that

EPA should promptly complete the process for issuing regulations, policies, and guidance that set out the system of review and regulatory parameters for pesticidal substances in transgenic pest-protected plants.

Clarity is critical in these issuances, and the agency should avoid the tendency to automatically fall back on policies and procedures that apply to traditional chemical pesticides. For example, EPA should move quickly to issue guidance on the data required for pesticidal substances in transgenic pest-protected plants regulated under FIFRA and FFDCA.

Transparency at the Food and Drug Administration

Under the coordinated framework, FDA considers some aspects of transgenic pest-protected plants under the general food safety clause and other provisions of FFDCA (section 1.2). With the exception of determining that it may require labeling for an allergenic plant-pesticide, FDA defers to EPA for evaluation of the pesticide component of transgenic pest-protected plants. FDA established guidance under the coordinated framework when it published its policy on novel foods in 1992 (FDA 1992). The policy provided direction to the regulated community and the public about when there was a need for consultation in lieu of submission of a food additive petition.

FDA has used its website to provide direction on how to use the policy to determine when a consultation should be used, what the expectations of the agency are for safety determinations, and how the consultation process works (FDA 1999a). The website also contains a list of completed consultations (FDA 1999b), which states the products and companies involved in the consultation.

However, the details of these consultations are not readily available for public scrutiny. If the public wants to obtain documents containing information and data submitted to FDA for consultation, they must request the documents from FDA through the Freedom of Information Act (FOIA). Processing and fulfillment of FOIA requests can often take a long time.

FDA maintains an internal database on the amino acid sequence of known human allergens that has been useful to both EPA and FDA in evaluating the potential allergenicity of plant-expressed pesticides and food additives. The database is not publicly accessible, thus making it more difficult for researchers and developers to assess allergenicity. FDA and EPA generally

discuss how such information is used to assess allergenicity potential in the summaries of their evaluations (FDA 1999b). However, funding constraints might affect FDA's ability to maintain and update this database as new information becomes available.

FDA does not directly address the issue of substantiation of CBI claims for novel foods derived from biotechnology. Like EPA, FDA does not have an explicit relationship with state regulators in this arena (as USDA-APHIS has with its state counterparts), so a perspective on its screening of CBI claims is not possible.

Integration of Information

The Internet has greatly enhanced agencies' ability to communicate their regulatory process to the regulated community and the public. The federal agencies involved in regulating transgenic pest-protected plant products have used this medium to varied degrees, as indicated above. However, although agencies provide cross-links to one another's resources (USDA 1999e), there is no current way to link the decisions that various agencies have made about individual plant products under their own statutes.

To improve transparency, the committee recommends that

To fulfill the intent of the coordinated framework, a database to link agencies' decisions should be developed to benefit a wide array of interested parties that are following developments in agricultural biotechnology. Such a database would enhance the information now provided by the agencies and the overall credibility of the framework. Alternative or varied funding mechanisms should be explored to maintain this database.

The above database should expand on the existing USDA-sponsored coordinated framework database (USDA 1999e) to include more public information about specific products and to link agencies' decisions about specific products.

With respect to CBI and public access to information, the committee found that

Consistent with protections afforded by law to trade secrets and CBI, agencies have made a considerable amount of information on product reviews and approvals available but there is room for improvement.

The committee recommends that

EPA, USDA, and FDA should require substantiation of CBI claims at the time of data submission.

4. IMPACTS OF THE COORDINATED FRAMEWORK

The impacts of the coordinated framework are likely diverse and difficult to characterize and quantify. Potential benefits associated with the regulation of transgenic pest-protected plants include increased health and environmental safety and consumer confidence. Direct costs of regulation include expenditures on additional testing (that is, above and beyond testing that would occur in the absence of regulation) and employee time spent overseeing the regulatory process and interacting with agencies' staff. They also include costs associated with delays in development and commercialization of products. If those direct costs are sufficiently high, they can increase the

potential size of the market (expected sales) needed to break even and thus justify investment in a new plant variety. As a result, some crop varieties (in particular minor crop varieties) may not be developed.

The committee reviewed an analysis of the costs associated with the regulation of pest-protected plants which was authored by one of its members (see appendix A [4]). From this analysis, the committee found that regulation of transgenic pest-protected plants under the coordinated framework and EPA's proposed plant-pesticide rule might affect small to medium-size seed companies, public sector breeders, and other small developers who are not accustomed to the testing and regulatory submissions. Therefore, the committee recommends that

Regulators should be sensitive to the unique issues facing researchers, plant breeders, and seed distributors, particularly those in the public sector or those who have not traditionally been subject to federal regulation.
Regulatory agencies should aggressively seek to reduce regulatory costs for small biotechnology startup companies, small to medium size seed companies, and public sector breeders by providing flexibility with respect to data requirements, considering fee waivers wherever possible, and helping these parties navigate their regulatory system.

5. RECOMMENDATIONS

- **EPA's rule and preamble should clearly restate the agency's position that genetically modified pest-protected plants (that is, plants modified by either transgenic or conventional techniques) are not subject to regulation as pesticides. EPA must remain sensitive to the erroneous perception that plants are being regulated as pesticides.**
- **EPA should make explicit a process for the periodic review of its regulations on the basis of new information or changed circumstances to identify additional categories of pesticidal substances expressed in plants that should be exempt from regulatory requirements and existing exemptions that should be revoked or restricted.**
- **EPA's rule should establish a process for applicants that do not qualify for an existing exemption to consult with the agency and seek an administrative exemption on a product-by-product basis when the pesticidal substance in the plant does not warrant registration. The process should be transparent, with sufficient information made available to allow subsequent applicants to benefit.**
- **EPA should publicly reexamine the extent to which FIFRA adverse effects reporting is intended to apply to plant breeders, researchers, and seed distributors of conventional pest-protected plants who have never been subject to FIFRA or EPA jurisdiction. For products that meet the definition of a pesticide but are exempt from registration under FIFRA, EPA should review the extent to which existing field monitoring systems could substitute for traditional FIFRA reporting requirements.**
- **USDA should clarify the scope of its coverage as there are some transgenic pest-protected plants that do not automatically meet its current definition of a plant pest.**
- **EPA and FDA should develop a memorandum of understanding (MOU) that establishes a process to ensure a timely exchange of information on plant-expressed pesticidal substances that are potential food allergens. The MOU should articulate a process under which the agencies can regulate potential food allergens in a consistent fashion— by EPA through tolerance setting and by FDA through food labeling.**

- **EPA, USDA, and FDA should develop a memorandum of understanding for transgenic pest-protected plant products that provides guidance to identify the regulatory issues that are the purview of each respective agency (for example, ecological risks and tolerance assessment for EPA, plant pest risks for USDA, and dietary safety of whole foods for FDA); identifies the regulatory issues for which more than one agency has responsibility (for example, gene transfer for EPA and USDA and food allergens for EPA and FDA); and establishes a process to ensure appropriate and timely exchange of information between agencies.**
- **Where regulation is not warranted, agencies should look for appropriate opportunities to promote nonregulatory mechanisms to address issues associated with transgenic pest-protected plant products, including encouraging development of voluntary industry consensus standards and product stewardship programs.**
- **FDA should put a high priority on finalizing and releasing preliminary guidance on the assessment of potential food allergens, while cautioning that further research is needed in this area.**
- **EPA, USDA, and FDA should develop a joint guidance document for applicants that identifies the common data and information the three agencies need to characterize products (for example, biology of the recipient plant, molecular biological methods used to develop the product, identification and characterization of inserted genetic material and their product(s), and identity and characterization of selectable markers).**
- **The USDA database on FPPA decisions is particularly useful and user-friendly, and should serve as a model for the other agencies. The committee recommends full funding for the maintenance of existing USDA databases.**
- **EPA should make data evaluations readily available on its website or in response to written requests.**
- **EPA pesticide fact sheets should be prepared with greater clarity and with more factual information to clearly and quantitatively present the results of safety testing.**
- **EPA should promptly complete the process for issuing regulations, policies and guidance that set out the review and regulatory parameters for pesticidal substances in transgenic pest-protected plants.**
- **To fulfill the intent of the coordinated framework, a database to link agencies' decisions for particular products would benefit a wide array of interested parties that are following developments of agricultural biotechnology. Such a database would enhance the existing information provided by the agencies and the overall credibility of the framework. Alternative funding mechanisms should be explored to maintain this database.**
- **EPA, USDA, and FDA should require substantiation of CBI claims at the time of data submission.**
- **Regulatory agencies should aggressively seek to reduce regulatory costs for small biotechnology startup companies, small to medium size seed companies, and public sector breeders by providing flexibility with respect to data requirements, considering fee waivers wherever possible, and helping these parties navigate their regulatory system.**

Footnotes

1 The FPPA supplements and extends the much older Plant Quarantine Act.

2 Since the program began, approximately 120 permit applications have been withdrawn.

3 The FDA's current policy on the labeling of foods derived from new plant varieties is discussed in the 1992 notice, 57 Fed. Reg. at 22991, and in a separate notice published in 1993, 58 Fed. Reg. 25837.

4 This appendix was authored by an individual committee member and is not part of the committee's consensus report. The committee as a whole may not necessarily agree with all of the contents of appendix A.

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