

Implicit precaution, scientific inference, and indirect evidence: the basis for the US Environmental Protection Agency's regulation of genetically modified crops

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ABSTRACT *In this study, we explore how the US Environmental Protection Agency (EPA) uses science in its overseeing of genetically modified (GM) plants producing their own pesticides (plant-incorporated protectants or PIPs). Our analysis is based on a systematic review of EPA's product assessments, regulatory decisions and policy documents on GM plants. In regulating PIPs, product characteristics remain the fundamental basis for the agency's risk assessment. However, a recent ruling by the EPA represents a departure from a strict "product" approach to risk assessment. By considering not only product characteristics, but also the process by which a GM crop was developed, the EPA may be seen as adopting a cautionary approach under conditions where current science is unable to resolve whether GM crops and foods impose unique risks by comparison with products derived through conventional breeding. The EPA's case-by-case evaluations of GM products rely heavily on models and indirect measurements interpreted through biological and biochemical principles.*

Introduction

Regulatory agencies in the US and elsewhere have generally emphasized that the overseeing of genetically modified crops and foods is guided by science-based evaluation of human health and environmental risks (Levidow, 2001; Anonymous, 2000; Jasanoff, 1995). For example, the US Environmental Protection Agency (EPA) conducted an extensive review of scientific evidence about risks prior to re-registration of certain GM crops "to assure that the decisions on the renewal of these registrations are based on the most current health and ecological data" (EPA, 2001d, p. I1). Such claims have drawn the attention of scholars and critics, whose analyses of GM crop regulation support divergent conclusions. Some analysts contend that the agency's authority complements the overseeing of GM crops and foods by other US agencies and that current

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regulations are appropriate, sufficiently transparent, and permit participation by not only scientific experts but also the public (Uchtmann & Nelson, 2000). Others have suggested that current science is insufficient to adequately resolve concerns about GM crop risks (Clark & Lehman, 2001; Wolfenbarger & Phifer, 2000) or that the agency does not seek scientific evidence necessary to answer questions about risks adequately (EcoStrat, 2000). Still others argue that EPA overseeing of GM crops is more restrictive than can be justified by science-based concerns about risk (Miller, 2001).

In developing science-based regulations, agencies have sought ways to render policy decisions before all scientific questions are resolved. The methods used to resolve controversial risk issues, through integration of uncertain or incomplete scientific data, do not satisfy all stakeholders. Examination of this type of decision making can help elucidate the roles of science and policy in risk assessment.

In this study, we explore how one US agency implemented science-based regulation of genetically engineered plant-incorporated protectants (PIPs) defined as plants that have been genetically modified with foreign genes that express chemicals with pesticidal properties. Our understanding of the agency's general principles for science-based regulations derives from an analysis of both regulatory rulemaking and case-by-case product risk assessments. We investigated how the agency responded to new empirical evidence related to various potential risks associated with these products.

Our research suggests that EPA regulatory decisions depend heavily on general scientific principles, models and indirect measures in assessing risks associated with genetically modified PIPs. Moreover, by considering product characteristics as well as the process through which GM PIPs are developed, the EPA may be seen as having adopted a cautionary approach under conditions where current science cannot resolve whether GM crops and foods pose unique risks by comparison with products derived through conventional breeding.

Regulatory framework

In 1986, the US Office of Science and Technology Policy (OSTP) issued the "Coordinated Framework for Regulation of Biotechnology" (OSTP, 1986). The Framework designated different government departments and agencies responsible for the overseeing of various genetically modified products that were nearing commercialization. The EPA was authorized, through the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA), to regulate pesticides produced through biotechnology, including plants that are genetically modified to produce their own pesticides.

Under FIFRA, the EPA oversees the development, sale, distribution, use, storage and disposal of pesticides [7 USC Section 136a(a)]. Product regulation is achieved through a process in which pesticides are either registered for specific uses or exempt from registration. For large-scale (ten or more acre) field tests

and seed increase, the EPA issues short-term, limited acreage pesticide registrations with crop containment restrictions. [Under the Coordinated Framework, the US Department of Agriculture (USDA) oversees small-scale field tests.] FIFRA grants the EPA the authority to require data from pesticide applicants prior to field tests and seed increase to demonstrate that the product does not pose an unreasonable risk to human health and the environment [7 USC. S 136a(c)(2)(A)] The agency requests additional data and reviews other relevant data sources to characterize human health and environmental risks and benefits prior to full registration of pesticides. The EPA must register a pesticide if the Administrator determines that (1) claims of activity are valid, (2) labeling complies with FIFRA requirements, (3) “it will perform its intended function without unreasonable adverse effects on the environment”, (4) “when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment” [7 USC. S 136a(c)(5)]. The agency considers unreasonable adverse effects for each pesticide on a case-by-case basis. If outstanding data needs exist, the agency may issue a conditional registration, which can be discontinued if data requirements are not fulfilled adequately during the time specified or if new data indicate that the product risks outweigh the benefits [7 USC. Section 136a(c)(7)(C)].

FFDCA Section 408 authorizes the EPA to establish safe levels of pesticide residues permitted in or on foods. These levels are called tolerances. The EPA is responsible for setting tolerance levels or exempting pesticides from a tolerance (EPA, 1997). Pesticides may be exempted from a tolerance if the Administrator “has determined that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information” [21 USC 346a(c)(2)(A)]. The EPA can issue a full registration legalizing unlimited commercial distribution of the product only after a tolerance level is set or a tolerance exemption granted for a pesticide (EPA, 1997). Even if it is found that normal use of a pesticide poses some risk to human health or the environment, the EPA may determine that benefits from use of a pesticide outweigh the costs and choose to register it, despite documented risks. The agency cannot be held liable for adverse effects caused by the use of a registered pesticide if the agency has determined that the benefits of use outweigh known risks (US Code Service, 2002)

Although the EPA lacked codified data requirements for risk assessment of GM PIPs, the agency registered 13 GM PIPs between 1995 and 2001 (Table 1), conducting product safety reviews on a case-by-case basis. Risk assessment of each product followed general principles developed by the agency in the late 1980s (Vaituzis, 1990). These principles were formally outlined in a proposed rule for regulation of PIPs published in 1994 (EPA, 1994). It was not until July 2001 that the agency promulgated final rules on PIP regulation, permitting the agency to proceed with codifying data requirements for GM PIP risk assessments (EPA, 2001c).

Examination of the agency’s proposed and final PIP rules and its overseeing

TABLE 1. Genetically modified PIPs registered by US EPA as of March 2002

Date of registration	Crop	Pesticide produced*	Company
May 1995	NewLeaf (<i>Bt</i>) Potato	Cry3A	Monsanto
August 1995 [†]	Event 176 Field Corn	Cry1Ab	Syngenta
August 1995 [†]	Event 176 Field Corn	Cry1Ab	Mycogen
March 1998 [†]	Event 176 Popcorn	Cry1Ab	Syngenta
October 1995	Bollgard (<i>Bt</i>) Cotton	Cry1Ac	Monsanto
August 1996	Bt11 Field Corn	Cry1Ab	Syngenta
February 1998	<i>Bt</i> 11 Sweet Corn	Cry1Ab	Syngenta
May 1996 [†]	Mon801 Field Corn	Cry1Ab	Monsanto
December 1996	Mon810 Field Corn	Cry1Ab	Monsanto
March 1997 [†]	Dekalbt (Cry1Ac) Field Corn	Cry1Ac	Dekalb/Monsanto
May 1998 [†]	Starlink (Cry9C) Field Corn	Cry9C	Aventis
October 1998	Potato	n/a [‡]	Monsanto
July 2001	Mycogen Brand <i>Bt</i> Cry1F Corn	Cry1F	Mycogen/Dow

*Numbers and letters included in Cry protein nomenclature to some extent indicate similarities between different protein sequences and structures.

[†]Registrations voluntarily cancelled by registrants prior to or during 2001.

[‡]Potato leaf roll virus resistance is conferred by the presence of the *orf1/orf2* gene which inhibits viral replication in the plant.

of GM PIPs in the 1990s reveal certain features about the agency's use of science in its regulation of these products.

GM plant-incorporated protectants

Two National Research Council (NRC) reports published in the late 1980s provided scientific support to those opposed to the regulation of GM. These reports concluded that recombinant DNA methods do not result in any unique hazards associated with GM plants products (NRC, 1987, 1989). Therefore, it was argued that the characteristics of the *product* and not the *process* should be the sole consideration in regulation.

The EPA's 1994 proposed rule for regulation of PIPs was consistent with the NRC's position. In the rule, the EPA made no distinction between conventionally bred PIPs and GM PIPs, as long as the GM PIPs expressed transgenes that were derived from sexually compatible plants (EPA, 1994). The agency suggested that neither of these types of PIPs would be subject to agency overseeing owing to a lack of novel exposure of humans or the environment to a new pesticidal compound. By contrast, GM PIPs expressing a product to which humans or other non-target organisms were not previously exposed would have to be reviewed by the agency prior to commercialization.

By 2001, however, in response to concerns raised by both scientists and the public, the EPA had adopted a more cautionary position in its final rules on the

regulation of PIPs. Modifying its 1994 position, the agency made a distinction between regulation of conventionally bred PIPs and GM PIPs expressing transgenes from sexually compatible plants. The final rules are consistent with the 1994 proposed rule in stating that the agency will not regulate conventionally bred PIPs but will regulate GM PIPs expressing transgenes that result in novel human or environmental exposure to a pesticide. The EPA deviated from its 1994 proposal, however, by requesting further comment over whether the agency should also regulate GM PIPs that express transgenes derived from sexually compatible relatives (EPA, 2001b). This represents a departure from the NAS perspective that the agency should regulate products based solely on their characteristics and not on the process by which they were produced.

Additionally, in the final rule, the EPA requested further comment on risks associated with viral-coat protein (*vcp*) mediated resistance, instead of exempting *vcp*-resistant plants from regulation, as proposed in 1994. Under certain conditions, viruses use coat proteins to create a barrier containing and protecting their genetic material. When inserted into the genome of a plant, the genes that encode these coat proteins may confer resistance to the plant against some viral infections (EPA, 2001b). The agency recognized that negative environmental impacts might occur should *vcp* genes migrate into wild relative populations and provide protection against viruses that might be essential for population control (EPA, 1994). The EPA addressed this risk as part of its 1998 registration of a potato engineered to be resistant to potato leaf roll virus by documenting that cultivated potatoes do not produce natural, viable hybrids with any wild relatives occurring in the US or its territories. The risk of gene migration, however, remains a concern for other crops. In a 2000 report, the NRC noted that there was a lack of data on how to evaluate the role of plant viruses in controlling wild populations (NAS, 2000). Taking a precautionary step, the EPA asked that commentators address whether the agency could best regulate *vcp*-mediated plants by requiring applicants to submit data on the likelihood of ecological disruption or by requiring applicants to monitor ecological impacts subsequent to registration (EPA, 2001b).

***Bt* plant-incorporated protectants**

The EPA also exercised precaution in its risk assessment of other GM PIPs during the 1990s. In the early part of that decade, manufacturers of corn, cotton and potatoes engineered to express different *Bt* toxins approached EPA for guidance on how to assess the human health and environmental risks associated with their GM crops prior to commercialization. *Bt* toxins are derived from different strains of a common soil bacterium, *Bacillus thuringiensis*, which demonstrate insecticidal properties (Cannon, 1996). The *Bt* toxins in question (Cry1Ab, Cry1Ac and Cry3A) were familiar pesticides, having been widely used in registered topical sprays by farmers since 1961 (EPA, 1998b). A substantial body of literature already existed on risks associated with use of these sprays. *Bt* toxins are notable because each typically is effective only against some species

within a single insect order, shows little or no toxicity to most other organisms, and rapidly biodegrades in the environment. Unlike conventional chemical pesticides, use of *Bt* sprays had not been associated with widespread, persistent effects on many types of non-target insects. No evidence of human toxicity or allergenicity had been observed, despite many years of use of *Bt* sprays in the field (EPA, 1998b).

Given long experience with *Bt* proteins, the EPA could have relied primarily on prior data about risks associated with conventional *Bt* sprays and required little new empirical data for *Bt* crop risk assessments. The agency, however, approached the risk assessment of *Bt* PIPs with caution. Because the genetic sequences introduced into the transformed plants were slightly modified from their original bacterial sequences to improve protein expression in the plants, the agency considered *Bt* PIPs to express novel pesticidal products (EPA, 2000a). While taking into consideration existing information about the limited risks associated with *Bt* sprays, the agency required data submissions from *Bt* crop applicants on the environmental fate of the toxin, exposure and hazard to non-target organisms as well as product characterization and human health effects.

As further indication of its precautionary approach to the overseeing of *Bt* PIPs, the EPA implemented a proactive approach to managing *Bt* resistance among target insect pests. Under high selection pressure, insects evolve resistance to pesticides, including *Bt* (Tabashnik, 1994). The agency previously had not taken steps to prevent insect resistance to conventional chemical pesticides. However, it had initiated emergency use provisions for certain unregistered pesticides as a means of controlling pests that had evolved resistance to registered pesticides (Matten *et al.*, 1996). The agency indicated that its efforts to preserve the effectiveness of *Bt* products resulted from its recognition that *Bt* PIPs and sprays were an important, relatively benign alternative to chemical pesticides (EPA, 2000a). With guidance from subpanels of the FIFRA Scientific Advisory Panel (SAP), the EPA and *Bt* crop manufacturers crafted resistance management plans (RMPs). Design and implementation of the plans drew from current ecological knowledge about delaying insect resistance. Monsanto voluntarily adopted an RMP as part of its registration of *Bt* potato (EPA, 1995c). The agency required that the manufacturers of *Bt* corn and cotton adopt RMPs and build upon existing knowledge through continued research on insect behavior, genetics of resistance and other areas relevant to RMP design (EPA, 1995a, b).

Uncertainty, indirect evidence and scientific inference

Because of the novel mechanism of pesticide delivery in PIPs, since the late 1980s, the EPA has consulted formally and informally with scientists and interested stakeholders to determine how best to measure risks associated with these new pesticides (EPA, 1999a). This ongoing discussion has included debate over the relevant questions and the data necessary to address the risks adequately.

Our review of EPA's regulation of GM PIPs suggests that owing to barriers presented by ethical concerns, logistical limitations and technical feasibility, the agency generally has had to answer relevant risk questions through the use of scientific inference and indirect evidence rather than through direct empirical studies. In some cases, the agency chose to rely on scientific inference and indirect evidence as the basis for decision making, even though empirical studies were possible. Scientists and policymakers used pre-existing data along with relevant scientific principles or personal familiarity with a system to draw a conclusion about risks. A summary of the questions asked and evidence presented during EPA's assessment of the risks of *Bt* are given in Table 2.

Human health effects

One issue addressed by the agency in its risk assessments is whether *Bt* protein is toxic to humans. Under current standards, it is not considered ethical for the agency to test a pesticide on human subjects. Consequently, the agency has used acute oral toxicity tests with mice, which are generally accepted by scientific experts as a proxy for direct measures of toxicity to humans. If an effect is observed at a single high dose ($> 2\text{--}5$ g/kg body weight), the agency requires additional data on the relationship between dose and response. In the case of *Bt* toxins produced in crops, no significant effects were observed in mice fed high doses of toxin; therefore, no additional studies were deemed necessary. The agency complemented the information generated through these mice studies with existing knowledge about human health effects of *Bt* sprays. The EPA considered the absence of any reported adverse effects associated with many years of use of *Bt* sprays an important piece of evidence suggesting limited to no risk of *Bt* PIPs to humans.

Along with toxicity, the EPA required studies of human allergenicity to the *Bt* proteins produced in plants. In this case, a direct test of allergenicity was not possible because allergic responses occur only after an unpredictable number of exposures to an antigen (FIFRA SAP, 2000a). Once again, the agency had to rely on indirect measures of risk. Current knowledge about food allergens indicates that these proteins tend to be resistant to degradation by heat, acid or proteases and may be glycosylated (have a carbon group attached to the protein) (EPA, 1998a). Consequently, the agency required tests to determine whether the *Bt* toxins demonstrated these biochemical characteristics common to food allergens. In the history of use of *Bt* sprays, the EPA had never confirmed any cases of allergenicity to the Cry proteins and considered this evidence to support the conclusion that there was a low risk of any *Bt* PIPs causing allergic response in humans (EPA, 2001d).

Non-target organism effects

In considering potential ecological impacts of *Bt* PIPs, the agency was faced with the impossibility of quantifying effects of the toxin on all exposed non-

TABLE 2. Questions asked and evidence used by the EPA in its risk assessment of *Bt* PIPs. The questions asked reflect the EPA's case-by-case tiered approach to risk assessment, which incorporated consideration of the gene insert and its product, the crop that is transformed, and the environment in which the crop is cultivated. Unless otherwise indicated, product applicants provided to the agency all new empirical data

Question asked	Evidence presented
What is the pesticide product?	Molecular, biochemical, and bioactivity data
Does the PIP pose a hazard to humans? <i>A. Is the PIP a toxin?</i>	Acute oral toxicity test with mice in the lab. (After 2000, sequence similarity to known toxins also required.) History of safe use of <i>Bt</i> sprays taken into consideration.
Does the PIP pose a hazard to humans? <i>B. Is the PIP an allergen?</i>	Lab studies of protein degradation in acid environment and at high temperatures. Partial sequence similarity to known allergens. (After 2000, more accurate sequence similarity to known allergens.)
What non-target organisms are likely to be exposed? <i>A. What level of toxin is expressed in the plant?</i>	Results of one or more greenhouse or field studies of one or more varieties expressing the <i>Bt</i> toxin
What non-target organisms are likely to be exposed? <i>B. Is it likely that the GM plant will be weedier than the same plant without the GM trait?</i>	No data required, but data available on similarity of agronomic traits between GM and non-GM plants. Assumption that crops demonstrating certain traits associated with lack of weediness (e.g. lack of wide seed dispersal) will not demonstrate increased weediness solely due to introduction of unrelated trait
What non-target organisms are likely to be exposed? <i>C. Is it likely that the transgene will introgress into populations of wild and/or weedy relatives and disrupt ecological systems?</i>	EPA literature review of distribution of and sexual compatibility between crop and wild relatives. If wild relatives exist (as for cotton) literature review and/or studies on rate of pollen flow between populations at different distances submitted by pesticide applicant
What non-target organisms are likely to be exposed? <i>D. Is horizontal gene transfer from the plant to soil bacteria likely to occur?</i>	EPA review of literature on horizontal gene transfer in lab and field environments
What non-target organisms are likely to be exposed? <i>E. How long does the protein persist in the soil?</i>	Lab studies of rate of degradation of pure protein and/or plant material submitted by applicant
Does the PIP pose a hazard to non-target organisms that might be exposed to the toxin? <i>A. Prior to 1999 (before monarch butterfly issue)</i>	Acute oral toxicity studies of species in the lab. Species selected to represent those that are assumed to be exposed (e.g. beneficial insects common in agricultural fields.) Voluntary field studies of non-target insect populations sometimes submitted by applicants.

Does the PIP pose a hazard to non-target organisms that might be exposed to the toxin?

A. After 1999 (after monarch butterfly issue)

Does the PIP pose a hazard to non-target soil organisms that might be exposed to the toxin?

What is the risk of resistance among target pests?

Field and lab studies determining effects on monarchs. Closer review of overlap between endangered species habitat and *Bt* PIPs. Field studies of non-target insect populations required for new registrations. Acute oral toxicity studies of earthworms and Collembola species. (After 2001, field studies of toxin persistence and effects on soil communities in different types of soils in different farming systems in different climates.)

Studies of baseline frequency of resistance alleles in pest populations, insect behavior and ecology studies, measurement of toxin dose administered by crops for various pests

target organisms. Consequently, in a similar approach to its assessment of risks associated with chemical and microbial pesticides, the agency required studies of effects of *Bt* toxin on species representative of those that might be exposed to the pesticide. The agency assumed that only organisms that fed on living or decaying plant tissue would be exposed to the toxin (EPA, 2000a). Representative species tested included: mice; northern bobwhite quail; beneficial insect pollinators, predators and parasites; *Daphnia magna*, a water invertebrate commonly used in toxicity testing of heavy metals and conventional pesticides; channel catfish; and soil invertebrate species. Acute oral toxicity tests were conducted with each species using a dose 10–100 times the estimated exposure in the field. Estimated exposure was based on quantification of the amount of toxin produced in different tissues during plant development in one or several crop varieties in greenhouse or field studies. Specific non-target organism tests were required on a case-by-case basis, reflecting different levels of exposure due to differential toxin expression in the plant tissues of various *Bt* PIPs. While recognizing that exposure to plant tissue was optimal for a rigorous risk assessment, the EPA permitted acute oral testing with purified toxin produced by microbes rather than purified toxin produced by the plant or the plant tissue itself. Substitution of protein purified from bacterial sources was permitted only when accompanied by additional data demonstrating that the toxin derived from the microbe had similar biochemical and bioactive properties as that derived from the plant (EPA, 1999b).

Transgene introgression

Unintended long-term persistence of *Bt* in the environment might result if the transgene successfully introgressed into populations of wild relatives. The presence of *Bt* in wild plants could have a negative impact on ecosystems if it

reduced insect herbivory, resulting in increased weediness among certain plant populations. Science cannot, with confidence, predict the rate at which genes will successfully migrate into wild populations and cause negative ecological effects (FIFRA SAP, 2001a). Consequently, the EPA had to resolve concerns about the risks related to hybridization through indirect methods. The agency did not require new empirical studies to investigate actual gene flow from crops to wild relatives. Instead, the agency extrapolated the likelihood of gene introgression from knowledge about sexual compatibility between crops and wild relatives and information it gathered on geographic boundaries of major crop areas and habitats of wild relatives.

Resistance evolution

A final example of EPA's reliance on scientific inference and indirect measures of risk is the design and implementation of the *Bt* crop RMPs. The agency's approach to resistance management is based on an ecological model coupling high dose expression of the toxin in the plant with a refuge of non-*Bt* host plants close to the *Bt* PIP field. High dose expression, defined as 25 times the amount of toxin needed to kill susceptible insects, would kill all homozygous and heterozygous susceptible insects, assuming resistance results from a single recessive allele. Under ideal model conditions, the nearby refuge would serve to maintain 500 susceptible insects for every single homozygous resistant insect that survives on the *Bt* crop. Random mating between susceptible insects from the refuge and any resistant individuals would prevent resistance from spreading through the insect population (EPA, 2001d). As part of the conditional registrations for *Bt* corn and cotton, the agency required crop registrants to conduct field studies to validate assumptions included in the high dose-refuge model of resistance management. Validation of all parameters under all conditions is impossible; consequently, the models will always offer limited representations of actual field conditions. Scientists inside and outside the agency have acknowledged that the models guiding the EPA's approach to resistance management cannot be fully tested until *Bt* resistance is observed in insect pests in the field. If resistance emerges, farmers may return to the use of more toxic chemical pesticides to prevent crop loss (FIFRA SAP, 2001a; EPA, 2001b). The agency hopes that resistance observed in the field can be mitigated through alternative pest management strategies (EPA, 2001b). Despite these limitations, the agency and others agree that the models are the only scientific means of guiding development and implementation of RMPs.

Resolving public concern about risks

Since 1995, two controversies over risks associated with *Bt* corn raised public concern about the safety of GM foods. To resolve these issues, the EPA turned to outside scientific experts for guidance and relied on new empirical evidence

in its reassessment of product risks, suggesting that indirect evidence and scientific inference were seen by the agency as insufficient to bring closure to controversial risk issues.

Allergenicity of Bt corn

In 1998, the EPA registered StarLink corn producing the *Bt* toxin Cry9C. In lab tests, this protein resisted degradation in a simulated gastric environment. Evidence on whether the protein was glycosylated, another characteristic common to food allergens, was also inconclusive. Consequently, the agency felt it could not resolve the question of whether the protein was or was not a human allergen. This particular toxin had not been present in any commercialized *Bt* spray so the agency could not use indirect evidence from the use of *Bt* sprays to support a conclusion of no risk, as it had for other registered *Bt* PIPs. Although the protein was produced in low concentrations in the corn relative to most food allergens, in 1998, the EPA approved the accepted tolerance level for Cry9C for animal feed only.

In the fall of 2000, Cry9C DNA was found in several food products containing corn. Reports of allergic response by consumers led the EPA to work with the USDA, the FDA and the Centers on Disease Control and Prevention (CDC) to restrict further entry of StarLink corn into the human food supply and to evaluate further the likelihood that Cry9C is a human allergen (EPA, 2001a). The agency relied on scientists serving at SAP meetings in November 2000 and July 2001 to provide guidance on both of these efforts. Scientists at these meetings concluded that StarLink corn was present at extremely low levels in the human food supply. Although the manufacturer, Aventis, provided new evidence to the SAP, the scientists found the data to be inconclusive and, reported to the EPA that the protein posed a moderate risk of allergenicity (FIFRA SAP, 2000b, 2001b). Following the July 2001 SAP meeting, in response to concerns about allergenicity, the agency announced that it would not grant a temporary tolerance for Cry9C to Aventis, as requested (Shadid, 2001). Additionally, the EPA stated that any genetically modified PIP perceived to pose an unacceptable risk to humans would not receive a registration, even if the application were exclusively for animal feed (EPA, 2000a).

Some decision makers might have considered the lack of evidence of a hazard as sufficient to conclude that all Cry proteins are not food allergens. A policy based on the lack of evidence when there has been no substantial effort to acquire the evidence is grounded in the “principle of ignorance”. In other words, no evidence of harm is not evidence of no harm. Other regulatory decisions on plant safety have been based on the “principle of ignorance” (Krimsky, Wrubel & Wetzler, 1992). In this case, however, despite the lack of evidence of human allergenicity to Cry proteins, the EPA sought primary data on degradation in heat, acid and proteases for all Cry proteins produced in plants prior to their commercialization.

The monarch butterfly

In 1999, concern about the effects of *Bt* corn on the monarch butterfly was raised after laboratory studies performed at Cornell University demonstrated that the protein was toxic to larvae (Losey, Raynor & Carter, 1999). The Cornell study received extensive coverage in both the print and TV media. Front-page stories in national dailies ran headlines such as “Engineered corn kills butterflies, study says” (Fackelman, 1999). Environmental groups viewed the data as evidence that the EPA had approved the GM corn for commercial production without conducting an appropriate environmental risk assessment prior to widespread planting of this crop (Mellon *et al.*, 1999). The monarch butterfly, a signature species for environmentalists representing nature’s beauty and vulnerability, triggered a strong public reaction.

In its initial risk assessments, the EPA had considered the effects of *Bt* corn on non-target Lepidoptera such as the monarch butterfly. At the time, the agency had concluded that the toxin could affect non-target Lepidoptera owing to the known range of bioactivity of Cry1Ab and Cry1Ac engineered in corn. The agency had assumed, however, that most non-target Lepidoptera populations would not be exposed to sufficient quantities of toxin to be significantly impacted (EPA, 1995a, 2000a). Additionally, aerial spraying of *Bt* toxins to control gypsy moth outbreaks in forests were known to have a short-term negative impact on Lepidoptera populations but have no lasting effect (EPA, 1998b).

Given the high level of public concern in the aftermath of the monarch study, the EPA turned to empirical studies to address an issue it had resolved to the satisfaction of its internal agency staff as early as 1995 (EPA, 1995a). In December 1999, the EPA requested from the *Bt* corn manufacturers new laboratory and field data addressing questions about the effects of their products on monarch butterfly populations. Research needs were identified at a USDA-sponsored meeting in early 2000. A steering committee, with representatives from USDA, academia, industry and environmental organizations, awarded grants on scientific merit, funded by the corn manufacturers and USDA (Sears *et al.*, 2001). The results of these studies were published in October 2001 in the *Proceedings of the National Academy of Sciences* (PNAS).

The studies further refined scientists’ understanding of acute toxicity of *Bt* pollen to monarch larvae and larval exposure to the toxin in the field. Protein from different *Bt* corn products exhibited different toxicity to monarch larvae. Field exposure to hazardous concentrations was extremely unlikely in all but 2% of the *Bt* corn acreage. Although longer-term studies are ongoing, the authors of the PNAS studies concluded that the impact of commercial *Bt* corn on monarch populations was negligible (Sears *et al.*, 2001). Subsequently, the EPA used these conclusions to support its decision to re-register *Bt* corn for seven years, an indication that the agency felt that the benefits of the use of this product outweighed any risks to monarchs or other non-target species.

Some scientists and environmental groups would have preferred that the EPA

had taken a more conservative approach to *Bt* corn regulation (Environmental Defense, 2001; Oberhauser, 2001; Union of Concerned Scientists, 2001). Scientists who participated in the monarch research project disagreed on the significance of data indicating toxicity of anther fragments to monarch larvae (Hellmich *et al.*, 2001; Jesse & Obrycki, 2000; Losey *et al.*, 1999). Some participants reported unpublished data to the EPA, suggesting that anthers were commonly found on milkweed plants in cornfields and felt that the USDA and industry-funded studies might have underestimated risk to monarchs because they did not investigate larval consumption of anthers in the field (Obrycki *et al.*, 2001). Another participant in the monarch research project argued, however, that anthers are only broken into pieces small enough to be consumed by caterpillars when corn pollen is collected from plants by researchers. According to this analysis, the risk to larvae is not present in the field (Pew Initiative on Food and Biotechnology, 2002). The EPA's decision to issue a conditional registration for *Bt* corn permits the agency to revisit this issue and restrict future use of this product if unacceptable risks can be documented within the next seven years.

Conclusion

In examining the regulation of GM PIPs by the EPA, we found that the agency's approach was tacitly precautionary, both in its *ad hoc* regulation of new products during the 1990s and in its recently released rules guiding future regulation.

In its 2001 decision not to deregulate genetically modified PIPs derived from sexually compatible plants, the EPA chose to accept, at least temporarily, the conservative hypothesis that these plants might pose greater risk than conventionally bred PIPs derived from sexually compatible plants. One issue of concern to the agency is whether unintended increases in known or novel toxin levels in the edible portion of the crop are more likely to occur with PIPs derived from genetic engineering than with those derived from conventional breeding of sexually compatible plants.

We found that the EPA generally chose a cautionary position in estimating and managing risks, even when scientific evidence indicating the presence of risk was lacking. The agency evaluates each GM PIP on a case-by-case basis prior to commercialization. Data requirements for each case follow certain risk assessment frameworks, which in the case of the EPA, is largely a chemical risk model, adapted when necessary to accommodate the novel mechanism of PIP application. The agency's product risk assessments, often wanting of direct evidence, rely heavily on using biochemical and biological principles in conjunction with ecological risk models. The use of indirect measures is often necessary in assessing the risks associated with GM PIPs when direct measurements are beyond current scientific techniques.

The EPA's decision to include insect resistance management as an integral part of its *Bt* crop registrations reflects a cautionary position taken by the agency in the face of scientific uncertainty. The agency's proposal to manage *Bt*

resistance illustrates its reliance on extrapolation from limited scientific knowledge as part of its effort to develop science-based regulations.

Developing pure science-based regulations for GM products continues to pose an enormous challenge for the EPA because appropriate and effective risk assessment for these products extends beyond the limits of current scientific knowledge and technical capability. For example, Power & McCarty (1997) raised concern about the ecological relevance of current non-target organism tests used in pesticide risk assessment generally. A Swiss consulting group, commissioned by Greenpeace International to critique the EPA's risk assessment of *Bt* PIPs, indicated similar concerns about the use of representative species testing in risk assessment of these GM PIPs (EcoStrat, 2000). Michelle Marvier, a professor at the University of California at Santa Cruz, closely examined the study design of a select number of such tests submitted to the EPA and found that current sample sizes limit statistical power such that none of the tests reviewed could have detected a 20% difference in survival, and only one of five could have detected a 50% difference in survival (unpublished observations). The agency has demonstrated awareness of such concerns and sought guidance on ecological testing from its SAP in 1999. New field data required by the agency as part of its re-registration of *Bt* corn and cotton in 2001 and as part of its pre-market review of pending *Bt* corn registrations demonstrate the EPA's efforts to address limitations of its current testing program (EPA, 2000b, 2001d). Poorly designed studies or inappropriate studies could undermine the agency's cautious approach to GM PIP regulation.

Within the framework of credible science, there is uncertainty and, on issues pertaining to risk, this uncertainty creates opportunities for discretionary choices. These choices are made under the rubric of "science-based policy". Postulated risks that have not been refuted or verified may either be ignored or seriously addressed. Setting the burden of proof constitutes a trans-scientific judgement that sets a course for the application of science. Our investigation of the science used by the EPA in assessing risks associated with genetically modified crops and foods reveals many instances in which normative judgments guide the direction of science informing the discussion of risks. Such judgments may be influenced by factors that lie outside science.

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