#174

DEPARTMENT OF PESTICIDE REGULATION'S REPORT ON BACILLUS THURINGIENSIS (Bt) REQUIRED BY THE SUPPLEMENTAL LANGUAGE OF THE 2000 BUDGET ACT

In 1994, the U.S. Environmental Protection Agency (U.S. EPA) published a proposed policy and regulation in the Federal Register stating their intent to regulate "plant pesticides" and further defined the regulated products and intended scope of regulatory activity, including establishing tolerance exemptions for these products.

U.S. EPA's authority to regulate plant pesticides contained in, or produced by, genetically modified plants comes from their authority under the Federal Insecticide, Fungicide, and Rodenticide Act to regulate pesticides in general. Further authority comes from the Coordinated Framework for the Regulation of Biotechnology as published in the Federal Register in 1986, which assigns oversight of various areas of biotechnology to different federal regulatory agencies. Historically, the Department of Pesticide Regulation (DPR) has followed U.S. EPA definitions of pesticides and has used their data requirements for registration as a basis for the review and registration of pesticides in California.

In developing the policy for regulating pesticidal substances in plants, U.S. EPA coined the term "plant pesticides" to clarify that they are regulating the pesticide, not the plant itself. In the case of crop plants containing the *Bacillus thuringiensis* (Bt) toxin, the regulated article is the toxin and the genes producing it which have been inserted into the plant, not the plant itself. U.S. EPA has stated their authority to regulate all plant pesticides, i.e., any and all compounds contained in and made by plants that have pesticidal characteristics or mitigate pests. However, they then proposed to exempt from further regulation (1) those plant pesticides that occur naturally and could have been transferred between sexually compatible species, and (2) certain other characteristics expressed in genetically modified plants, such as coat proteins from plant pathogenic viruses which confer disease resistance to the plant. In practical terms, this means they will regulate most pesticidal characteristics inserted into genetically engineered plants that are not from close plant relatives. This includes genes for Bt toxins which are inserted into different crop plants.

In the case of registering plant pesticides, it should be noted that U.S. EPA registers the gene and gene products that are inserted into the crop plant and subsequently produce the pesticidal characteristics in the plant. However, the plant or the seed are not registered. Thus, the bag of seed corn containing a Bt corn variety is not a registered pesticide. Certain information from the company regarding the characteristics of the seed must accompany the sale and use of such seed, but the seed is not a registered pesticide.

Current Status

U.S. EPA has proposed regulations for plant pesticides under a rule that is anticipated to be finalized in the near future. Since these regulations have not been finalized, the actual data requirements for registration of plant pesticides have not been completely determined. Up to now, plant pesticides and the data to support their registration have been reviewed by U.S. EPA on a case-by-case basis. Since DPR routinely relies on U.S. EPA pesticide definitions and also follows their data requirements in conducting its review of pesticide products, the absence of final rules and data requirements has made any registration activity on plant pesticides difficult to implement. Up to the present time, DPR has left the regulatory oversight for plant pesticides to U.S. EPA.

DPR provided a preliminary response to the issues identified by the Joint Legislative Budget Committee in a letter to Senator Tom Hayden dated March 22, 2000 (attached). The following information provides more detail in each of the areas under discussion.

- **DPR's plan to investigate the scientific basis for registration of Bt-containing crops in California.**

  DPR has formed an internal working group to make recommendations to the Director as to what registration activity is appropriate at the state level. This committee will review U.S. EPA data requirements and registration process, the nature of the products being registered (including pertinent health and environmental effects of those products), the proposed U.S. EPA rules for the registration of plant pesticides (and their final rules when available), and the regulatory options available to DPR. An ongoing responsibility of the working group will be to assess the data requirements for plant pesticide registration as they are developed by U.S. EPA and to evaluate their applicability and usefulness to the California registration process. This will in turn provide the basis for the evaluation of plant pesticides and their use in the State.

- **The development of a risk/benefit ratio for allowing this pesticide in crops.**

  Up to this point, there has been no formal review by DPR concerning the use of Bt in crops. In all routine evaluations concerning the registration and use of a product, DPR evaluates risks, but does not use a risk/benefit ratio, *per se*. As a part of our analysis of the registration of plant pesticides, including the Bt toxin incorporated into plants, DPR will study the issue of risks and benefits further. One study DPR will use in its analysis is the April 2000 report from the National Research Council (NRC) entitled "Genetically Modified Pest-Protected Plants: Science and Regulation." Dr. Tobi Jones, Assistant Director of our Registration and Health Evaluation Division was a member of the committee which wrote the report. She will be able to provide insight into the committee's approach to its charge from the NRC to investigate the risks and benefits of genetically modified pest-protected plants. A copy of the Executive Summary from this report is attached.

- **DPR's assessment of the ecological safety of Bt toxoid left in soil.**

  Again, DPR has not conducted a formal review of this data. However, the common Bt toxins produced by crops are proteins with no unusual stability characteristics with regard to protease digestion or degradation in the environment. In fact, there is a substantive body of evidence that demonstrates degradation via routine microbial activity in the soil profile as occurs with other proteins of biological origin, which are incorporated into the soil.

  We are aware of certain conflicting studies on the longevity of Bt toxin in the soil. However, the work regarding the unusual persistence of Bt has come primarily from a laboratory study whose results are not consistent with an array of other studies showing a relatively short half-life of days to weeks, regardless of the source of the toxin. We will continue to follow U.S. EPA's review of these products and their establishment of data requirements in this area, as well as publications in the scientific literature.

- **The potential consequences, if any, of the presence of Bt in silage used for livestock.**

  Given the highly specific and well-known target insect pest range for Bt, and the lack of mammalian toxicity for Bt which has been established over the years, DPR is not aware of any special concerns which feeding silage containing the Bt toxin would present, especially to ruminants such as cattle. The Bt toxin is highly specific for the insect gut, due to the alkaline environment needed for toxin activation and the presence of specific toxin receptors in the gut. Neither of these characteristics is present in mammalian digestive systems. Consequently, the ingestion of Bt toxin has never been described as a hazard to mammals, having been directly tested at much higher doses than would occur in corn plants. Information presented in the Federal Register from U.S. EPA notices also describes the various Bt toxins as being readily digestible. While recent attention has focused on the Cry9C toxin, corn containing that gene is not widely available, and it was approved for use only as an animal feed. In fact, this plant pesticide registration was recently voluntarily cancelled due to the feed corn inappropriately being used for human food.

Attachments

dpr

Department of Pesticide Regulation

Paul E. Helliker
Director

Gray Davis
Governor

Winston H. Hickox
Secretary, California Environmental Protection Agency

March 22, 2000

The Honorable Tom Hayden
Member of the Senate
State Capitol, Room 2080
Sacramento, California 95814

Dear Senator Hayden:

Thank you for your recent letter regarding the registration of crops that contain genes for the delta endotoxin from *Bacillus thuringiensis* (Bt), and thank you for the opportunity to answer your questions concerning the activity of the Department of Pesticide Regulation (DPR) on this issue.

For many years DPR has followed the regulatory activities at the federal level with respect to transgenic plants. At the present time, DPR has left the regulatory oversight up to the U.S. Environmental Protection Agency (U.S. EPA) for what they have defined as "plant pesticides." U.S. EPA has proposed regulations to regulate plant pesticides; however, these regulations have not yet been finalized. So far, the actual data requirements for registration of the plant pesticides are not part of the proposed rule and are being applied on a case-by-case basis. U.S. EPA intends to propose additional rules on data requirements and labeling. Since DPR relies on the U.S. EPA data requirements, the absence of final rules would make any registration activity here premature. Once these rules are finalized, DPR will again examine the issue of the registration of plant pesticides.

In your letter you ask if DPR has investigated the scientific basis for registering crops containing Bt in California. DPR has not required the registration of plant pesticides for use in California. There are several reasons for this policy:

1. The registrations at U.S. EPA are not for actual products being sold. The plants containing the plant pesticides are not themselves registered pesticidal products. U.S. EPA registrations are for the toxin protein and the genes required for its expression in plant cells. In granting these registrations to the manufacturer, U.S. EPA may impose other restrictions on the cultural practices and use of these modified plants. These restrictions are to be administered by the registrant as part of the registration of the plant pesticide. However, the plants containing the Bt toxin are not registered. The closest analogy in existing pesticide products is the use of a pesticide product to preserve or protect a secondary product, or "treated article." The pesticide product is registered but the secondary "treated article" is not registered as a pesticide. An example would be lumber treated with a wood preservative,

whereby the preservative is registered and is used to treat the lumber, but the treated lumber is not a pesticidal product and is not registered as such.

2. Due to the absence of the target pest pressure experienced in other parts of the United States, the use of crops containing plant pesticides has only recently been initiated in California and is expanding at a much slower rate than uses nationwide. The California Department of Food and Agriculture has indicated that slightly over 100,000 acres (about 12 percent of the State's crop) of Bt cotton were planted in 1999.

3. DPR has followed the development of the proposed rules by U.S. EPA. However, this is still an area of flux and controversy, with some commentors saying that more regulation is needed, and others saying that even this level of plant pesticide regulation is unneeded. We will continue to stay apprised of the regulatory status of these plant pesticides. This area is also the subject of an ongoing study by the National Academy of Science. That study will also provide useful input as to whether any additional regulatory activity at the state level is needed. We have experienced almost 40 years of Bt use as a biocontrol agent and microbial pesticide and, in that time, have reviewed all aspects of its use and impacts. There has been a continued lack of hazard and environmental impact from its use. The addition of Bt toxin to crop plants, while significant, still is supported by its history of safe use.

Secondly, you question the reviewers' assessment of the benefit/risk ratio for allowing this pesticide in crops since some such crops, notably Bt cotton (either alone or "stacked" with herbicide-resistant genes), are already in commerce. As we state above, there has been no formal review of the Bt crop data by DPR, either with or without stacked genes.

Next, you ask how DPR assesses the ecological safety of Bt use given the persistence of Bt toxoid in soils. We are aware of conflicting studies on the longevity of Bt toxin in the soil. In fact, the work regarding unusual persistence has come primarily from one laboratory whose results are not consistent with an array of other studies showing a relatively short half-life of days to weeks, regardless of the source of the toxin. When we get involved in the registration of plant pesticides in the future, DPR will directly review the available data on this question.

Finally, you ask about the potential consequences, if any, of Bt's presence in silage used for livestock. Given the highly specific and well-known target insect pest range for Bt and the lack of mammalian toxicity for Bt that has been established over the years, DPR is not aware of any special concerns that feeding silage containing the Bt toxin would present.

Again, thank you for your letter. If you have any additional questions, please call me at (916) 445-4000.

Sincerely,

Paul Helliker

Paul E. Helliker
Director
(916) 445-4400

cc: Mr. William J. Lyons, Jr., Secretary
California Department of Food and Agriculture

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TOM HAYDEN
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CHAIR:
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SUBCOMMITTEE ON COASTAL AND OCEAN PROTECTION AND RESTORATION
COMMITTEES:
BUDGET AND FISCAL REVIEW
EDUCATION
ENVIRONMENTAL QUALITY
TRANSPORTATION

March 6, 2000

Paul Helliker, Director
Department of Pesticide Regulations
Sacramento, CA 95814

Transmitted by facsimile: (916) 324-1452

Dear Mr. Helliker:

We are most interested in how the Department of Pesticide Regulations is integrating the recent EPA proposals for regulating crops which contain Bacillus thuriengiensis (Bt) toxoid genes. As I am sure you know, such crops are regulated by EPA as pesticides. Our staff has recently received and reviewed the entire file of EPA'S comments on ingestion studies for Bt and finds them lacking in studies which have examined the preformed toxoid as it appears in GMO plants. The present circumstances raise a number of questions:

1. Has DPR investigated the scientific basis for registration of Bt containing crops in California?

2. Since some such crops, notably Bt cotton (either alone or "stacked" with herbicide resistant genes), are already in commerce, what was the reviewers' assessment of the benefit/risk ratio for allowing this pesticide in crops?

3. Given the persistence of Bt toxoid in soils, how does the DPR assess the ecological safety of Bt use?

4. What are the potential consequences, if any, of Bt's presence in silage used for livestock?

I would greatly appreciate your views and responses to these queries prior to our budget hearing March 22. If you have any questions, they can be directed to our technical assistant, Dr. Marc Lappe, who could provide any needed background to our concerns.

Thank you for your consideration and timely response.

Sincerely,

Senator Tom Hayden

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GENETICALLY MODIFIED PEST-PROTECTED PLANTS

SCIENCE AND REGULATION

Committee on Genetically Modified Pest-Protected Plants

Board on Agriculture and Natural Resources

National Research Council

NATIONAL ACADEMY PRESS
Washington, D.C.

Executive Summary

Pest and pathogen management to optimize crop health, productivity, food quality and safety is critical to global food security, and ultimately, to the cost and affordability of food. Several methods have been used for pest and pathogen management including the growing of conventionally bred pest-protected crops, use of chemical pesticides as the primary means of plant protection, and integrated pest management (IPM).

In recent decades, major advances in the science of plant biotechnology have permitted wider access to genetic sources of plant protection against insects and pathogens. Transgenic plants engineered to contain genes for pest-protection have been field tested since 1988 and grown commercially since 1995. From 1995 to 1999, the commercial planting of transgenic pest-protected plants has dramatically increased. Along with these rapid advances in plant biotechnology and its commercial applications, the need to periodically review public oversight and regulation of transgenic plants has emerged.

ES.1 PURPOSE AND SCOPE OF THIS STUDY

In the past, the National Academy of Sciences (NAS) and National Research Council (NRC) have provided guidance to scientists, regulatory agencies, and the public concerning biotechnology and transgenic products. The NRC determined that there was a need for an overview of the current issues surrounding transgenic plants, in particular those engi-

neered to resist pests.[1] As a result, the NRC appointed and funded a committee in 1999 to conduct the study reported here. The committee was charged with the following task:

> The committee will investigate risks and benefits of genetically modified pest-protected (GMPP) plants, and the Coordinated Framework for Regulation of Biotechnology (Coordinated Framework) affecting the use of these plants. The study will 1) review the principles in the NAS Council's white paper, *Introduction of Recombinant DNA-Engineered Organisms into the Environment* (1987), for their continued scientific validity and assess their appropriateness for current decisions regarding GMPP plants, 2) review scientific data which address the risks and benefits of GMPP plants, 3) examine the existing and proposed regulations in light of the identified risks and benefits, 4) examine existing and proposed regulations to qualitatively assess their consequences for research, development, and commercialization of GMPP plants, and 5) provide recommendations to address the identified risks/benefits, and, if warranted, for the existing and proposed regulation of GMPP plants.
>
> Note: The study does not address philosophical and social issues surrounding the use of genetic engineering in agriculture, food labeling, or international trade in genetically modified plants.

As instructed by the charge, the committee focused on transgenic pest-protected plants; however, many of its conclusions and recommendations are applicable to other categories of transgenic plants. Because of public concerns about the safety of our food supply, the committee has placed less emphasis on potential benefits of transgenic pest-protected plants than on potential risks, even when some of these risks seem remote.

During a four-month period, the committee met three times to discuss the issues, review data, and obtain input from the public. Representatives from government-agencies, industry, and nongovernment organizations were invited to discuss the issues and their challenges and concerns. In addition, the committee hosted a public workshop on May 24, 1999, to obtain input from a variety of experts and other interested parties (appendix C). The committee requested data that were submitted for regulatory review of transgenic pest-protected plants from the US

[1]For consistency, the committee adopts the broad definition of *pest* used by the statutes which govern the Coordinated Framework for the Regulation of Biotechnology (for example, the Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Plant Pest Act). This definition includes not only invertebrate animals such as insects and nematodes, but also microorganisms such as protozoa, viruses, bacteria, or fungi. In some disciplines, a more narrow definition of pests is used. For example, plant pathologists typically refer to insects as *pests* and disease-causing microorganisms as *pathogens*.

Environmental Protection Agency (EPA), the US Food and Drug Administration (FDA), US Department of Agriculture (USDA), and product registrants (appendix B) and used examples of the data during its analysis.

After reviewing the above information, the committee drafted this report. Chapter 1 introduces the scientific and regulatory issues, chapter 2 focuses on the scientific impacts of conventional and transgenic pest-protected plants, chapter 3 addresses how the scientific information is reviewed in the regulatory framework and presents guiding principles for review, and chapter 4 discusses the positive and negative elements of the current regulatory framework and suggests improvements for the review and exchange of scientific information.

The following pages highlight the committee's major findings, conclusions, and recommendations. Not all of the committee's recommendations could be included in this brief executive summary; therefore, the most general conclusions and recommendations are presented in this section and the more detailed ones are included in chapters 2, 3, and 4.

ES.2 FUTURE STUDIES AND LIMITATIONS OF THE CURRENT STUDY

This study was conducted with a broad scope and in a short time period in order to provide stakeholders with opportune guidance on a variety of issues. As a result, the committee could not comprehensively analyze all available data on the numerous scientific and regulatory issues. In particular, much data are submitted by developers of transgenic products for regulatory approval (appendix B). The committee could only review examples of such data and of published studies regarding transgenic pest-protected plants.[2] The committee chose examples that covered a range of issues and that were provided by scientific experts representing diverse disciplines and affiliations. The committee focused on the general issues that would be applicable not only to prior product approvals, but also to upcoming decisions related to commercialization.

The committee was able to address several categories of scientific and regulatory issues and develop general conclusions and recommendations to advise researchers, producers, regulators and users of transgenic pest-protected plants. The general conclusions and recommendations identify areas where more analysis is needed. In order to help conduct future analyses, the NRC recently convened a Standing Committee on Biotech-

[2]In addition, the committee did not have an opportunity to fully discuss or analyze data published after its last meeting in July 1999. However, some of the more recent information is mentioned in the report.

nology, Food and Fiber Production, and the Environment. This standing committee will identify emerging issues and provide intellectual oversight for subcommittees focusing on particular issues in agricultural biotechnology. Through this mechanism, the NRC expects to publish a series of more detailed, comprehensive reports concerning agricultural biotechnology and looks forward to the opportunity to play a larger role in analyzing and reporting upon the scientific issues.

ES.3 REPORT TERMINOLOGY

ES.3.1 EPA Terminology

The committee recognizes that the term *plant-pesticide*, used by the US Environmental Protection Agency (EPA) to describe the scope of products subject to regulation under its 1994 proposed rule, is controversial. To some extent, the controversy stems from the mistaken impression that EPA will classify plants as pesticides. EPA has consistently stated that the "pesticide" will be defined as the "pesticidal substance that is produced in a living plant and the genetic material necessary for the production of the substance, where the substance is intended for use in the living plant." At least in partial response to the controversy, the agency has recently sought public comment on possible alternatives to the term *plant-pesticide*. The committee agrees that the agency must be sensitive to this issue, but it takes no position on the most appropriate term used for regulatory purposes. Therefore, pesticidal substances, pest protectants, pest resistance genes, and other variations are used throughout this report.

ES.3.2 Genetically Modified Plants

Plant breeders use a variety of genetic techniques to enhance the ability of plants to protect themselves from plant pests. Regardless of the technique used, the committee considers these plants to be genetically modified. Although the committee recognizes that there is no strict dichotomy between the products of conventional and transgenic technologies (see ES.4), in this report it has used the following terms:

> *pest-protected plant or genetically modified pest-protected (GMPP) plant*: refers to any plant that has been genetically modified to express a pesticidal trait[3], regardless of the technique used[4];

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[3]The committee's definition includes both structural and chemical traits that deter or resist pests.

[4]The committee's definition of pest-protected plants does not include herbicide-tolerant plants.

transgenic pest-protected plant: refers to any plant that has been genetically modified with modern molecular techniques (rDNA technology, commonly referred to as genetic engineering) to express a pesticidal trait;

conventional pest-protected plant: refers to any plant that has been genetically modified by classical or cellular plant breeding techniques (such as hybridization or tissue culture) to express a pesticidal trait.

For completeness, the committee notes that many plants have evolved a natural protection against pests without any type of genetic modification done by humans. This report refers to those plants as *naturally pest-protected plants*.

ES.4 REVIEW OF THE 1987 NATIONAL ACADEMY OF SCIENCES PRINCIPLES

As the first assigned task, the committee reviewed the 1987 NAS white paper, *Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues*. The 1987 paper focused on the safety of rDNA techniques and on ecological issues associated with the potential spread of transgenic organisms or genes associated with transgenic organisms, and it provided the following conclusions:

- point 1 "There is no evidence that unique hazards exist either in the use of rDNA techniques or in the movement of genes between unrelated organisms."
- point 2 "The risks associated with the introduction of rDNA-engineered organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods."
- point 3 "Assessment of the risks of introducing rDNA-engineered organisms into the environment should be based on the nature of the organism and the environment into which it is introduced, not on the method by which it was produced."

The committee discussed the above principles in light of its knowledge of the underlying scientific processes involved in conventional and transgenic methods. It is important to point out that the committee is not aware of controlled field studies which directly compare the ecological effects of transgenic and conventional pest-protected plants bred for the same pesticidal traits. Therefore, the committee's conclusions about the 1987 NAS principles are not based on data from such comparisons, but on mechanistic knowledge and scientific information about the resulting genetically modified plants. For example, conventional breeding often in-

volves the transfer of traits which are controlled by several interacting genes and often occurs without specific knowledge of which genes and gene products are involved. Therefore, some of the plants produced by this method could have unanticipated properties. With transgenic methods, there is often more knowledge about the genes and gene products being transferred, but diverse traits and genes from unrelated organisms can be transferred so some specific products could have unique properties. Because both methods have the potential to produce organisms of high or low risk, the committee agrees that the *properties* of a genetically modified organism should be the focus of risk assessments, not the *process* by which it was produced (point 3).

The committee also agrees with points 1 and 2 in the sense that the potential hazards and risks associated with the organisms produced by conventional and transgenic methods fall into the same general categories. As this report discusses, toxicity, allergenicity, effects of gene flow, development of resistant pests, and effects on non-target species are concerns for both conventional and transgenic pest-protected plants. In this regard, the committee found no strict dichotomy between, or new categories of, the health and environmental risks that might be posed by transgenic and conventional pest-protected plants (points 1 and 2), and recognizes that the magnitude of risk varies on a product by product basis (point 3).

The present committee found the three general principles to be valid within the scope of issues considered by the 1987 paper, and the present report further clarifies and expands on these principles.

This report expands on the 1987 principles by describing various methods of both conventional and transgenic plant breeding, and their potential consequences.

ES.5 POTENTIAL HEALTH AND ECOLOGICAL IMPACTS AND RESEARCH NEEDS

Conventional pest-protected plants have substantially improved plant health and agricultural productivity and have often lessened the need for chemical pesticides. Transgenic pest-protected plants have the potential to make similar contributions, as has already been documented with transgenic pest-protected cotton (section 1.5.5). Human health and environmental benefits could arise from reductions in the application of chemical pesticides resulting from the commercial production of certain transgenic pest-protected plants. However, the relative risks and benefits will depend on the particular transgenic pest-protected plant in question.

Historically, pest-protected plants have rarely caused obvious health or environmental problems, but there is a potential for undesirable effects. Therefore, a major goal for further research and development of transgenic and conventional pest-protected plants should be to enhance agricultural productivity in ways that also foster more sustainable agricultural practices, enhance the preservation of biodiversity, and decrease the potential for health problems that could be associated with some types of pest-protected plants. Although the committee focused its discussions on transgenic pest-protected plants, many of the following recommendations for research and development also apply to conventional pest-protected plants.

ES.5.1 Health Impacts And Research Needs

Health impacts that the committee considered fall into three general categories: allergenicity, toxicity, and pleiotropic[5] effects of genetic modifications.

The potential for allergenic responses to novel gene products was considered. Such responses have not been documented for commercialized transgenic pest-protected plants, although one incident has been documented at the research stage. Several indirect tests for allergenicity are available. For novel proteins, the most common methods involve analyzing the protein for its digestibility, estimating the level of protein expression and consumption, and assessing homology to known allergens. While these indirect tests can be good indicators of potential allergenicity, the development of more direct tests is highly desirable. Therefore, the committee recommends that

Priority should be given to the development of improved methods for identifying potential allergens in pest-protected plants, specifically, the development of tests with human immune-system endpoints and of more reliable animal models.

The committee reviewed data concerning toxicity testing and potential pleiotropic or secondary effects of genetic modification. The committee concluded that monitoring for pleiotropic changes in plant physiology and biochemistry during the development of pest-protected plants should be an important element of health-safety reviews, in addition to testing the toxicity of the introduced gene products (see ES.6.4). Although results of tests for changes in the levels of certain endogenous plant toxi-

[5]Defined as *simultaneous effects on more than one character of the organism.*

cants are presented during consultation with FDA, there is a lack of an extensive database on the natural levels of such compounds in both transgenic and conventional pest-protected plants. The committee recognizes the challenges associated with detecting changes in those compounds given insufficient analytical information, and therefore, recommends research to

Assess and enhance data on the baseline concentrations of plant compounds of potential dietary or other toxicological concern, and determine how concentrations of these compounds may vary depending on the genetic background of the plant and environmental conditions.

In addition to the above research, the committee recommends that

The EPA, FDA, and USDA collaborate on the establishment of a database for natural plant compounds of potential dietary or other toxicological concern.

The committee recognizes that a significant amount of time and resources will be needed to establish such a database, given the complexity of these plant compounds.

For some novel pest-protectants developed for future commercialization, longterm toxicity testing may be warranted. Tests which involve feeding of large quantities of pest-protected plants to animals have limitations, and the results can be difficult to interpret especially when the animal's natural diet does not consist of the type and quantities of the plant being tested (section 2.5.2). Therefore, the committee recommends research to

Examine whether longterm feeding of transgenic pest-protected plants to animals whose natural diets consist of the quantities and type of plant material being tested (for example, grain or forage crops fed to livestock) could be a useful method for assessing potential human health impacts.

In conclusion, although there is the potential for the adverse health effects discussed in this section,

The committee is not aware of any evidence that foods on the market are unsafe to eat as a result of genetic modification.

ES.5.2 Ecological Impacts and Research Needs

Three major ecological impacts[6] were considered by the committee: effects on nontarget[7] species, effects of gene flow[8], and evolution of pest resistance to pest-protected plants.

The committee reviewed studies concerning nontarget effects. The committee found that both conventional and transgenic pest-protected crops could have effects on nontarget species, but these potential effects are generally expected to be smaller than the effects of broad-spectrum synthetic insecticides. Therefore, the use of pest-protected crops could lead to greater biodiversity in agroecosystems where they replace the use of those insecticides (section 2.6.3). The use of transgenic pest-protected plants should also be compared with sustainable agriculture methods for crop protection. The committee recommends research to

Determine the impacts of specific pest-protected crops on nontarget organisms, compared with impacts of standard and alternative agricultural practices through rigorous field evaluations.

Gene flow between cultivated crops and wild relatives was the second ecological impact considered by the committee. On the basis of the literature, the committee found that pollen dispersal can lead to gene flow among cultivated crops and from cultivated crops to wild relatives but that only trace amounts of pollen are typically dispersed further than a few hundred feet (section 2.7). The committee found that the transfer of either conventionally bred or transgenic resistance traits to weedy relatives potentially could exacerbate weed[9] problems, but such problems have not been observed or adequately studied. Therefore, the committee recommends further research to

Assess gene flow and its potential consequences: develop a list of plants with wild or weedy relatives in the United States; identify key factors that regulate weed populations; assess rates at which pest resistance genes from the crop would be likely to spread among weed populations; and evaluate the impact of specific, novel resistance traits on the weed abundance.

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[6]The committee's ecological assessment focused on potential impacts of food and fiber crops, not on the potential impacts of other types of transgenic pest-protected plants that might be commercialized in the future (for example, forest trees).

[7]Organisms that are not the target for the particular plant-pesticide.

[8]The transfer of genetic information from one organism to another.

[9]The committee's definition of a weed includes plants that are unwanted in human-dominated or natural habitats.

Develop transgenic or other techniques that decrease potential for the spread of transgenes into wild populations.

Evolution of pest resistance to pest-protected plants was the third major ecological impact addressed by the committee. The committee concluded that pest resistance to pest-protected plants could have a number of potential environmental and health impacts such as a return to the use of more harmful chemicals or replacement of an existing pest-protected variety with novel varieties for which there is less information available about health and environmental impacts. The committee recommends that

If a pest-protectant or its functional equivalent is providing effective pest control, and if growing a new transgenic pest-protected plant variety threatens the utility of existing uses of the pest-protectant or its functional equivalent, implementation of resistance management practices for all uses should be encouraged (for example, Bt proteins used both in microbial sprays and in transgenic pest-protected plants).

In addition to the above recommendations, the committee recommends general ecological research to

Improve our understanding of the molecular basis of pest-plant interactions and of the population ecology and genetics of target pests so that more ecologically and evolutionarily sustainable approaches to the use of pest-protected plants can be developed.

Develop more specific expression systems for transgenes in ways that lessen nontarget exposure and delay pest adaptation (for example, use of promoters[10] that would limit expression to certain tissues).

Monitor ecological impacts of pest-protected crops on a long term basis to ensure the detection of impacts that may not be predicted from tests conducted during the regulatory approval process.

ES.6 THE COORDINATED FRAMEWORK FOR REGULATION

ES.6.1 Background and History

In 1986, the Coordinated Framework for the Regulation of Biotechnology apportioned jurisdiction over transgenic products by using exist-

[10]DNA sequences which regulate the expression of genes.

ing legislation: for example, plants came under the jurisdiction of the Federal Plant Pest Act (FPPA) administered by the USDA; food and feed under the jurisdiction of the Federal Food, Drug, and Cosmetic Act (FFDCA) administered by the FDA; and microorganisms and substances used for pest control under the jurisdiction of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and parts of FFDCA, administered by the EPA. Transgenic pest-protected plants were not addressed in the original framework document.

USDA published its policy under the coordinated framework providing for field testing permits for transgenic plants in 1987 and field testing notifications in 1993 and 1995. In 1993, it finalized its policy for determining when certain plants would no longer be regulated articles. In 1992, FDA published its policy for foods derived from new plant varieties based on its role under FFDCA. In 1994, EPA proposed a rule to regulate the pesticidal substances in pest-protected plants as plant-pesticides under FIFRA and FFDCA. Several groups opposed that statutory interpretation on both legal and scientific grounds; others supported the EPA's oversight of transgenic pest-protected plants, given the agency's mission to address environmental concerns. In the last few years, there have been concerns expressed by several professional societies and other groups over the broad scope of the proposed EPA rule and opposite concerns expressed by consumer and environmental groups that the EPA rule does not adequately cover all of the risk issues.

ES.6.2 Overall Approach

The committee recognizes that

There is an urgency to complete the regulatory framework for transgenic pest-protected plant products because of the potential diversity of novel traits that could be introduced by transgenic methods and because of the rapid rate of adoption of and public controversy regarding transgenic crops.

Accordingly, the committee has chosen to take EPA's proposed rule and the overarching coordinated framework as given and as designed for transgenic products[11], and to examine ways in which this current regulatory approach and its use of scientific information might be improved. In so doing, the committee does not suggest that this is the only possible approach to regulating these products. It is beyond this committee's

[11]Although the committee focuses on the regulation of transgenic pest-protected plants, conventional pest-protected plants are discussed for scientific comparisons.

scope to determine which of the three federal agencies (USDA, EPA, or FDA) is best suited to regulate pesticidal substances expressed in transgenic plants.

EPA's current proposal for regulating pesticidal substances in pest-protected plants claims broad jurisdiction over such products in all seeds and plants sold with claims of pest-protection, but it grants a generic exemption from registration to those bred by conventional means. The committee agrees with EPA's proposed exemption of pesticidal substances in conventionally bred plants, because the committee recognizes that there are practical reasons for exempting those substances based in part on historical experience of safe use of, and the benefits provided by these crops. However, the committee questions the *scientific* basis used by EPA for this exemption because there appears to be no strict dichotomy between the risks to health and the environment that might be posed by conventional and transgenic pest-protected plants.

The committee found that, in some cases, the use of conventional pest-protected crops might have the potential to lead to human and animal health impacts; therefore

There is a need to significantly increase research aimed at assessing the potential risks posed by conventional pest-protected plants, and make improvements of conventional breeding procedures, if found appropriate.

ES.6.3 Scientific Basis for the 1994 Proposed EPA Rule

Consistent with the coordinated framework and its statutory mandates, EPA has asserted jurisdiction over pesticidal substances in transgenic pest-protected plants in its 1994 proposed rule. The committee reviewed the scientific basis of EPA's 1994 proposed rule and the exemption of certain categories of *transgenic* pest-protected plants under this rule. The committee found most of the criteria used by EPA for assessing *transgenic* pest-protected products to be scientifically valid, but there were some exceptions.

EPA proposes to exempt all plant-pesticides where the structural gene for producing the plant-pesticide is derived from a sexually compatible plant. The committee found that the current EPA rule would exempt transgenic pest-protectants if the structural gene came from a sexually compatible plant, regardless of the source of the promoter for expression of the gene. This categorical exemption of transgenic pest-protectants derived from transgenes from sexually compatible plants could result in no EPA regulation of genetically engineered products which contain higher levels of toxicants. The committee agrees that, in many cases,

exemptions for certain sexually-compatible transgenic pest-protectants will be warranted; however, it questions the *categorical* exemption of these products. The committee recommends that

Given that transfer and manipulation of genes between sexually compatible plants could potentially result in adverse effects in some cases (for example, modulation of a pathway that increases the concentration of a toxicant), and given the public controversy regarding transgenic products, EPA should reconsider its *categorical* exemption of *transgenic* pest-protectants derived from sexually compatible plants.

The committee also examined EPA's proposed exemption for viral coat proteins[12] expressed in transgenic pest-protected plants. Viral coat proteins in transgenic pest-protected plants are not expected to jeopardize human health, inasmuch as consumers already ingest these substances in nontransgenic food, so the committee agrees with the exemption of these proteins from EPA jurisdiction under FFDCA. However, the committee questions the EPA's *categorical* exemption of all viral coat proteins under FIFRA due to concerns about the potential for outcrossing with weedy relatives. The committee agrees that exemption of particular viral coat proteins in certain plant species will be warranted. However, the committee suggests that

EPA should not *categorically* exempt viral coat proteins from regulation under FIFRA.

ES.6.4 Scientific Data Used by the Agencies in the Regulatory Process

The committee reviewed examples of data submitted by applicants to the regulatory agencies for currently commercialized transgenic pest-protected plant products (that is, products with Bt and viral coat proteins). The federal agencies already address most of the categories of scientific concerns presented in this report (see table 4.3). However, the committee found some areas where the risk assessment process for transgenic pest-protected plants could be improved.

In reviewing toxicity testing relevant to human health, the committee found that,

When the active ingredient of a transgenic pest-protected plant is a protein and when health effects data are required, both short-term oral

[12]Virus-derived proteins that form a capsule around viral DNA or RNA.

toxicity and potential for allergenicity should be tested. Additional categories of health effects testing (such as for carcinogenicity) should not be required unless justified.

Additional categories of toxicity testing do not appear justified for currently commercialized products such as many Bt proteins (Cry1A and Cry3A) and viral coat proteins. However, it is important that the tests that are performed be rigorous, logical, and scientifically sound. Novel or less familiar plant-pesticides (that is, in comparison to viral coat proteins and Bt toxins) may require additional categories of toxicity testing.

Although the committee realizes that it is often difficult to obtain enough plant-expressed protein for toxicological testing; tests should be conducted whenever possible using the protein as it is expressed in the plant. The committee recommends that

The EPA should provide clear, scientifically justifiable criteria for establishing biochemical and functional equivalency when registrants request permission to test non plant-expressed proteins in lieu of plant-expressed proteins.

In addition to human health toxicity testing, allergenicity testing is very important. The committee recognizes that the FDA has developed preliminary information on the assessment of potential food allergens that could be helpful to applicants as they evaluate potential products and develop product-specific data to address questions concerning 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.

The committee found some room for improvement in the procedures used in USDA's review of outcrossing or gene flow for virus-resistant squash (section 3.1.4). USDA's commercialization of the squash was controversial because the transgenic squash potentially could transfer its acquired virus-resistance genes via pollination to wild squash (*Cucurbita pepo*), which is an agricultural weed in some parts of the southern United States. USDA's assumption that transgenic resistance to viruses will not affect the weediness of wild relatives might be correct, but longer-term empirical studies are needed to determine whether this is true. The committee recommends that

USDA should require original data to support agency decision-making concerning transgenic crops when published data are insufficient.

ES.7 OPERATIONAL ASPECTS AND IMPACTS OF THE COORDINATED FRAMEWORK

ES.7.1 Elements of an Effective Regulatory Framework

The committee finds that, operating under the coordinated framework, EPA, USDA, and FDA have successfully applied existing statutes to address the introduction of transgenic pest-protected plant products, but concludes that there is room for improvement. In particular, those agencies have achieved a significant degree of coordination in their oversight of transgenic pest-protected plants, but certain aspects of this coordination could be enhanced. Only through effective coordination can the three lead agencies minimize duplication, avoid inconsistent regulatory decisions, address potential gaps in oversight, and ensure that regulations evolve with experience and scientific advancements. Ultimately, the credibility of the regulatory process and acceptance of products of biotechnology depend heavily on the public's ability to understand the process and the key scientific principles on which it is based.

The committee identified five elements of an effective regulatory system which support the objectives of the coordinated framework (Box ES.1).

For example, to improve the transparency of the regulatory process under the coordinated framework, the committee recommends that

The quantity, quality and public accessibility of information on the regulation of transgenic pest-protected plant products should be expanded.

The USDA-sponsored coordinated framework database to link agencies' regulations and decisions (USDA 1999e) is useful, but should be

Box ES.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.

expanded by all three agencies to include more public information about specific products and to link agencies' decisions about specific products. The EPA pesticide fact sheets for transgenic plant pesticides should be improved because they currently do not clearly and quantitatively present the results of safety testing.

Another element in box ES.1 is consistency of regulatory scope. The scope of agency oversight, in some cases, needs to be clarified (see section 4.3.3).

With new recombinant DNA methods, USDA can no longer rely on the production of transgenic pest-protected plants with regulatory sequences[13] from plant pests (for example, *Agrobacterium tumefaciens* vectors and cauliflower mosaic-virus promoters). Some new products may be developed using natural plant regulatory sequences. It is not clear if USDA would consider these products "plant pests." Therefore, the committee recommends that

The 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.

The delineation of lead and supporting agency jurisdiction over transgenic pest-protected plant products is generally well defined. Agency reviews generally lack duplication and achieve consistency. However, the committee identified some examples where communication and coordination could be improved.

To improve coordination among the three regulatory agencies, EPA, FDA, and USDA should develop a memorandum of understanding (MOU) for transgenic pest-protected plants that provides guidance to identify the regulatory issues that are the purview of each agency (for example, ecological risk and pesticide tolerance assessment for EPA, plant pest risk 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 flow 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 interagency consultations, they should be adequately explained to ensure that regulatory decisions are not in conflict and do not have the appearance of conflict.

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[13]Non-coding regions of genes which are involved in controlling the expression of genes.

The committee found that the three agencies have common data requirements specifically for biology of the recipient plant, molecular biology methods used to develop the product, identification and characterization of inserted genetic material and its product(s), and identity and characterization of selectable markers. Therefore, the committee recommends that

To enhance consistency of review, 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.

Taking into account the above suggestions, the committee hopes that the regulatory framework for transgenic pest-protected plants can be quickly completed by clarifying, revising, and finalizing the EPA 1994 proposed rule; publishing guidance on regulatory requirements; and developing additional interagency MOUs. However, once established, the committee recommends that

Regulations should be considered flexible and open to revision, so that agencies can adapt readily to new information and improved understanding of the science that underlies regulatory decisions. The agencies have attempted to maintain a dynamic regulatory process, but more could be done to retain flexibility in the future (see chapter 4).

ES.7.2 Economic Costs Associated With Regulation

Positive impacts of regulation might include reduced health and environmental effects and increased consumer confidence in the food supply. However, there are also economic costs associated with the regulation of transgenic pest-protected plants. The committee reviewed an analysis on the economic costs of regulation (section 4.4 and appendix A[14]). From this review and other discussions in chapter 4 (see sections 4.2 and 4.3), the committee concludes 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. In particular, the committee recommends that

[14]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.

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 systems.

The committee does not recommend waiving necessary regulatory requirements; however, 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.

ES.8 STRIVING FOR THE IDEAL REGULATORY FRAMEWORK

In the time allotted for this report, the committee focused on providing meaningful input to improve the review of scientific data under the coordinated framework and the proposed EPA plant-pesticide rule. The committee's findings, conclusions, and recommendations will need to be tested before they are confirmed as useful methods to enhance scientific review during the regulation of transgenic pest-protected plants. The committee realizes that these improvements may not be possible without increased resources for the federal agencies involved in agricultural biotechnology and for research focused on the risks and benefits. A solid regulatory system and scientific base are important for acceptance and safe adoption of agricultural biotechnology, as well as for protecting the environment and public health. In general, the current US coordinated framework has been operating effectively for over a decade. However, the committee has identified several kinds of improvements that would be helpful in the face of a larger number of commercialized transgenic pest-protected plants and novel gene products introduced into these plants. Those improvements might be necessary for increased confidence in US agricultural biotechnology both domestically and worldwide.

dpr

Department of Pesticide Regulation

Paul E. Helliker
Director

Gray Davis
Governor

Winston H. Hickox
Secretary, California Environmental Protection Agency

November 1, 2000

The Honorable Steve Peace
Chair, Joint Legislative Budget Committee
State Capitol, Room 3060
Sacramento, California 95814

Dear Senator Peace:

The Supplemental Report of the 2000 Budget Act requires the Department of Pesticide Regulation (DPR) to provide specified information on Bacillus thuriengiensis (Bt) to the Chairs of the Joint Legislative Budget Committee and the fiscal committees of both houses, by November 1, 2000.

Supplemental report language specifically requested the status of:

A. DPR's plan to investigate the scientific basis for registration of Bt-containing crops in California.

B. The development of a risk/benefit ratio for allowing this pesticide in crops.

C. DPR's assessment of the ecological safety of Bt toxoid left in soil.

D. The potential consequences, if any, of the presence of Bt in silage used for livestock.

If you have any questions, please feel free to contact me.

Sincerely,

Paul Helliker

Paul E. Helliker
Director
(916) 445-4000

Attachment

cc: See next page.

cc: (all listed received attachment)
Senator James Brulte, Vice Chair, Budget and Fiscal Review Committee
Assembly Member Denise Moreno Ducheny, Chair, Assembly Budget Committee
Assembly member George Runner, Vice Chair, Assembly Budget Committee
Senator Tom Hayden, Senate Budget Subcommittee 2
Senator Byron Sher, Senate Budget Subcommittee 2
Senator Cathie Wright, Senate Budget Subcommittee 2
Assembly Member Virginia Strom-Martin, Assembly Budget Subcommittee 3
Assembly Member Tony Cardenas, Assembly Budget Subcommittee 3
Assembly Member Dave Cox, Assembly Budget Subcommittee 3
Assembly Member Fred Keeley, Assembly Budget Subcommittee 3
Senator President Pro Tempore John Burton
Assembly Speaker Antonio Villaraigosa
Senator Patrick Johnston, Chair Senate Appropriations Committee
Senator Tim Leslie, Vice Chair, Senate Appropriations Committee
Assembly Member Carole Migden, Chair, Assembly Appropriations Committee
Assembly Member Marilyn Brewer, Vice Chair, Assembly Appropriations Committee
Ms. Elizabeth Hill, Legislative Analyst
Mr. Mark Newton, Legislative Analyst's Office
Mr. Fred Klass, Department of Finance
Ms. Adrienne Alvord

bcc: (all listed received attachment)
Senator Jim Costa, Chair, Senate Agriculture and Water Resources Committee
Assembly Member Dennis Cardoza, Chair, Assembly Agriculture Committee
Assembly Member Hannah-Beth Jackson, Chair, Environmental Safety and Toxic Materials Committee
Mr. Winston Hickox, Secretary, California Environmental Protection Agency
Mr. Brian Haddix, Undersecretary, California Environmental Protection Agency
Ms. Patty Zwarts, Cal/EPA Acting Legislative Director
Mr. Paul Gosselin, DPR Acting Chief Deputy Director
Ms. Veda Federighi, DPR Communications Director
Mr. Doug Okumura, DPR Assistant Director
Dr. Tobi Jones, DPR Assistant Director
Ms. JoAnne Payan, DPR Assistant Director
Mr. Ron Oshima, DPR Assistant Director
Dr. Gary Patterson, Chief, DPR Medical Toxicology Branch
Mr. Chuck Andrews, Chief, DPR Worker Health and Safety Branch
Mr. Barry Cortez, Chief, DPR Pesticide Registration Branch
Dr. John Sanders, Chief, DPR Environmental Monitoring and Pest Management Branch
Mr. David Duncan, Acting Chief, DPR Pesticide Enforcement Branch