

September 18, 2001

Public Information and Records Integrity Branch (PIRIB)
Information Resources and Services Division (7502C)
Office of Pesticide Programs (OPP)
Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460.

Re: Docket control number OPP-300370B

Enclosed is the American Phytopathological Society (APS) response to Docket control number OPP-300370B. The APS, representing nearly 5,000 plant pathologists, welcomes this opportunity to comment on the four questions raised in the Supplemental Proposal to the EPA final rule on "Plant-Incorporated Protectants" (formerly "Plant-Pesticides"). APS has put an extensive amount of work over the past several years into this issue.

APS, founded in 1908, is the premier organization advancing modern concepts in plant health management in agricultural, urban, and forest settings. Members represent a broad cross section of the scientific community including research scientists, teachers, extension professionals, students, sales representatives, private consultants, administrators, technicians, agricultural field representatives, and pest management personnel.

Yours sincerely,

A handwritten signature in black ink, appearing to read "Noel Keen", with a long, sweeping underline that extends to the left.

Noel Keen
APS President

To: Public Information and Records Integrity Branch (PIRIB)
Information Resources and Services Division (7502C)
Office of Pesticide Programs (OPP)
Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460

Subject: Docket control number OPP-300370B.

The American Phytopathological Society (APS), representing nearly 5000 plant pathologists, welcomes this opportunity to comment on the four questions raised in the Supplemental Proposal to the EPA final rule on “Plant-Incorporated Protectants” (formerly “Plant-Pesticides”). Plant pathologists, plant breeders, and agronomists have a long history of successes in the use and management of genetics and breeding to control plant diseases and insect pests. In the decades of use of host-plant resistance, during which time thousands of traits for host plant resistance have been transferred through genetic modification and placed into commercial use, we are not aware of a single documented example of an adverse effect on nontarget organisms in the environment or on human health due to resistance genes or their products.

Summary of responses to the four issues raised in the Supplemental Proposal

1. We support the option to exempt all plant-incorporated protectants derived from plants sexually compatible with the recipient plant, regardless of the method used to transfer these traits between sexually compatible plants. A blanket exemption for traits where the only difference is method of gene transfer between sexually compatible plants would represent a major clarification and improvement in the EPA rule over what was proposed initially in 1994. We disagree as a general principle that the process by which host-plant resistance to pests or pathogens is derived is an appropriate distinction for regulatory purposes. We suggest that the *“reporting of unreasonable adverse effects for exempted plant incorporated protectants,”* proposed by EPA for conventionally bred crops, is also sufficient if not even more sufficient as a safeguard for crops developed to express the same or similar traits using transgenic technologies.
2. We consider the USDA review of potential plant-pest related issues relative to viral coat proteins under the Federal Plant Pest Act as both appropriate and adequate for the use of coat-protein mediated resistance to plant viruses, making it unnecessary and duplicative for EPA to also examine this endpoint. If USDA review is not accepted by EPA as adequate, we support Option 1, i.e., exempt all plant-incorporated protectants based on viral coat proteins. We are not aware of any unreasonable or unique risk either to the environment or human health associated with this genetic approach to control of plant viruses that would not also apply to other genetic approaches to plant virus control, such as through conventional breeding, which the EPA already intends to exempt from regulation under FIFRA and the FFDCa other than the adverse effects reporting rule.
3. We agree that “plant-incorporated protectants” that act primarily by affecting the plant should not be subject to regulation under either FIFRA or FFDCa. We support including the hypersensitive response of plants to pathogens, also known as programmed cell death or apoptosis, in this exempted category of protectants that act primarily by affecting the plant, where the mechanisms of plant protection is functionally unmodified. Any unexpected adverse effects of such traits, however remote, are adequately covered under the requirement of the developer to report such an effect. This assumes that the requirement to report potential adverse effects applies *after* rather than before commercial use of the pest-resistant cultivar and does not include the need to report a new pest outbreak on the cultivar since such reporting is not now required for crops developed by conventional plant breeding.
4. We also find the NAS report, “Genetically Modified Pest-Protected Plants,” inconsistent in its conclusions and recommendations. On the one hand, the report concludes that there is no dichotomy between traits introduced by conventional plant breeding versus the same traits introduced by genetic engineering, and that the *“properties of a genetically modified organism should be the focus of risk assessment, not the process by which it was produced.”* On the other hand, the report only supports a blanket exemption of plant-incorporated protectants introduced by conventional breeding. We agree that conventionally bred crops should receive a blanket exemption, but would point out that there is more relevant knowledge of traits introduced by r-DNA engineering. This is because the gene and its product typically are known when introduced by r-DNA engineering, and therefore any risk of these genes or their products can be more readily recognized or

anticipated compared to traits for pest-defense introduced by conventional plant breeding where the phenotype and often the number of genes and their location on a genetic map are known but their product(s) and mechanism(s) of action typically are not known. We agree with the NAS report that exemption of traits introduced by genetic modification by conventional plant breeding is a practical matter, but would submit that the matter of practicality is because not enough information of the gene(s) and its(their) product(s) is available to make regulation possible/meaningful.

Regulation based on process—plant-incorporated protectants derived through genetic engineering from plants that are sexually compatible.

We support, for both FIFRA and FFDCFA, the option to exempt all plant-incorporated protectants derived from plants sexually compatible with the recipient plant, regardless of the method used to transfer these traits between sexually compatible plants, assuming that the plant-defense mechanism identified with the trait has not been functionally modified from the source. A blanket exemption for traits where the only difference is method of gene transfer between sexually compatible plants would represent a major improvement in the EPA rule over what was proposed initially in 1994, to which 11 scientific societies including APS declared was “scientifically indefensible” (IFT, 1996).

We would consider genetic modification of a defense mechanism leading to such outcomes as more timely expression or more consistent expression in response to the full spectrum of biotypes of the pest, so as to prevent the pest from defeating/adapting to the defense mechanism, examples of *not* functionally modified from the source. “Functional modification” should mean changes that introduce or add an entirely different pest-defense mechanism, such as the use of a plant resistance-gene to trigger expression of a Bt gene in addition to its normal function in expression of a hypersensitive response.

We would extend this broad exemption to include structural genes for plant-incorporated protectants derived from plants not sexually compatible with the recipient plant, where the gene is of a family of genes highly conserved and functionally equivalent within the plant kingdom. An example would be the conserved family of plant resistance-genes (R genes) associated with the hypersensitive response of plants to pathogens and insect pests and that fit the gene-for-gene model for host-parasite interaction. The resistance responses identified with these genes are “substantially equivalent” to what could have been and has been derived through conventional breeding. For example, Tai et al., (1999) showed that the *Bs2* gene for resistance to *Xanthomonas campestris* pv. *vesicatoria* in pepper conferred resistance to specifically controlled expression of the hypersensitive response when expressed in tomato and tobacco in addition to pepper, and it conferred resistance to *X campestris* pv. *vesicatoria* in tomato. These workers suggested that, because the corresponding *avirBs2* gene in the pathogen is widely present in strains of this pathogen in the field, and plays a role in fitness of the pathogen, “the *Bs2* gene may be durable in the field and provide resistance when introduced into other plant species.”

The only “risk” identified with R genes such as *Bs2* transferred between sexually compatible plants by conventional plant breeding has been the risk of the pest adapting to and defeating these genes. One purpose in transferring functionally equivalent (substantially equivalent) genes across plant species is to delay or prevent the pathogen from adapting to this mechanism of defense. In this case, while the mechanisms of resistance are “substantially equivalent” in terms of basic function, the “risk” of emergence of new virulent types in the pathogen population, may actually be less with genes derived from outside rather than within the crop species.

We stand by the conclusions reached by the National Academy of Science (NAS, 1987) and the National Research Council studies (1989; 2000), that regulation should be based on the product, i.e., the nature of the pest-control trait transferred to the plant, not the process used to transfer the trait to the plant.

This scientific principle should apply to protoplast fusion and induced mutations as well r-DNA engineering. For example, the 1989 NRC study on “Field Testing Genetically Modified Organisms” concluded that:

“Crops modified by molecular and cellular methods should pose risks no different from those modified by classical genetic methods for similar traits.”

The recent NRC (2000) study on “Genetically Modified Pest-Protected Plants” reaffirmed the conclusion that regulation should be based on product not process, and concluded further that there is no dichotomy between traits

introduced by conventional plant breeding versus the same traits introduced by genetic engineering. This report states (Page 6):

Because both methods [conventional and transgenic] have the potential to produce organisms of high and low risk, the committee agrees that properties of a genetically modified organism should be the focus of risk assessment, not the process by which it was produced.

The committee also agrees...that the potential hazards and risk associated with the organism produced by conventional and transgenic methods fall in the same 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, and recognizes that the magnitude of risk varies on a product by product basis.

Likewise a committee representing seven academies of science, including the Brazilian, Chinese, Indian, Mexican, Third World, Royal Society of London, and the U.S. National Academy of Scientists, in a White Paper “Transgenic Plants and World Agriculture,” published in 2000 reaffirmed that

“Decisions regarding safety should be based on the nature of the product, rather than on the method by which it was modified.”

We would submit further that the *dichotomy* for regulatory purposes is not between transgenic technologies and conventional breeding, but rather, whether or not the “plant-incorporated protectant” is known at the molecular level genetically and biochemically. If unknown, as in the case of the vast majority of pest-defense traits introduced by conventional breeding, it is technically very difficult if not impossible to evaluate the safety of the trait for regulatory purposes; if the “plant-incorporated protectant,” is known, as in the case of Bt, for example, it is then possible to also evaluate safety of the trait for regulatory purposes.

Because of lack of knowledge of the mode of action of traits transferred historically by conventional plant breeding, we have serious reservations concerning the option of “*case-by-case*” *review of eligibility for exemption through notification process.*” We believe this option would place an additional and unnecessary burden on transgenic technologies, simply because the molecular basis for the pest defense mechanism is known when using this modern method of genetic modification. This option could even discourage research into the mechanism(s) of defense conferred by traits currently transferred between plants by conventional breeding for fear that the more that is known, the greater the likelihood of a regulatory review or required notification.

Using conventional breeding of wheat as an example, what “plant-incorporated protectant(s)” account(s) for the resistance bred into wheats used in the Great Plains states to control soilborne mosaic virus? There is still no clear evidence as to whether the resistance is to the soilborne vector or the virus itself. What “plant-incorporated protectant” accounts for the resistance used through conventional breeding to control Russian wheat aphid? Hessian fly? Greenbug? Are these protectants residual in the grain at harvest so as to require review and possible approval under the FFDCA? There is no way to know without knowing the mechanisms of these defenses at the molecular level. Grinding up the plant or otherwise conducting toxicological tests on extracts from the plant or grain would be meaningless. Further, requiring plant breeders to determine the mode of action of such traits for purposes of FFDCA before release of varieties with these traits would bring this method of pest management to a grinding halt, leaving crop production potentially even more vulnerable to damage from plant pests and diseases or dependent on pesticides.

As pointed out in a report issued by 11 scientific societies (IFT, 1996) as an analysis of the EPA rule originally proposed in 1994:

Page 7: “The successes in breeding for plant resistance have been achieved despite the fact that often little or nothing is known about the biochemical, physiological, and/or morphological mechanisms that underlie the genetic resistance. Many pest resistant traits are attributed to genes that have been mapped to specific sites on specific chromosomes. Although these genes have been in use and the resistance they confer has remained effective for years, their function in terms of gene control, mode-of-action, and expression product have remained largely uncharacterized.

The 2000 White Paper “Transgenic Plants and World Agriculture,” produced by the seven academies, also acknowledges this fact when comparing plants modified by transgenic technologies with those modified by conventional breeding.

A feature of GM technology is that it involves the introduction of one or, at most, a few well-defined genes—rather than the introduction of whole genomes or parts of chromosomes as in traditional breeding. This makes toxicity testing for transgenic plants more straightforward than it is for conventionally produced plants with new traits, because it is much clearer what the new feature are in the modified plant.

We agree with the need to assure that “*plant-incorporated protectants derived through genetic engineering from plants sexually compatible with the recipient plant are as safe as those derived through conventional breeding.*” We would note, however, that the case for safety of the pest-resistance phenotypes derived by conventional plant breeding is based on the decades of safe use of these kinds of plants to people and the environment (equivalent to what the Food and Drug Administration refers to as “generally recognized as safe” [GRAS] for food). However, our knowledge of these phenotypes is typically little more than knowledge that the phenotype is controlled by Mendelian genetics. We believe that derivation of the same phenotype by rDNA methods, following characterization and cloning of the gene(s) and with knowledge of the gene products and their mode of action could then either affirm or call into question the safety of that trait whether derived by conventional plant breeding or by rDNA method but would not introduce a new risk to people or the environment because of the method used to transfer the trait.

In accepting the broad exemption rather than case-by-case review, we suggest that the “reporting of unreasonable adverse effects for exempted plant incorporated protectants” proposed for conventionally bred crops is just as appropriate if not more appropriate as a regulatory safeguard for crops developed to express the same or similar trait using transgenic technologies. This could cover such effects cited in the Supplemental Proposal as:

- Use of a promoter or other regulatory element to effect tissue-specific expression of a toxicant in the edible part of a plant;
- Phenotypes with ability to produce unusually high levels of a “plant-incorporated protectant,” and to interbreed with a wild, weedy relative, in turn making them resistant to the insect pest or pathogen controlled by that plant-incorporated protectant;
- Potential for production of a novel toxicant, where portions of the metabolic pathways necessary to produce the toxicant already exists in the parental species and the mingling of the genetic material results in a complete pathway for production of the toxicant.

We suggest the use of “reporting of unreasonable adverse effects for exempted plant incorporated protectants” to cover any unexpected effects for the following reasons.

First, outcomes such as ability of the plant to produce a toxicant in the edible part, phenotypes with ability to produce an unusually high level of a protectant and transfer that ability by outcrossing with a relative, and mingling of genetic material to complete a pathway for production of a toxicant all are also possible outcomes of conventional plant breeding, whether or not such an outcome is detectable in the phenotype. Since EPA proposes to protect the environment and human health against these remote outcomes of conventional plant breeding under provisions described as “reporting of unreasonable adverse effects for exempted plant incorporated protectants,” we would submit that the same provisions are adequate to protect the environment and human health against these even more remote outcomes of rDNA engineering.

Second, the likelihood of recognizing, predicting, or being able to test for the plant-incorporated protectant in the edible part of the plant, for unusually high levels of expression, or for the product of a completed metabolic pathway, and to then report this potential *unreasonable adverse effect*, is greatest when the gene, its product, and position of the gene product in a metabolic pathway are known. This will almost always be the case for rDNA engineering and will almost never be the case with conventional plant breeding.

Third, there are no circumstances of which we are aware that an institution, company, or plant breeder was or is likely to release a variety with pathogen or pest resistance, knowing that it would have a potential adverse effect on

the environment or human health. Being able to move genes for host-plant resistance to pests and diseases between breeding lines using the tools of rDNA-engineering rather than conventional breeding is the result of knowledge and understanding specific of that trait, and makes it both easier and more likely to predict and then reject progeny with potential for an unreasonable adverse effect caused by that trait.

Regarding the requirement of the developer, e.g., plant breeder, to report any unexpected adverse effects of pest defense traits, we are assuming that this rule refers to an adverse effect *after* rather than before commercial use of the pest-resistant cultivar since such phenotypes identified in the course of variety development are typically if not always discarded as a normal course of selecting the best all-around variety for commercial use. We also assume that the requirement to report any unexpected adverse effects of a pest-defense trait does not include the need to report the adaptation of the pest to this trait since a) such adaptation is a common outcome of pest evolution and b) such reporting is not now required for crops developed by conventional plant breeding.

Regarding the issue of whether antibiotic- or herbicide-resistance used as a selectable marker presents a risk for traits transferred by rDNA-engineering that would not occur for traits transferred by conventional breeding, we submit that any risk of these products is too remote to justify the use of process as a trigger for regulation under FIFRA for the following reasons.

- The probability that a microorganism in the gut of a person or an animal will obtain a gene or genes from the food eaten by that person or animal is extremely low—estimated at about 10^{-23} (WHO, 1993). The probability that a gene obtained by a microbe from food eaten by the person or animal is the specific gene for antibiotic resistance used as a marker in the crop and is integrated in the right orientation with a promoter for its expression is many orders of magnitude lower, except under highly artificial laboratory conditions requiring sequence homology in the recipient cells and selective conditions (DeVries, et. al. 2001; Gebhard and Small, 1998). This hardly justifies regulatory oversight.
- The herbicide-resistance genetic markers such as bialophos (*bar*) and others would raise a safety concern for gene transfer only if that herbicide was also used on that crop to control its weedy relatives. This need not and has not been the case.
- Increasingly, the technology is coming into use whereby marker genes can be eliminated from the genome of the transformed plant after transformation and before use of that plant as a commercial crop. This makes the need for regulatory attention unnecessary.

Use of viral coat protein as a plant-incorporated protectant

We consider the USDA review of potential plant-pest related issues relative to viral coat proteins under the Federal Plant Pest Act as both appropriate and adequate for the use of coat-protein mediated resistance to plant viruses, making it unnecessary and duplicative for EPA to also examine this endpoint. While the risks identified with the use of coat-protein-mediated resistance are still hypothetical, they include the risk of emergence of new virus strains or virus-vector relationships or gene transfer to weedy relatives of the crop—all representing risks of new or enhanced pests. These are risks appropriately regulated by USDA under the Federal Plant Pest Act. Emergence of new virus strains was addressed in detail in an American Institute of Biological Sciences Workshop: “Transgenic Virus-Resistant Plants and New Plant Viruses,” sponsored by the USDA Animal and Plant Health Inspection Service and the Biotechnology Industry Organization, Inc. August 1995. The full text of the report of this workshop and abstracts of presentations at is online at <http://www.aphis.usda.gov:80/bbep/bp/pubs.html#report>

Thus, to the EPA question of whether the USDA review of potential plant-pest related issues relative to viral coat proteins is adequate, we submit that the USDA has the expertise, that the current USDA review is adequate, and the agency has the appropriate regulatory authority. Thus APS suggests that there is no need for EPA to also examine this endpoint.

We would also refer EPA to a “*Decision Guide for EPA Review of Pest Resistant Plants*, provided to the Agency by the 11 scientific societies as a follow-up to the 1996 report (IFT). Of six categories of pest-resistance mechanisms, category five reads: “*Are the substances produced as products or modifications of genes derived from the pathogen targeted for control by the new trait (pathogen-derived resistance), such as coat-protein-mediated resistance used for control of plant viruses?*” If yes, the Guide reads, “*Outside the scope of plant pesticide (already regulated by USDA)*”

If EPA does not accept the USDA review of plant virus genes as adequate, we support Option 1, i.e., exempt all plant-incorporated protectants based on viral coat proteins as originally proposed by EPA in 1994. We are not aware of any unreasonable or unique risk either to the environment or human health associated with this genetic approach to control of plant viruses that would not also apply to other genetic approaches to plant viruses control, such as through conventional breeding, which the EPA already intends to exempt from regulation under FIFRA and the FFDCA other than the adverse effects reporting rule.

Further, we would reiterate our point that any risk identified during laboratory or field evaluation of coat-protein-mediated resistance intended for commercial use would, except under the most extenuating of circumstances, result in rejection of those genotypes from further consideration for commercial use, and that risks identified after commercial production can be handled under the provision that requires the developer to report adverse effects.

Very little if any research has been done to determine or estimate the probability of whether, through outcrossing, a gene for virus resistance could confer a selective advantage on wild or weedy relatives of crop plants, i.e., (1) allow a wild plant to increase its range or population density; and/or (2) permit a plant's population density to increase so that the plant dominates a community where it was far less common before acquisition of the trait. To the extent that such gene transfer merits review as a safety issue, the review should be based on valid criteria such as availability of weedy relatives of the crop plant within the range of cultivation and not the source of the gene or method of gene transfer.

Weedy relatives of crop plants are often reservoirs of viruses, which are then carried by vectors to crop plants, but whether the viruses also suppress growth, development, fecundity or otherwise contribute to biological control of the weedy relative are just beginning to be studied. The fact that many of these weeds are symptomless carriers of viruses important on crop plants could indicate that these viruses are not critical determinants of either their population or geographic range as weeds. Indeed, in cases of weedy relatives serving as reservoirs of virus inoculum, natural transfer of a resistance gene to such a weed could help eliminate this virus reservoir while having only a minor or no significant affect on range or population density of the weed. Many of these points were discussed at a 1999 USDA-sponsored workshop on *Ecological Effects of Pest Resistance Genes in Managed Ecosystems*, the proceedings of which are available at <http://www.isb.vt.edu/cfdocs/proceedings.cfm>.

“Plant-incorporated protectants” that act primarily by affecting the plant,

We agree that these host-plant resistance mechanisms such as a barrier to attachment of the pest to the host plant, a structural barrier to penetration of the pest into the host plant, the production of wax or lignin, or length of trichomes (plant hairs), and other mechanisms of plant defense that act primarily by affecting the plant, should be exempt under FIFRA and FFDCA. Further, any unexpected adverse effect following commercial use, however remote, would be adequately covered under the requirement of the developer to report such an effect.

We agree that included in this category of host-plant resistance mechanisms are the EPA's examples of “*The pesticidal substance acts in the host plant to inactivate or resist toxins or other disease-causing substances produced by the target pest and the pesticidal substance acts by creating a deficiency of a plant nutrient or chemical component essential for pest growth on/ in the host plant.*” These kinds of traits for host-plant resistance have been used for decades through conventional breeding, and we are not aware of a single example of such a trait having moved through outcrossing to a wild relative.

We also support the EPA listing of host-plant resistance mechanisms based on the **hypersensitive response** as part of the exempted category of mechanisms that function by affecting the plant. There is now a large body of evidence to indicate that this mechanism of plant defense is similar to if not evolutionarily related to the microbial defense mechanism referred to as innate resistance in humans and animals and expressed as programmed cell death, also known as “apoptosis.” In both cases, the host sacrifices a few cells as a means to contain and starve an invading microbe, while protecting the remaining tissue. A recent Colloquium sponsored by the National Academy of Sciences brought together for the first time both plant and animal scientists working, respectively, on the hypersensitive response and **programmed cell death**, to share information on “Host-pathogen Interactions: Common Features Between Plants and Animals” (Keen et al., 2000). Of particular interest were the common features used by the host to recognize an invader and trigger a response that includes a complex of biochemical and genetic mechanisms with the endpoint of containment/starvation/rejection—all clearly part of a complex mechanism of defense that acts by affecting the host.

Referring again to the *Decision Guide* offered to EPA by the 11 scientific societies, category three of the six categories of pest defense mechanisms given in this guide reads “3. *If the new pest-defense trait is attributable to biologically active substances produced by the plant, are these substances components of an active or potentially active cascade of defense responses involving pest recognition, local and systemic signaling, and arrest of the infection/pest attack, such as the resistance expressed as localized incompatible interactions (hypersensitive response), programmed cell death, and localized and systemic acquired resistance?*” If yes, the *Decision Guide* places these traits as not of a character to be regulated as “plant pesticides.”

We encourage the Agency to add the language to the regulatory text at 40 CFR part 174 to clearly show that substances involved in hypersensitive or hypersensitive-type responses are exempt, this language reading as proposed in the supplemental proposal: *By initiating, potentiating, or enhancing hypersensitive or hypersensitive-type responses that, in response to invasion by a phytopathogen, results in necrosis of specific areas of plant tissue thereby limiting the spread of the pathogen in or on the plant.*

We concur that issues of safety might arise if the plant-incorporated protectant has been functionally modified. An example, in the case of the hypersensitive response, might be the use of an R gene in the plant to trigger expression of a gene for production of an insecticidal protein in addition to its role in initiation through signal transduction of the cascade of biochemical steps associated with the hypersensitive response and subsequent downstream plant defense mechanisms. On the other hand, we would not consider the plant-incorporated protectant as “functionally modified” in cases where an R gene is transferred by r-DNA engineering from one plant species to another, since the function of its gene product, to “recognize” and interact with an effector (elicitor) molecule of an invading pathogen, has remained unchanged. We would also consider genetic modifications of plants designed to lessen the chances of the pathogen adapting to and thereby not triggering the hypersensitive response as functionally unchanged. Such genetic modification would enhance the durability but not change the basic function of this kind of host plant resistance.

We agree that plant hormones, where they are involved in host-plant resistance to pests, do so through mechanisms that act primarily by affecting the plant and not the pest or pathogen. Plant hormones act as part of a signaling response within plants that may be expressed as the hypersensitive response, systemic acquired resistance, production of a secondary metabolite, or other mechanism of defense against a pest or pathogen. The ability to produce these signal molecules, and their functions, are highly conserved within the plant kingdom. We favor a broad exemption for plant hormones where the basic function or role of the hormone in plant-defense response has not been changed by the genetic modification. An increase in the amount or timing of production of a plant hormone, expressed as plant phenotype more resistant to a pest or pathogen, presumably could be achieved either fortuitously by conventional plant breeding or deliberately by r-DNA engineering. Again, where the information is available following commercial use to indicate a potential adverse effect, however remote, this can be covered for regulatory purposes by the requirement of the developer to report the adverse effect.

Comments on the NAS report, “Genetically Modified Pest-Protected Plants: Science and Regulation”

APS at its annual meeting in New Orleans in August, 2000, held a special session to discuss the NAS report entitled “Genetically Modified Pest-Protected Plants: Science and Regulation.” A summary of that discussion, published in *Phytopathology New*, is attached herewith as part of our response to this question.

Based on our response above to the EPA question of plant-incorporated protectants derived from viral coat proteins, we obviously disagree with the NAS recommendation that EPA reconsider this exemption originally proposed in the proposed rule as published in 1994.

With respect to the option to regulate based on the method of genetic modification (process), rather than product, we find the NAS report inconsistent. Specifically, we find that its conclusion that there is no dichotomy between traits introduced by conventional plant breeding versus the same traits introduced by genetic engineering, and the statement that the “*properties of a genetically modified organism should be the focus of risk assessment, not the process by which it was produced,*” are inconsistent with its recommendation to EPA that “*though the risks of many transgenic pest-protected plants containing genes from sexually compatible species are expected to be low and would justify exemption, lack of experience with these products and public concern over genetic engineering suggest that a blanket exemption for them is inadvisable.*” From this statement, it would seem that the NRC

recommendation is in response to public perceptions of genetic engineering and not the experience and scientific evidence that consistently indicates the extremely low risk and high measure of safety of these products.

Where the report states “The NRC *“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”* (page 12).” we agree that conventionally bred crops have a remarkable record of safety to the environment and human health but would point out that there is more knowledge of the traits introduced by genetic engineering. This is because both the gene and its product typically are known in the case of traits transferred by r-DNA engineering but not in the case of conventionally plant breeding. We agree with the NAS report that genetic modification by conventional plant breeding should be exempt, as a practical matter, but would submit that the matter of practicality exists because there is not enough information of the gene(s) and its(their) product(s) to make regulation possible and scientifically defensible.

References:

DeVries, J., P. Meier, and W. Wachernagel. 2001. The natural transformation of the soil bacteria *Pseudomonas stutzeri* and *Acinetobacter* sp. by transgenic plant DNA strictly depends on homologous sequences in the recipient cells. *FEMS Microbiol. Lett.* 195:211-215.

Gebhard, F. and K. Smalla. 1998. Transformation of *Acinetobacter* sp. strain BD413 by transgenic sugar beet DNA. *Appl. Environmental Microbiol.* 64: 1550-1554.

Keen, N.T., Cook, R. J., Staskawicz, B. J., Mekalanos, J. J. and Ausubel, F. M. Eds. 2000. Colloquium on Virulence and Defense in Host-Pathogen Interactions: Common Features Between Plants and Animals. *Proc. Nat. Acad. Sci.* 97: 8752-8867.

Institute of Food Technologists. 1996. Appropriate oversight for plants with inherited traits for resistance to pest—a report from 11 professional scientific societies. Institute of Food Technologists, Chicago, IL 35 pp.

National Research Council. 2000. Genetically Modified Pest-Protected Plants Science and Regulation. Nat Acad Press, Wash. DC. 263 pp.

National Research Council. 1989. Field Testing Genetically Modified Organisms. Nat. Acad. Press, Wash. DC. 170 pp.

National Academy of Sciences. 2000. Transgenic Plants and World Agriculture. Nat. Acad. Press, Wash. DC. 40 pp.

National Academy of Sciences. 1987. Introduction of Recombant DNA-Engineered Organisms into the Environment: Key Issues. Nat. Acad. Press, Wash. DC. 24 pp.

Opinion on the potential dissemination of antibiotic resistance genes. (In French). World Health Organization. Health aspects of marker genes in genetically modified plants. Report of a WHO workshop. Geneva, 1993.

Tai, T.H.; Dahlbeck, D.; Clark, E.T, Gajiwala, P., Pasion, R., Whalen, M.S., Stall, R.E., and Staskawicz, B.J. 1999. Expression of the Bs2 pepper gene confers resistance to bacterial spot disease in tomato. *Proceedings of the National Academy of Sciences* 96: 14153-14158.

Attachment 1

Cook, R. J. 2000. APS Members Discuss the NRC Report on the science and regulation of genetically modified pest-protected plants. *Phytopathology News* 34: No. 11.

The APS National Plant Pathology Board (NPPB) sponsored a discussion session at the meeting in New Orleans on the recent National Research Council (NRC) report “Genetically Modified Pest-Protected Plants, Science and Regulation.” This report, released in April 2000, was called for by the Council of the National Academy of Sciences (NAS) in response to the negative reactions from the plant, microbial, and food science communities to the EPA proposed rule that the substances produced by plants in their defense against diseases and pests, and the genes necessary to produce these, are pesticides subject to regulation under federal statutes developed for chemical pesticides.

The NPPB on behalf of APS has tracked this rule since it was first proposed in November 1994. In fact, it was because APS had established the NPPB with a budget that APS not only provided a written response to the proposed rule during the official comment period, but was also poised to help develop a coordinated response from the broader scientific community. This response included a workshop held in Washington DC, cochaired by Cal Qualset of the American Society of Agronomy and me and hosted by the American Society of Microbiology. APS was represented at this workshop by five APS members in addition to me, including Roger Beachy, Peter Day, Dave Gilchrist, Anne Vidaver, and Sue Tolin.

The January workshop resulted in the production of the report “Appropriate Oversight for Plants with Inherited Traits for Resistance to Pests,” endorsed by 11 scientific societies and released in July, 1996. A key conclusion in this report is that “It is scientifically indefensible to regulate the inherited traits of plants for pest and disease resistance under statutes developed specifically for chemical pesticides applied externally to plants.”

Among the problems, the proposed rule singles out for regulation, traits added specifically by plant transformation. This is contrary to conclusions of a 1987 NAS white paper to consider the product and not the process used to produce the product when addressing safety. An Issues Paper published in October, 1998, by the Council for Agricultural Science and Technology (CAST), pointed this out, stating that “The proposed EPA Regulations abrogate the principle enunciated by several scientific panels; namely, genetically modified crops should be judged on their safety, allergenicity, toxicity and other properties, and not the means by which the trait has been introduced.”

The good news is that the recent NRC report reaffirms three important principles set forth in the 1987 NAS white paper, including:

- There is no evidence that unique hazards exist either in the use of rDNA techniques or in the transfer of genes between unrelated organisms.
- The risks associated with the introduction of rDNA-engineered organisms are the same in kind as those associated with the introduction into the environment of unmodified organisms and organisms modified by other genetic techniques.
- 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 will be introduced [product], not on the method [process] by which it was modified.

The bad news is that, while this NRC report concludes that there is no dichotomy between crop plants genetically modified by traditional breeding and crop plants genetically modified by plant transformation, it calls for a bolstering of regulations of plants with transgenes for pest and disease resistance, and also that EPA reconsider its proposal to exempt virus genes used as transgenes as a source of host plant resistance. It cites but does not discuss either the report produced by the 11 scientific societies or the Issues Paper produced by CAST.

The main question addressed in the discussion session at New Orleans was “How will plant pathology be impacted by this report?” After a lively and long discussion, including with input from Jim Carrington who served on the NRC panel that wrote the report, the only answer to this question was that it depends on the extent to which the EPA, USDA, and FDA follow the recommendations in the NRC report.

It has not been the intention of APS nor of the scientific societies consortium that there should be no federal oversight for disease or pest resistance traits. Rather, we on the NPPB on behalf of APS, and working mainly with the American Society of Agronomy/Crop Science Society of America, the American Society of Plant Physiologists, and the Institute of Food Technologist, have tried to bring about two basic changes in the rule. Both changes have to do with the basic question of what is a pesticide.

One of our objections, where there was unanimous agreement among the representatives of the scientific societies, has been with the term “plant-pesticide.” This is a new term, counterpart to the term “microbial pesticide,” but introduced to include the genes and gene products in plants intended for pest or disease control. The EPA rationale for this term is that genes and their products are substances and, when intended for pest or disease control as with plant breeding, they meet the FIFRA definition of a pesticide as any substance or mixture of substances intended for pest control. The EPA recognizes that this term is problematic. In March, 1999, at a meeting hosted in Washington DC by the American Crop Protection Association, representatives of the CAST, the 11 scientific societies consortium, and the Biotechnology Industry Organization (BIO) agreed on an alternative term, “plant-expressed protectants.” The EPA considered this alternative term, but apparently is now intending to use the term, “plant-incorporated protectants.”

The other major objection to the proposed rule was its inclusion of all defense traits on the basis that resistance genes and their products are substances or mixtures of substances. Our point was that resistance is a phenotype involving, in the great majority of cases, many genes and a cascade of complex biochemical interactions, and that these substances are not of a character to be treated as pesticides. The proposed rule would exempt most of these kinds of defense responses from requirement for tolerance under FIFRA or the Federal Food Drug and Cosmetic Act (FFDCA), particularly if introduced or modified by traditional breeding, but we objected fundamentally to even including these traits under FIFRA or the FFDCA, regardless of the method used for genetic modification.

We then produced a decision guide that grouped the different defense strategies used by plants into broad categories, one of which includes defenses because of substances that are of a character to be considered as pesticides. One criterion for this specific group of defense traits is that the substance responsible for the trait, when extracted from the plant, can be or is already used as a natural-product pesticide, e.g., the Bt protein.

Our categories of defense mechanisms that would be excluded from federal regulations as pesticides was similar to the defense mechanisms that EPA proposed to include under the statutes but exempt from requirement for tolerance. The difference is that whereas the EPA proposed rule considered all defense mechanisms as “guilty until proven innocent,” our proposed guidelines took just the opposite approach of treating all defense mechanisms as “innocent until proven guilty.”

Both of our alternative proposals—the change in terminology and the narrowing of the scope of the proposed rule—were presented at a hearing held in late March, 1999, before the Risk Management, Research, and Specialty Crops Subcommittee and the Department Operations, Oversight, Nutrition, and Forestry Subcommittee of the U.S. House of Representatives Committee on Agriculture. I testified on behalf of the scientific societies consortium, Arthur Kelman testified on behalf of CAST. BIO also presented testimony in support of our alternative proposals.

The recent NRC report obviously weakens the positions of the scientific societies consortium and CAST.

The EPA is now moving to finalize this rule, presumably to lock in this major policy change during the current Administration. The agency has notified both the Secretary of Agriculture and the House and Senate Agriculture Committees that it is about to promulgate a final rule regarding “plant-incorporated protectants.” Your NPPB along with our counterparts in the other societies are now considering what further responses we should make, if any, and depending on the final rule, which we have not seen. The most valuable purpose served by the discussion in New Orleans was the opportunity to help everyone become better informed on this subject so relevant to our discipline and with such important implications for how we will manage plant diseases in the future.

R. James Cook, on behalf of the National Plant Pathology Board