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Regulatory Analysis and Development
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Comments Re: Environmental Impact Statement; Introduction of Genetically Engineered Organisms

Center for Food Safety (CFS) appreciates the opportunity to comment on the preliminary development of new APHIS regulations and the accompanying programmatic environmental impact statement for genetically engineered organisms. CFS is a non-profit public interest organization that works to protect human health and the environment by curbing the proliferation of harmful food production technologies and by promoting organic and other forms of sustainable agriculture. CFS engages in legal, scientific and grassroots initiatives to guide national and international policymaking on critical food safety issues.

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APHIS is of critical importance to the regulation of genetically engineered (GE) crops and other organisms, especially because it is often the first agency to evaluate their safety. Even where APHIS shares regulation with FDA or EPA, APHIS-approved field trials often occur before assessment by these other agencies. And in many cases APHIS is the only federal agency reviewing the safety of an organism. After field trials are performed, further risk assessment by FDA, EPA, or APHIS, is typically needed to assure safe commercial use of the GE organism. For environmental risk assessment generally, and some aspects of human safety, data collected during field trials is often critically important. Because field trial data is the foundation for the rest of the regulatory process, changes in field trial regulations, such as the imposition of a low-risk GE crop category, could have serious implications for subsequent regulatory action. In addition, transgenes or transgenic organisms that escape confinement during field trials could cause significant human or environmental exposure before necessary safety evaluations have occurred.

After field trials, APHIS may be petitioned to deregulate a GE crop. APHIS relinquishes regulation of a GE crop once it is deregulated. But field trial and other data that are relied upon for deregulation decisions and commercialization may not adequately assess the safety of GE crops because of the limited size and duration of field trials. Therefore the current lack of oversight after deregulation, when commercial-scale planting may be more likely to cause environmental harm, is a serious deficiency in current APHIS regulation. Reassessment of USDA regulation of GE organisms that addresses this regulatory deficiency is welcome. But APHIS needs to emphasize making its regulations more thorough, rigorous and cautious, and to continue regulatory oversight after commercialization, rather than weakening its regulations by approving crops with known “minor” risks, or through exemptions or low-risk categories. Our comments are therefore based on the need for APHIS to generally do more thorough risk assessment, confinement, and monitoring rather than find ways to do less. CFS also notes that APHIS undertaking of an EIS for any regulatory proposal does not eliminate the need of the agency to perform PEIS for specialized programs within its purview or EIS/EAs for individual field trials.

CFS’ comments and recommendations to APHIS are organized according to the numbered sections in the Federal Register notice announcing the request for comments.¹ Recommendations are summarized below and are found in bold type in the main body of the text, where they are explained in greater detail. Certain comments, for example, concerning confinement and gene flow, pertain to several sections and are cross-referenced to indicate that is the case. CFS also endorses the comments by Peter Jenkins submitted on behalf of CFS’ sister organization, the International Center for Technology Assessment.

Recommendations

- 1. APHIS should broaden its regulatory scope to include GE plants that may pose a noxious weed risk.**
As defined, regulating GE crops as noxious weeds as well as plant pests will improve APHIS’ ability to regulate environmental impacts beyond the immediate agricultural setting by explicitly considering broader environmental impacts than are encompassed by plant pest risks.
- 2. APHIS should regulate GE biocontrol organisms, including GE arthropods and nematodes. Alternatively, USDA should confer with EPA to decide which agency would be more appropriate for regulating GE nematodes.**
Biological control organisms have caused substantial environmental harm in several cases. GE-enhanced biological control insects, nematodes, and other organisms with increased aggressiveness or altered host ranges could have serious environmental impacts. Biological control nematodes,

¹ 69 Federal Register, 3271-3272, January 23, 2004

members of an extremely abundant and ecologically important group of organisms, are currently largely unregulated.

3. APHIS should not develop a low-risk category for field trials, and not exempt any GE crops from the permit or notification process.

A low-risk category has not been justified, because there is no adequate evidence that current field trial regulations pose an undue burden on either the public or private sector, and because it is not feasible to reliably identify low-risk organisms prior to field trials. Because risk is determined by a combination of gene, organism, and environment, confidence that a GE organism is low-risk depends on data from the field. That is, field trial data is generally needed *prior* to adequately categorizing the potential risk of a GE organism. Classification of GE organisms as “low-risk” prior to field trials may therefore mischaracterize some higher-risk organisms.

4. APHIS should follow a policy of stringent confinement during field trials for organisms that pose a noxious weed risk, produce pesticidal substances, or have an unknown phenotype, and have a wild relative, can become feral, or where the non-GE crop is used for food or feed.

Gene flow to wild relatives may amplify risk compared to GE organisms restricted to the confines of the field trial by increasing exposure to the environment. And escaped genes or feral GE crops often cannot be eradicated unless discovered very early, prior to wider dispersal. The lack of monitoring of gene flow could allow such dispersal, so that genes without fitness costs that escape will likely persist in the environment. Similarly, contamination of non-GE crops by GE field trials poses a food safety risk, especially because field trials typically occur prior to food safety assessments.² Stringent confinement, which employs redundant methods of confinement at each possible gene escape route, should be used with field trials of these crops.

5. APHIS should not allow the production of pharmaceuticals or industrial products in food or feed crops, or in crops that can become feral or have wild relatives.

Complete containment cannot be assured; therefore APHIS should not allow the production of pharmaceuticals or industrial chemicals in food crops. Instead, USDA should limit development to non-food/feed organisms for producing pharmaceutical and industrial chemicals.

² Current food safety assessments conducted by FDA are voluntary and do not constitute a safety approval by the agency. CFS does not endorse the current FDA regulations, but advocates mandatory safety approval regulation under food additive provisions of FFDCA with substantially improved rigor in safety testing. However, the current process provides a minimal level of food safety assessment and therefore may detect some risks that would not be known at the time that many field trials are conducted.

6. **APHIS should set restrictions on commercialized GE crops for monitoring or risk mitigation purposes. However, GE crops should not be commercialized if there are unresolved risks, even if they are considered minor at the time.**

Current laboratory non-target toxicity tests and small scale field trials conducted for relatively short duration cannot discover some potential risks that occur only at the landscape level or develop only after several years. Similarly, the magnitude of recognized hazards often cannot be adequately delineated at this stage of risk assessment. Therefore, risks that may appear minor in the lab or in field trials may have broader impact after commercialization. APHIS needs to monitor GE crops after commercialization to address the inadequacy of current risk assessments, and to impose risk mitigation where needed.

7. **APHIS should regulate non-viable GE material under noxious weed regulations because they may cause environmental harm.**

Depending on how the GE material is processed and how it is used, it may still pose an environmental risk. For example, a non-viable GE crop used as a soil amendment may still contain intact transgenes or transgene products, which would then expose soil organisms. APHIS should require testing based on the routes of environmental exposure to assure that the material does not pose a significant risk.

8. **APHIS should not allow adventitious presence of transgenes from crops that have not completed regulatory approval for reasons given in recommendation 4. APHIS should also require that field trial applicants and applicants for deregulation provide the agency with the necessary means for monitoring adventitious presence by the most practical and sensitive methods available prior to approval. Finally, APHIS should actively monitor adventitious presence from both commercialized crops and field trials.**

The lack of measurement of adventitious gene flow and other contamination sources leaves us in the dark about the extent and importance of non-GE crop contamination. In addition to environment and human health risks, adventitious contamination can also have significant economic and trade implications and may render food “adulterated,” all of which should be considered by APHIS.

9. **APHIS should not expedite or exempt any “low-risk” GE crops of non-domestic origin from review.**

As discussed in recommendation 3, we do not believe that a low-risk category is justified.

10. **APHIS should also: 1) develop detailed guidance for the assessment of environmental risk of GE crops, 2) implement mandatory resistance management regulations and guidelines for herbicide resistant crops,**

3) sponsor research to better understand gene flow and to develop technologies to reduce it, and 4) increase transparency at all levels.

1) Detailed guidelines for risk assessment are needed to assure that the best science is used in the risk assessment process. 2) The lack of mandatory resistance management requirements leads to the loss of pest management options for farmers. 3) The technology to limit gene flow has not kept pace with the development and deployment of GE crops. The federal government needs to make research on confinement methods a priority. 4) The limited public availability of safety data and excessive use of Confidential Business Information (CBI) prevents the full involvement of public resources, such as review by the broader scientific community, and raises public suspicion.

Section 1: Should APHIS Broaden its Regulatory Scope to Include Noxious Weeds and Biological Control Organisms?

APHIS should broaden its regulatory scope to include GE plants that may pose a noxious weed risk. Doing so would clarify APHIS' ability to regulate GE plants that could harm the non-agricultural environment. Many GE plants could pose such broader risks. For example, stress tolerance genes may increase the fitness of GE plants or wild relatives not currently considered to be noxious weeds, thereby allowing spread in natural areas (NRC, 2004). Increased geographic range of stress-tolerant plants could cause harm by displacing other species or exposing non-target organisms to transgene products that could be harmful.

APHIS should regulate GE biological control organisms because they may harm the environment. Biological control species typically harm some organisms, in particular their target pests, but also may harm non-target species. The properties that make biological control organisms effective may increase the likelihood that they will also harm some non-target organisms. Some biological control organisms have very narrow host ranges or a small number of target species, and may therefore be less likely to harm non-target organisms. However, there are many cases where organisms have been introduced to control a pest, only to cause substantial harm to non-target species (Louda et al., 2003). Genetic engineering to enhance the virulence (Chet and Inbar, 1994, Maeda, 1991, St. Leger et al., 1996), aggressiveness, or survival of biological control organisms may cause harm by unintentionally increasing host or geographic range. Also, many biological control organisms can survive and reproduce in the environment. It is therefore important that biological control organisms are rigorously assessed for environmental safety. For live biological control organisms, this assessment should occur before environmental release.

EPA regulates conventional and GE biological control microbes if they are intended to control or mitigate a pest. APHIS regulates insects that may be plant pests, such as non-domestic biological control arthropods. APHIS should also regulate any other GE

biocontrol organisms not already regulated by EPA or APHIS. GE biological control arthropods should be regulated regardless of origin because genetic enhancement may alter host range or other environmental properties.

Biological control nematodes, whether conventional or GE, are typically not regulated by EPA or APHIS. Although there do not appear to be any commercialized biological control GE nematodes at the present time, it is unclear whether GE nematodes would be regulated.

Several entomopathogenic non-GE nematodes are currently used for biological control, especially species in the genera *Heterorhabditis* and *Stinernema* (Liu et al., 2000). The model nematode *C. elegans* has been genetically engineered for a number of years, and the sequence of its genome may stimulate genetic engineering of biological control nematodes. Genetic engineering of biological control nematodes is being explored (Gaugler, 1997), suggesting that GE nematodes may be introduced into the environment in the future.

Nematodes are extremely abundant and important soil organisms, fulfilling many roles including as saprophytes; insect and plant pathogens; and as fungivores and bacteriovores. Because of their importance ecologically, biological control nematodes should be regulated for safety. It is especially important to regulate GE nematodes, which could have unanticipated harmful effects such as increased host range or altered habitat.

APHIS should regulate GE and conventional nematodes or confer with EPA to decide which agency would be more appropriate. EPA regulates for human safety as well as environmental impact, unlike APHIS. Because biological control nematodes may end up in food, especially on root crops, EPA may be the more appropriate agency for regulating nematodes. It may be less important which agency takes the lead than assuring that GE nematodes are properly regulated.

Section 2: Should APHIS Adopt Specific Risk-Based Categories?

APHIS has requested comments on three risk-based categories of GE organisms for assessing field test applications. The proposed categories are a) products that are shown to have low environmental risk, b) products that pose a noxious weed risk, contain sequences of unknown phenotype or contain plant-incorporated protectants, and c) pharmaceutical or industrial chemical producing crops not intended for use as food or feed.

CFS believes that there is currently insufficient scientific data to establish a low-risk category. There is also inadequate justification to increase risk to the public by the lower level of regulatory scrutiny that a “low-risk” category implies.

We also discuss important considerations for assuring the safety of the other two categories of field trials, “b” and “c” above, under consideration by APHIS. Our primary concerns with category “b” and “c” field trials involve gene flow or crop contamination. Field trials undergo less risk assessment than later stages of GE crop development, in part because their limited size and duration involves less direct exposure of people and the environment to the GE organism than do most commercialized crops. Gene flow can subvert this assumption of limited exposure by allowing the GE organism or gene to escape the confines of the field trial.

Pharmaceutical and industrial substances are not intended to be consumed in food, and may therefore be more likely to cause harm if they enter the food supply than substances intended for dietary consumption. Furthermore, pharmaceutical compounds are intended to be biologically highly active in humans or animals, and may cause harm when consumed in food or by organisms in the environment.

Section 2a: Lack of Justification for a Low-Risk Based Category of Field Trials

The most compelling reason to adopt a low-risk category would be to reduce regulatory burden that inhibited important GE research, provided that any regulatory change protected the environment. For example, it would be undesirable for academic researchers studying the risks and benefits of GE organisms to be discouraged from pursuing their work due to stifling regulatory burden. In addition, a low-risk approach could reward developers of less risky GE crops with less regulatory expense, thereby encouraging the development of such crops rather than more risky counterparts. The importance of built-in safety design has been recognized (Kapuscinski et al., 2003, National Research Council, 2004), and encouraging such design would be desirable. However, we are unaware of any adequate evidence that current regulatory burden at the field trial level is inhibiting research or development of GE crops. To the contrary, USDA field trial data suggest the lack of significant regulatory burden.

Justification for a low-risk category is sometimes based on unsupported arguments that the burden of current regulations impedes the development of beneficial GE organisms and GE risk assessment in the field (Strauss, 2003, USDA, 2001). Contrary to such assertions, analyses of USDA field trial application data (Gurian-Sherman, unpublished; field trial data from USDA Field Test Release database, <<http://www.nbiap.vt.edu/cfdocs/fieldtests1.cfm>>) indicate that field trial applications increased rapidly through the 1990s, contrary to expectations if regulations make it “increasingly difficult” to conduct field trials (Strauss, 2003). Applications of field trials that may be more impacted by regulatory burden, such as minor crops or from public institutions, increased as rapidly as private sector major-crop applications (see Appendix A).

More importantly, the number of applications for GE crops affected by regulatory changes should respond more than for crops not subject to those changes. For example, field trials for six major crops could be applied for by notification beginning in 1993,

marking a reduction in regulatory requirements compared to the previous permit process. Such a reduction in regulatory requirements might be expected to result in an increase in the rate of major crop field trial applications compared to minor crop field trials, which continued under the permit process, after the March 1993 implementation (Appendix A, Figures 2 and 4). To the contrary, applications for the six major crops included in the 1993 notification increased about 4-fold from 1992 through 1996 (Appendix A, Figure 4), while minor crop applications, not included in the notification regulation, increased about 5-fold during the same period, contrary to expectations.³

Minor crops and all other crops not included in 1993 were added to the notification regulation in May 1997. Therefore minor crop application rates may be expected to increase after 1997 compared to previous years if regulatory burden affects field trial applications. Instead, minor crops increased only 48% from 1997-1999, the two years after notifications were implemented, but 81% for 1995-1997, the two years before notifications (Appendix A, Figure 2). Minor crop applications declined by about 39% over the four years of 1997-2001, while increasing 143% over the four years of 1993-1997, prior to the 1997 notification regulation. Furthermore, the decrease of all categories of field trial applications in the late 1990s did not correspond to any increase in domestic regulatory burden.

Although the correlative data presented in Appendix A does not prove that there is no undue regulatory burden on academic researchers and minor crops, we are aware of no evidence to the contrary. It is not known why there are fewer academic and minor crop field trial applications than major crop applications, but it does not appear to be due to regulatory burden. In any case, the reasons for different application numbers should be well understood before any consideration of regulatory relief, which should not be based on mere speculation about regulatory burden. And although we agree that it is important that safety considerations enter into the design of GE crops, the apparent lack of substantial regulatory burden at the field trial level suggests that a low-risk category would provide little incentive to consider such safety-driven design.

Another justification for a low-risk category may be to reduce cost of government. But such streamlining is only justified if the primary mission of APHIS, protection of the environment, can still be adequately accomplished. As discussed below, we do not believe that adequate protection of the environment or human health can be assured if a low-risk category that reduces risk assessment requirements is implemented.

Furthermore, for a low-risk category to adequately protect human and environmental safety, detailed guidelines explaining inclusion criteria and testing methods would be needed. Otherwise, the resulting *ad hoc* decisions may not be based on rigorous scientific criteria, as has occurred in past APHIS decisions (National Research Council, 2002), and would not adequately protect the public. Because such guidelines are not currently available, a low-risk category of GE organisms should not be implemented.

³ It is relevant to examine the application rates prior to 1993, but we have data for only one year prior to 1993 for the six major crops. Applications increased 47% between 1991 and 1992 for the six major crops and 33% for minor crops.

Section 2a: Arguments Opposing a Low-Risk Field Trial Category Based on the Inability to Reliably Identify Low-Risk GE Crops Prior to Field Trials

Implementing a low-risk safety category depends upon our ability to accurately identify low-risk GE organisms or transgenes, but determining which GE organisms are “low-risk” is often difficult. It has been suggested that the use of “domesticating genes” (Strauss, 2003) in GE organisms would be of low risk because such genes, even if they escaped to wild relatives, would impose a fitness cost and thereby disappear from wild populations. However, some genes that might be considered to be “domesticating” could confer advantages in some environments. Some genes in a particular organism and in the right environment would certainly reduce fitness and thereby disappear from wild populations. However, earlier attempts to associate particular traits with invasiveness of weeds, for example, were not always successful (Williamson, 1994).

There is evidence that traits that are often associated with domestication of crops may actually make weeds more aggressive under certain circumstances. For example, johnsongrass (*Sorghum halapense*), considered one of the world’s worst weeds, is believed to be a hybrid of sorghum and a wild species, *S. propinquum*, and arose after the wild species and crop hybridized (Paterson et al., 1995). Evidence also suggests that a biotype of johnsongrass that has extended the range of the weed northward into Canada resulted from acquisition of several crop traits from sorghum. The northern johnsongrass biotype acquired several traits usually associated with domestication, and lost traits previously associated with invasiveness in the southern part of its range (Warwick et al. 1984). For example, the northern biotype shows little seed dormancy, a trait associated with domestication. On the other hand, rhizomes have been lost or reduced in the northern biotype although this trait is associated with invasiveness in johnsongrass’ southern range (Paterson et al., 1995).

The forgoing discussion about johnsongrass illustrates the importance of considering the combination of crop, gene, and environment in making a determination about the potential risk level of a GE organism. Genes that may have reduced the fitness of johnsongrass in the main part of its range may have increased its fitness and extended its range in the north. Such an evaluation argues against a low-risk determination prior to conducting field trials, because the necessary experimental data are not available to accurately determine that the crop would fit the category. Field trials are usually necessary to determine potential fitness effects of transgenes.

Another concern that argues against a low-risk category is that gene flow can amplify risk beyond what is otherwise encountered at the field trial level because gene flow increases exposure. Escaped genes can also be difficult or impossible to eliminate if initial judgments about risk levels are incorrect. For example, even several years after efforts to remove Starlink from the corn crop, small amounts continue to be detected. Gene flow to wild relatives, or escaped non-domesticated GE crops, would be even more difficult to eradicate if they conferred a fitness advantage or were “fitness-neutral” unless

discovered soon after their occurrence – an unlikely prospect with the current lack of monitoring.

A recent report by the National Research Council of the National Academies of Science (NRC, 2004) determined that there are currently few biological confinement mechanisms, and those that are available are imperfect, making eventual gene flow almost inevitable. Physical confinement methods are also imperfect, and are susceptible to human failure. Although the relatively small size and duration of field trials reduces the likelihood, as well as the magnitude, of gene flow, harm may still occur.

Genes that introgress into a wild relative are expected to increase in frequency if they provide a fitness advantage. Therefore, initially low amounts of gene flow could be amplified in such circumstances. The NAS report noted that, in general, if an allele confers a fitness advantage, it would generally increase in frequency *even if introduced only once* (National Research Council, 2004). Therefore even low levels of gene flow could eventually cause considerable harm if the gene product increased weediness or harmed non-target organisms.

Gene flow to crop seed sources appears to be common according to a new report from the Union of Concerned Scientists (UCS) (Mellon and Rissler, 2004). And although it has occurred at low levels, such contamination nevertheless presents risks. Several of these risks involve human health or international trade caused by initial pest or environmental risks. Because APHIS is the first or only agency that can control gene flow by regulating field trials, ignoring the potential of those non-environmental risks by developing a low-risk category could jeopardize public safety.

Although the UCS report was restricted to commercialized crops rather than field trials, due to the unavailability of testing reagents (e.g. gene sequences needed to make PCR primers), gene flow from field trials to surrounding crops cannot be dismissed. There is little or no monitoring to determine how much gene flow occurs from field trials. There is reason to believe that some gene flow is likely to occur given the hundreds of field trials that are performed every year. This is especially troublesome because field trials typically occur prior to food safety assessments. And gene products not intended for human consumption are not evaluated for food safety under the current regulations, so the food safety risks of such crops are not well known. Most GE crops that undergo field trials are never evaluated for food safety even if they contain pesticidal genes or are in food or feed crops. There have been close to 10,000 field trial applications under APHIS permits or notification since 1987, but less than 100 GE crops have completed food safety assessments at FDA or EPA. In addition, unintended exposure to transgene products through dietary consumption could be considerable for foods eaten whole and unprocessed, such as most fruits and vegetables.

The question of gene flow or contamination of food crops raises the issue of how USDA would assure food safety. Currently other agencies, FDA and EPA, are responsible for determining that GE foods or animal feed are safe to consume. USDA does not assess food safety of GE crops, and does not have the statutory authority to do

so, and therefore must depend on the other agencies to determine the dietary safety of GE crops. A GE crop should not be classified as low-risk without a food safety assessment if it might get into the food supply through gene flow.

The environmental impacts from the unintended effects of otherwise low-risk genes are not well understood and need to be accounted for before a GE crop could be considered to be low-risk. Unintended effects are common in GE crops (see Gurian-Sherman, 2003, Kuiper et al., 2001), but have typically been evaluated in the context of human dietary safety rather than environmental impact.

Several instances of unintended effects that may have environmental implications have been noted in GE plants. In one case, *Arabidopsis* genetically engineered for herbicide tolerance had a significantly higher outcrossing ability than the wild-type plant (Bergelson et al., 1996). Altered fecundity may have fitness implications that could not easily be predicted without experimentation. Bt corn containing the Cry1Ab gene was recently shown to have higher lignin content than non-Bt corn (Saxena and Stotzky, 2001). Although other experiments failed to find any harm to soil inhabiting organisms from Bt corn, the issue of potential increased fitness was not addressed. Increased fitness of a crop like corn that would not survive in the wild and that has no wild relatives in the U.S. is not an important concern. But for crops with wild relatives, increased lignin might increase fitness by increasing resistance to insects or pathogens or reducing lodging.

In both the *Arabidopsis* and Bt corn cases, the unintended effects might have fitness implications even if the transgene product does not. Other unintended effects may be harmful to non-target organisms. Until the issue of unintended effects on the environment is adequately considered, a low-risk product category would be difficult to define.

Horizontal gene transfer (HGT) to microorganisms also needs to be considered before a low-risk designation could be given to a GE crop. Data to date show that HGT from plants to microorganisms occurs at extremely low levels unless DNA homologous to the microbe (bacteria) is present in the transgene or vector. While not related to field trials, the recently documented case of transfer of the CP4-EPSPS gene from glyphosate resistant soy to human intestinal bacteria demonstrates the possibility of HGT in practice (Netherwood et al., 2004). Several additional considerations for potential risk from HGT that should be considered are whether the transgene is already present in the biota of the crop environment, and if not, whether the gene might provide a fitness advantage to microbes that acquire the transgene through HGT.

Defining terminology for low-risk GE organisms is also a problem. Part “2b” of the USDA proposal includes “Product types...of unknown plant pest risk...or unknown phenotypic function...” This definition implies that product types placed under the low-risk category have a known phenotype. Thoroughly defining phenotype prior to field trials, that is, before experimentation in the environment, may be difficult.

It is unclear how well the phenotype of the gene must be understood for inclusion in the low-risk category. In practice, a phenotype associated with the transgene is almost always known, because that phenotype forms the basis for developing the GE organism. However, a particular gene product often has several functions, or phenotypes, which may go unrecognized by single-minded product developers, and be unknown prior to field trials. For example, cytoplasmic male sterility in corn (called Texas Male Sterile, or TMS) provided a male-sterile phenotype that facilitated the production of hybrid corn. Unfortunately, another phenotype associated with TMS greatly increased susceptibility of corn to the toxin produced by a previously minor plant pathogen, causing one of the largest losses of corn in U.S. history (Levings, 1993). There is a real danger that simple-minded definitions of phenotype could be used to inappropriately list a GE organism as low-risk.

For all of these reasons, CFS recommends that 1) USDA not institute a low-risk category for field trials, and 2) no GE organisms should be exempted from permitting requirements.

If USDA decides to go forward with a low-risk category, it should first develop rigorous and cautious guidelines for determining criteria for inclusion. Such guidelines should be developed with input from non-agency academic and public interest scientists, other agencies that regulate GE organisms, as well as USDA. A low-risk category should not include GE organisms that 1) have a wild relative in the U.S., are non-domesticated, or can become feral, 2) are food or feed crops, or 3) present a potential risk through HGT to microbes.

Section 2b: Risk Factors Concerning Non-Low-Risk GE Organisms: Plant-Incorporated Protectants (PIPs)

Because GE field trials may be generally of limited acreage⁴ and duration, direct risks to humans or non-target organisms may be limited. Gene flow may be relatively more important because it can increase exposure beyond the field trial site. An exception is direct harm to endangered species, which also have restricted populations and geographic range. Therefore, crops containing PIPs might be harmful and should be isolated from endangered species. For large field trials of longer duration, such as with genes with unknown phenotype or noxious weed potential, APHIS should consider a formal risk assessment prior to permitting, including relevant non-target testing.

Genes transferred to a wild relative will generally persist and increase if the gene confers a fitness advantage, thereby potentially increasing risk. Genes that are fitness-neutral will typically be maintained at gene flow levels. But as with other traits, it may be difficult to determine what level of fitness a PIP will confer prior to field trials.

⁴ For pest-incorporated protectants, EPA assumes jurisdiction for field trials over 10 acres. Some field trials are much larger, at least hundreds of acres.

For example, lepidopteran-active Bt endotoxin increases fecundity in wild sunflower, and may confer a fitness advantage (Snow et al., 2002). By contrast, resistance to white mold (*Sclerotinia*) apparently does not confer a fitness advantage in several environments despite susceptibility of wild sunflower to the pathogen (Burke and Rieseberg, 2003).

Recent research has demonstrated the importance of herbivores and pathogens in limiting the invasiveness of some species (Rees M. and Paynter, 1997, Mitchell and Power, 2003, Klironomos, 2002). Therefore, testing aimed at understanding the importance of pathogens and herbivores in limiting the weediness of wild relatives of the GE crop may be helpful in determining whether gene flow to a wild relative may increase invasiveness. Pathogens and herbivores that are important for limiting weediness of the wild relative may be tested for susceptibility to the transgene product. Unfortunately, knowledge about pathogens and herbivores important to the restriction of wild relatives is currently limited and needs to be better understood.

Because the fitness of a PIP in a wild relative will usually not be known at the time field trials are performed, it is critical that gene flow not occur. Once a gene that confers a fitness advantage escapes to a wild relative, it is unlikely that those wild relatives will be eradicated.

As discussed above, the recent report on biological confinement by the NRC (National Research Council, 2004) notes that current biological containment methods are not well developed. And physical confinement methods are subject to error or inadequate design. For example, the isolation distances used by crop-seed growers and for guidance with GE crops typically allow low levels of cross-pollination. But for PIPs that have not been assessed for food safety by EPA, even low levels of such contamination would constitute adulteration, and could present a food safety risk.

To assure that contamination and outcrossing do not occur, APHIS should develop criteria for stringent confinement of PIPs in crops that have wild relatives, for non-domesticated crops or other GE organisms, or where non-GE varieties of the crop are grown for food or feed. By stringent confinement, we mean following the recommendations of the NAS report on Biological Confinement (National Research Council, 2004).

Confinement methods should have several levels of redundancy for each possible route of gene escape. For example, if gene escape can occur through seed, stolons, and pollen, then several confinement methods should be in place for each of these routes. **These methods should differ in their vulnerabilities, i.e., in the ways that they can fail, so that conditions causing failure in one method would not cause failure in another.** HGT should be separately considered based on criteria discussed above.

It is also critical to carefully develop and test confinement methods for the particular crop, gene, and environment, so that failure rates are known. For example different male sterility genes typically have different failure rates that can be affected by environmental conditions, and that should be known prior to field trials.

Changes in the reproductive behavior of PIPs and other GE organisms in this proposed category need to be determined prior to field trials. For example, unexpected increases in outcrossing rates, as seen in GE Arabidopsis (Bergelson et al., 1998), could change gene flow rates. Similarly, increases in seed dormancy could compromise control of volunteers if not taken into account.

Finally, in cases where there is reasonable potential for significant harm from gene flow, APHIS should deny the permit or notification.

Section 2c: Risk Factors Concerning Non-Low-Risk GE Organisms: Crops Producing Pharmaceutical or Industrial Substances not intended for Food or Feed

Recent reports from the NAS and UCS, along with several contamination incidents with pharmaceutical field trials and commercialized crops (National Research Council, 2004, Mellon and Rissler, 2004, Gillis, 2002) indicate that contamination of food and feed crops with pharmaceutical and industrial genes is likely, even under APHIS's recently revised guidelines. The NAS report on biological confinement concludes: "Alternative nonfood host organisms should be sought for genes that code for transgenic products that need to be kept out of the food supply." **Pharmaceutical and industrial substances should not be produced in GE food or feed crops in the environment.** Growth in contained structures needs to follow methods that do not allow gene flow to occur. For example, typical greenhouse vent systems would allow pollen to escape.

It has been argued that corn is often the crop of choice to produce pharmaceuticals because its genetics is so well known, relatively high concentrations of the product can be stored in the seed, and it is easy to manipulate using molecular tools. However, other non-food species have similar properties. For example, molecular methods for tobacco are advanced, and high levels of product can be made using chloroplast transformation (Staub et al., 2000). Other enclosed systems also show promise (Mayfield, 2003). We should not settle on a technology that is risky merely for convenience, but rather develop methods that are safe, efficient, and effective.

Because pharmaceutical compounds are intended to be highly biologically active in higher animals, especially mammals and birds, these animals may be particularly susceptible to harm from exposure in the field. Similarly, industrial compounds are not intended for consumption and therefore may have a higher possibility of harming non-target organisms. **Such substances should therefore never be produced in crops with wild relatives or that can become feral, where non-target organisms may be exposed.**

Section 3: Regulatory Flexibility and Continuing Regulatory Oversight

APHIS is considering whether some GE crops could be commercialized before all risks are resolved, while retaining regulatory oversight. Currently, APHIS has little authority over GE organisms once they are deregulated. It would be desirable for APHIS to be able to retain regulatory oversight after commercialization. For example, **APHIS should be able to set restrictions on commercialized GE crops for monitoring or risk mitigation purposes.**

However, **GE crops should not be commercialized if there are unresolved risks, even if they are considered minor at the time.** Because of the limitations of risk assessment at the field trial stage, risks that may appear to be minor could prove to be more substantial after the increased scale of commercialization. All regulatory issues that can be answered prior to commercialization should be resolved. The desire to market a product should not be used to allow known risk issues to remain unresolved before commercialization.

Many observers have noted that field trials are inadequate for resolving all environmental issues (Karieva et al. 1996 National Research Council, 2002, Snow et al. 2004). Many environmental effects occur at large field or landscape scales and do not become apparent for several years (Karieva et al., 1996). This presents a dilemma for the APHIS system that relies on data from relatively small-scale field trials to come to decisions about deregulation.

APHIS should therefore develop a regulatory framework where such scale questions can be adequately addressed rather than looking for means to allow commercialization when there are unresolved risk issues. Another way of looking at this issue is to address questions of scale after commercialization, since they could not be answered before, providing there are no other risks. **APHIS must in that case retain the ability to remove the crop from commercialization if risks are discovered after commercialization.**

For post-commercial monitoring to be effective, baseline data are needed for comparison with the transgenic crop. Such data should be developed by APHIS. In addition, **we endorse an adaptive management approach as discussed by the NAS and a recent position paper of the Ecological Society of America (National Research Council, 2002, Snow et al., 2004). Such an approach uses cycles of goal setting and implementation, where each cycle informs the next until adequate data are acquired. APHIS needs to work with the academic and stakeholder communities to determine when and how such an adaptive management system should be implemented. An *ad hoc* approach to this complex issue will not result in efficient or effective experimental design.**

Finally, an adaptive management system requires experimental controls to allow comparisons for determining impacts. **The predominant agricultural practices often serve as controls, but “no treatment” and viable alternative practices such as organic, biointensive IMP, or other agroecological approaches, should also be included as controls to obtain an accurate and complete picture of relative**

environmental impact. As with all technologies, agriculture should strive to improve not only productivity, but also to minimize impact on the environment and enhance society. Successful agricultural methods that advance those goals should be included in experimental designs for comparative purposes.

Section 4: Permit Conditions for Plants that Produce Pharmaceutical or Industrial Compounds

As discussed under section 2c above, non-food and non-feed compounds should not be produced in food or feed crops. Such compounds may generally be more likely to be harmful to non-target organisms, because they are not intended to be consumed, or only to be consumed for medical purposes. For example, the industrial product avidin produced in corn has insecticidal properties (National Research Council, 2002). Also, some industrial enzymes are allergenic, and many pharmaceutical compounds have harmful side effects.

If APHIS does not prevent the use of food/feed crops for such substances, the current system should be improved by adopting several measures. First, such crops should only be used in confined structures or with strict geographical isolation from fields of the crop used for food or feed production and from wild relatives. Such isolation should greatly exceed standards based on conventional seed purity, which allow some contamination.

Section 5: Regulation of Non-Viable GE Material

Non-viable GE material may have environmental effects, and should therefore be regulated under noxious weed regulations. Depending on how the material is processed, protein or other transgene products are likely to remain present after the material is harvested. For example, drying of plant material may leave much of the transgenic protein and transgenic DNA intact. If incorporated as a soil amendment, proteins may bind to clay but remain active for a considerable period of time (Tapp and Stotzky, 1998).

Risk assessment of non-viable material should therefore be based on possible routes of exposure. For example, soil-incorporated material should be subjected to a risk assessment of non-target soil organisms and soil functions such as nutrient and carbon cycling (Kowalchuk et al., 2003).

It is also critical to assess whether all propagules that may be included in “non-viable” material are really not viable. It is not uncommon for commercial-scale processes to be less than 100% effective. Such escapes could have risk consequences

as volunteers or allow gene flow to wild relatives. Therefore APHIS should carefully assess the efficacy of the processing of non-viable material.

Section 7: Provisions for Adventitious Presence of GE Material

For reasons discussed under “section 2” above, adventitious presence should not be considered acceptable. In addition to potential risk issues, adventitious presence can be very difficult to eliminate if it occurs in saved seed or crop-seed sources, as has been the case with StarLink. Below some undetermined concentration, adventitious presence will not be reliably detected without great effort and cost. The limitations of detection will also prevent complete elimination of contamination if the need arose, for example, if subsequent studies found the substance to be harmful at the exposure levels caused by the contamination.

In addition, trade in the contaminated crop may be reduced due to detectable adventitious presence, placing an unfair burden on farmers and their customers. That may be especially true for organic growers.

The extent of adventitious presence needs to be better understood in order to determine how best to address it. The current lack of testing for adventitious presence leaves everyone in the dark concerning the extent of the problem. Compounding this problem is the lack of the necessary tools to monitor adventitious presence caused by field trials or deregulated GE crops. **APHIS should therefore require that field trial applicants and applicants for deregulation provide the necessary means for monitoring adventitious presence by the most practical and sensitive methods available prior to approval. APHIS should actively monitor for adventitious presence from both commercialized crops and field trials and should determine the extent of adventitious presence from field trials as well as deregulated crops.** In many cases, sequence data for PCR primers, immunoassay reagents or test kits would be the best methods for detecting adventitious presence or gene flow to wild relatives. Providing PCR primer sequences would almost always be feasible because GE crop developers almost always determine the sequence of the transgene prior to developing the transgenic plant.

Section 8: Should APHIS Expedite or Exempt Review of Certain Low-Risk GE Commodities Reviewed in their Country of Origin and not intended for Propagation?

For reasons elaborated under Section 2a, low-risk GE crops cannot be reliably determined. This is true for GE crops developed outside as well as inside the U.S. Therefore the basic premise for the acceptance of low-risk GE crops from other countries is unsupportable. **APHIS should not expedite or exempt any GE crops of non-domestic origin from review.**

A basic assumption of this question is that crops not intended for propagation would in fact not be planted. Recent experience in Mexico with the likely illegal planting of GE corn suggests that such proscriptions may not be reliably followed. Illegally propagated crops that escape confinement may become a permanent part of the landscape. Regulatory provisions that have a good chance of failure should not be adopted.

Other Issues that APHIS should Consider

APHIS should take several steps to improve its risk-assessment process to better protect the environment and the public health. APHIS should take steps to: **1) develop detailed guidance for the assessment of environmental risk of GE crops, 2) implement mandatory resistance management regulations and guidelines for herbicide resistant crops, 3) sponsor research to better understand gene flow and to develop technologies to reduce it, and 4) increase transparency at all levels of operation.** These recommendations are discussed briefly below.

1: Development of Detailed Guidance

The absence of detailed environmental safety testing guidance does not send a clear message concerning the standards for environmental safety. The resulting *ad hoc* approach to determining risk cannot substitute for careful development of testing standards for risk assessment. Questions about how to determine environmental harm, appropriate non-target organisms used in risk assessments, and appropriate experimental protocols, among other considerations, need to be determined. The development of safety testing guidance through a public process involving unbiased experts also assures the public that the highest standards for safety are used. Public confidence in the APHIS assessment process will otherwise suffer.

2: Mandatory Resistance Management

In the absence of mandatory resistance management, resistant weeds are developing in response to the increasing use of glyphosate. Glyphosate resistant horseweed (*Conyza canadensis*) is directly attributed to the use of GE glyphosate resistant soybeans (VanGessel, 2001). That contrasts with Bt crops where non-Bt refuges are required to delay resistance development. Increasing frequencies of Bt resistance or resistance alleles have so far not been reported in connection with Bt crops, such as pink bollworm (*Pectinophora gossypiella* Saunders) on cotton, which is closely monitored (Shelton, et al., 2002, Carriere, et al., 2003). In contrast, without resistance-management plans, pesticide resistance is common.

3: Development of New Methods to Restrict and Prevent Gene Flow

Gene flow mechanisms and frequencies also need to be better understood, and tools to limit or prevent it need to be developed. The recent NAS report on biological confinement noted that there are few available biological confinement techniques. USDA needs to fund research to improve existing methods and develop new methods for biological and physical confinement.

4: Transparency

Finally, much of the risk assessment and safety data for GE organisms reviewed by APHIS are not available to the public. Lack of transparency engenders suspicion and should be avoided. Transparency is addressed at greater length in comments by the International Center for Technology Assessment, but from the perspective of risk assessment, the lack of transparency prevents experts in the public to augment the efforts of APHIS scientists. Even the NAS found that restricted access to GE risk assessment data impeded their evaluation of the APHIS risk assessment process (National Research Council, 2002). Environmental issues of GE crops are complex and involve several scientific disciplines including ecology, population genetics, plant breeding, molecular biology, and several fields of agricultural sciences. Furthermore, relevant data and theory from these disciplines are often not available or are only in rudimentary form. Therefore, notwithstanding the expertise of APHIS scientists, the input of independent experts would allow an additional level of safety for this new and evolving area of risk assessment.

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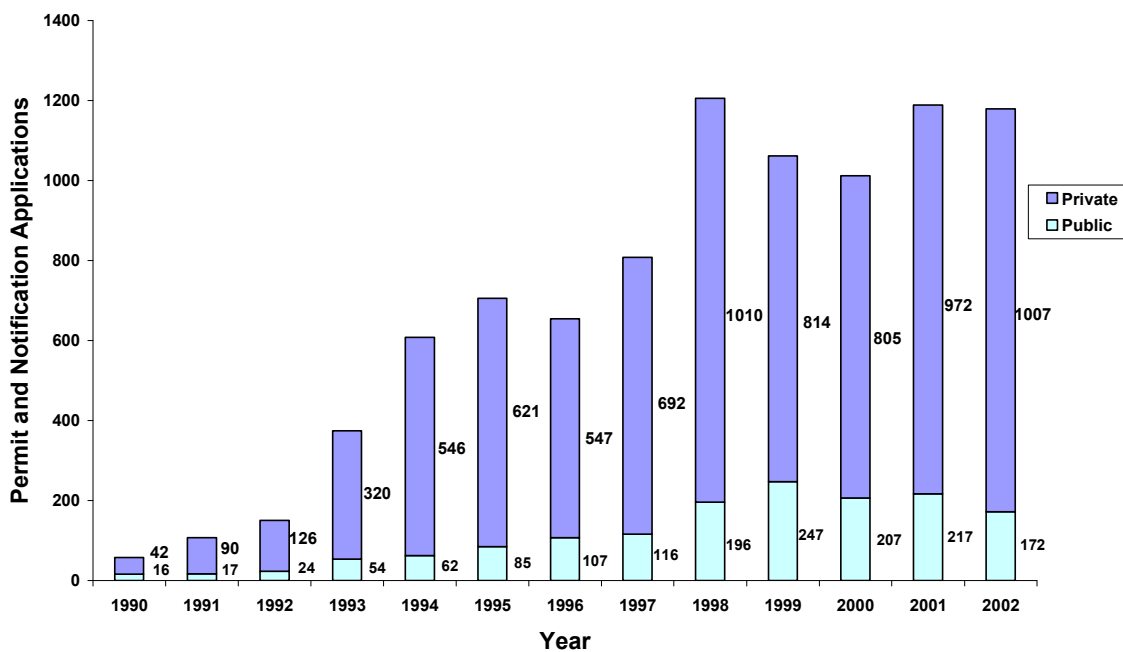
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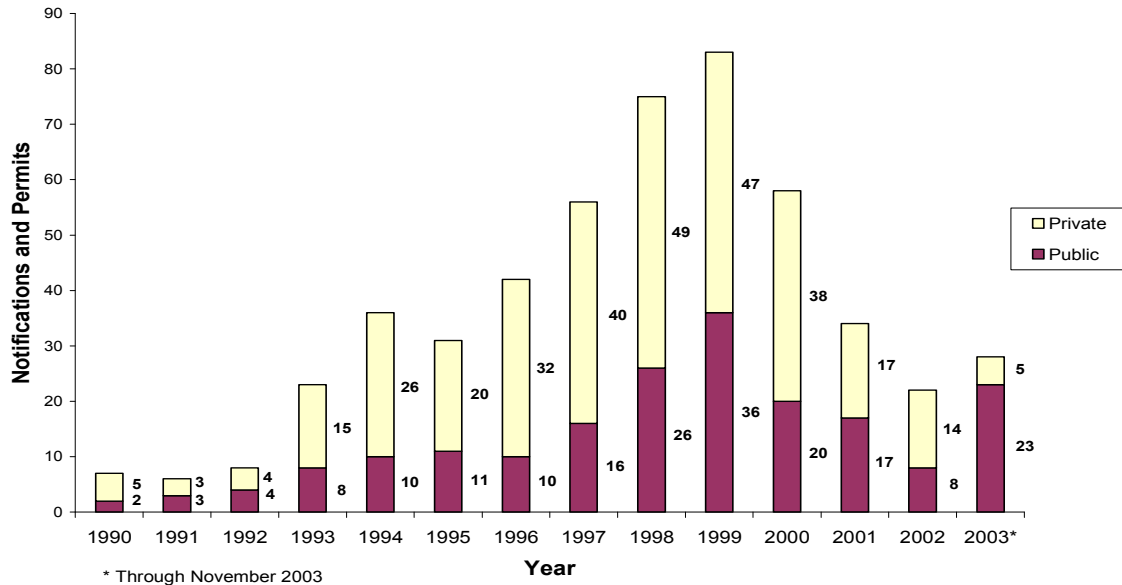
Appendix A

Figure 1 - USDA Field Trial Notification and Permit Applications for Public and Private Institutions



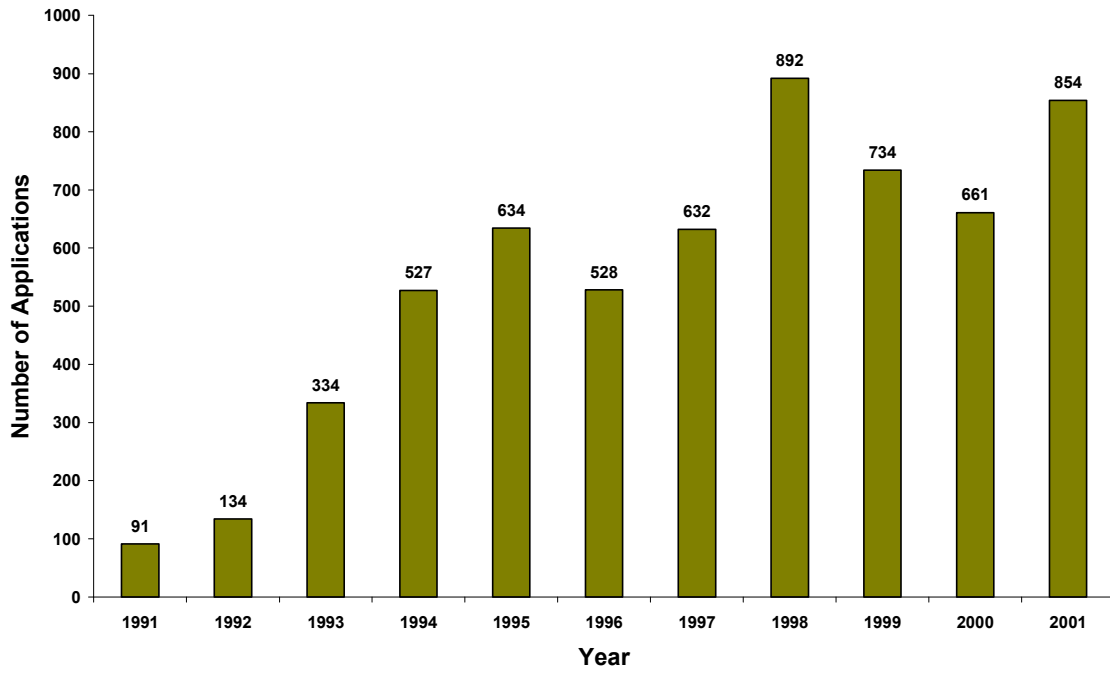
Based on USDA field trial data available at:
<<http://www.nbiap.vt.edu/cfdocs/fieldtests1.cfm>>. Field trial applications increased rapidly during the 1990s for both private and public institutions, where the latter were primarily universities.

Figure 2 - Minor Crop Notification and Permit Applications



Based on data from < <http://www.nbiap.vt.edu/cfdocs/fieldtests1.cfm> > . Major crops were annual crops of over 10^6 acres or a value of at least $\$10^9$, based on USDA data, while minor crops are annual crops of less than those values, or any perennial crops.

Figure 4 - USDA Field Trial Applications for Six Major Crops



Based on data from < <http://www.nbiap.vt.edu/cfdocs/fieldtests1.cfm> >. The six major crops subject to the 1993 notification regulation are: corn, soybeans, tomatoes, potatoes, cotton, and tobacco.