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Environmental Protection Agency
Office of Pesticide Programs
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

RE: Comments on "Plant-Incorporated Protectants; Potential Revisions to Current Production Requirements"

Docket Identification No.: EPA-HQ-OPP-2006-1003

The Center for Food Safety appreciates the opportunity to comment on EPA's Potential Revisions to Current Production Regulations related to Plant-Incorporated Pesticides. CFS has long held that FIFRA is an inadequate regulatory framework for regulating pest-resistant plants, such as Bt crops, for many of the same reasons that EPA now feels compelled to revise the PIP Rule. For instance, chemical pesticides are produced in a factory, vs. production in the crop with PIPs; chemical pesticides are applied to the crop and in some cases at least can be washed off the crop prior to consumption, while it is virtually impossible to remove PIPs from PIP-containing crops. In addition, pest-resistant plants are not properly considered as conventional plants to which PIPs have simply been added. Rather, the genetic engineering techniques involved in creation of a pest-resistant crop give rise to potentially hazardous unintended effects that may have little or nothing to do with the specific properties of the PIP itself. EPA has ignored such unintended effects, which are not adequately considered in the context of FDA's voluntary consultation process.

Because EPA has not indicated in the ANPRM what "potential revisions" to the PIP rule it is considering, our comments below focus on desired outcomes from whatever PIP Rule changes are made. Whenever possible, we will tie our recommendations to the specific questions to which the EPA has requested comments (Section IV of the ANPRM).

I. Need for Accurate Reporting of the Quantity of Pesticides Produced in Pest-Resistant Crops

In our view, a major failing of EPA regulation is the lack of reliable data on the actual quantities of plant-incorporated pesticides produced in pest-resistant plants. CFS therefore supports changes to the PIP Rule that would require EPA to collect and report reliable data on PIP levels in pest-resistant plants.

Such data are of importance for several reasons. First, EPA has explicitly encouraged the development of so-called "high-dose" pest-resistant crops to slow development of pest resistance to PIPs. Reliable figures on the amount of the PIP(s) generated in the various tissues of pest-resistant crops is obviously necessary for EPA to make accurate assessments related to the high-dose strategy. Most basically, is a particular pest-resistant plant "high-dose" or not? Is the "high-dose" strategy effective in forestalling insect resistance with respect to any particular event or crop production area? These and related questions require better data than has been generated thus far. Second, although all PIPs in pest-resistant crops approved for commercial use thus far have (to our knowledge) been exempted from the requirement of a tolerance, the EPA may decide to impose PIP tolerances for specific pest-resistant crops in the future to prevent harms to human health or the environment. This would likewise demand reliable figures on PIP levels. Third, accurate data on expression levels is of great importance in judging the adequacy of company studies submitted to the EPA for assessments of potential environmental impacts (e.g. non-target organism impacts) of the pertinent PIP. We note that many such studies have been of extremely poor quality (e.g. SAP 2006).

EPA may argue that such data are already available. Indeed, biotech companies do provide figures for PIP expression levels in various tissues of their pest-resistant plants. Yet such data are demonstrably unreliable. A recent published study on Cry1Ab expression in leaves of Novelis corn derived from MON810 reveals Cry1Ab levels that differ substantially from those reported by Monsanto for MON810 to the EPA and European authorities in the mid-1990s. While the mean Cry1Ab levels reported by Monsanto in four field trials in the US and Germany ranged from 8.95 to 12.15 mcg/g fresh weight, Nguyen & Jehle (2007) report mean levels ranging from 2.4-6.4 mcg/g fresh tissue, several-fold less. A study commissioned by Greenpeace found still lower levels of Cry1Ab leaf expression in MON810 hybrids grown in Germany: mean levels of 0.5 to 2.2 mcg Cry1Ab/g fresh weight, roughly an order of magnitude lower than Monsanto's figures (Greenpeace 2007). Significantly, the Greenpeace results show a substantial number of plants with leaves containing < 0.1 mcg Cry1Ab/g fresh weight, and a lesser but surprisingly high number of leaves with no detectable Cry1Ab expression at all.

While it is beyond the scope of these comments to discuss these results in detail (i.e. varying levels of Cry1Ab over the growing season; environmental factors impacting Cry1Ab expression levels), the upshot is clear, and extends well beyond MON810.

These studies suggest that PIP production in general can vary dramatically by two orders of magnitude and more in a single tissue of a single event, while the amount of conventional pesticides applied is precisely calculable (at least in theory). They also suggest that aggregate company-reported figures on PIP expression may be extremely unreliable. Thus, EPA needs to demand and evaluate much more extensive data on PIP expression levels for each event than it has thus far. Factors that EPA needs to take into consideration include, but are not limited to, variations in PIP expression due to:

1) Genetic background (specific hybrid into which the event has been incorporated);
2) Environmental influences on PIP expression levels in various tissues (soil type, water availability, etc.);
3) Changes in PIP expression levels in various tissues over the growing season.

CFS urges EPA to revise the PIP Rule to require the Agency to collect the data necessary to (more) accurately establish PIP expression levels in various tissues – for each plant variety incorporating the relevant PIP event; for plants grown under a range of environmental conditions; and for various growth stages of the plant. CFS recognizes that doing this would require collection and assessment of considerably more data than EPA presently requires. Yet this is necessary for the Agency to make meaningful assessments with respect to the development of insect resistance to PIPs, non-target organism impacts, etc., as outlined above.

Two real-world examples highlight the need for such data. Event176 Bt corn pollen was associated with potential adverse impacts on Monarch butterflies, due presumably to high Cry1Ab expression levels in pollen and anther tissues, but perhaps also to specific properties of Event176's version of Cry1Ab versus those of the other Cry1Ab-based events, MON810 and Bt11.[1] A recent honeybee study suggests the possibility that honeybees infected with the microsporid *Nosema* suffer higher mortality when exposed to Cry1Ab, suggesting a potential synergistic effect between *Nosema* infection and Cry1Ab exposure (Kaatz 2005). The potential for such synergistic effects between Cry1Ab and microorganisms is supported by a recent study demonstrating that Bt toxin exerts its lethal effect only in the presence of gut bacteria, such as E. coli (Broderick et al 2006). This suggests that the long-assumed mechanism of Bt toxicity (starvation due to puncturing of insect epithelial cells) is wrong; rather, mortality is attributable to colonization of hemolymph by resident gut bacteria that gain access to it by Bt toxin-induced punctures. In both of these cases, accurate knowledge of PIP expression levels (more precise than "within two orders of magnitude") is obviously of fundamental importance for research and risk assessment purposes.

[1] In this particular case, the registration of Event176 was allowed to lapse by its developer around the time that the Monarch butterfly controversy arose. However, if this had not been the case, accurate data on Cry1Ab pollen expression levels may have become crucial in assessing the risks to Monarch butterflies.

II. Need for Accurate Reporting of the Quantity of PIPs Introduced into the Environment and the Acreage Planted to Various Pest-Resistant Crops

Reliable data on the quantity of PIPs introduced into the environment is needed for many of the same reasons cited above with respect to PIP expression levels by tissue/event, for instance to enable accurate assessment of the efficacy of "high-dose" strategies for slowing pest resistance, and to enable accurate assessment of the scope of potential non-target organism impacts presented by various PIP-containing crops. Such data should be collected on an event- and variety-specific basis, with regional breakdowns as needed.

Aggregate figures on the amount of a particular PIP introduced into the environment would be the product of PIP expression per plant (as discussed in Section I) and the number of PIP plants introduced. Acreage figures (and average planting density) for PIP crops would supply a reasonable proxy for the number of PIP plants introduced.

EPA frequently cites figures on the amount of chemical pesticides displaced by pest-resistant plants (for instance, in the "Benefits" section of the Biopesticides Registration Action Documents developed for the 2001 re-registration process), but surprisingly, fails to supply figures on the amounts of various PIPs introduced into the environment by those same plants. This skewed reporting obscures the fact that any displacement of chemical pesticide use is offset (to some degree) by introduction of PIPs.[2] In effect, the EPA's failure to collect and report data on the amount of PIPs introduced into the environment amounts to a denial of the simple fact that PIPs are indeed pesticides.

CFS therefore supports changes to the PIP Rule that would require EPA to collect and report reliable data on aggregate levels of PIPs introduced into the environment (by weight), together with corresponding acreage figures, broken down by crop species, event and variety. Obviously, the first part of this equation would require considerably better-quality data on overall PIP expression levels, as well as reporting of ranges, due to wide variations in PIP expression.

The second part of the equation involves reliable acreage figures. The USDA's Agricultural Marketing Service (AMS) already collects variety- and state-specific acreage figures for genetically engineered upland cotton (as well as conventional cotton)

[2] We note that studies on alleged reductions in chemical pesticide use attributable to introduction of pest-resistant plants are frequently unreliable, due to assumption of a false baseline. For instance, some studies have assumed that all or most growers of pest-resistant plants would resort to chemical pesticides if they were instead growing conventional versions of the crop, when in many cases use of chemical pesticides to control the PIP-targeted pest or pests is/was minimal (e.g. according to the National Academy of Sciences (2000), only 5.2% of US corn acreage was sprayed to control European corn borers prior to introduction of Bt crops targeting ECBs). Another related flaw in EPA's "Benefits" assessments is the assumption that the only alternative to a PIP crop is application of chemical pesticides to a conventional counterpart. In fact, the growing adoption by farmers of organic crops with no chemical pesticide use argues strongly that EPA should compare PIP-containing, conventional and organic crops in future assessments rather than the former two alone.)

on an annual basis,[3] demonstrating the feasibility of such data collection. (Event-specific acreage figures are not reported, but may be calculated by aggregating variety-specific figures, based on event-specific variety names.) The only other regularly reported governmental data on acreage of biotech crops of which we are aware are statistics developed by USDA's National Agricultural Statistics Service, and reported by USDA's Economic Research Service (NASS-ERS).[4] Unfortunately, these statistics are extremely suspect. CFS has found very serious discrepancies between AMS and NASS-ERS reporting with respect to stacked and insect-resistant cotton. The more reliable AMS figures show that in 2006, 87% of US upland cotton acreage was biotech; simple calculations based on AMS figures reveal that 64% was stacked for HT and IR; 22% was herbicide-tolerant alone; while just 1% was insect-resistant alone (Freese 2007). The corresponding figures reported by NASS-ERS are 83% biotech; 39% stacked; 26% HT alone; and 18% insect-resistant alone. Thus, NASS-ERS vastly overestimates the acreage planted to cotton with the IR trait alone (by more than 18-fold).

The vast discrepancies in such basic data on acreage of pest-resistant crops planted in the United States is extremely troubling. As the lead federal agency in charge of regulating pest-resistant crops, EPA needs to take the lead in collection and reporting of reliable data as suggested above.

III. Need for Event-Specific Treatment of PIPs

At present, EPA registers PIPs under FIFRA on an event-specific basis, but sometimes equates different PIPs for the purposes of setting tolerances or granting tolerance exemptions. The prime example of this is Bt corn events that contain differing versions of Cry1Ab (e.g. MON810, Bt11 and Event176). The EPA's practice is to assume that the Cry1Ab produced in each of these crops is the same substance for tolerance purposes, when in fact they can differ substantially in such basic characteristics as molecular weight. MON810, for instance, contains DNA encoding a truncated 92 kD fragment of Cry1Ab, while Bt11 contains DNA encoding a smaller fragment of roughly 65 kD. Since different PIPs can have different effects (whether based on the same Cry protein or not), EPA should treat them separately for tolerance purposes, just as they are treated separately for FIFRA registration purposes.

IV. Need for Enhanced Inspection and Enforcement Authority

CFS urges the EPA to revise the PIP Rule in such a manner that it has enhanced inspection and enforcement authority. Syngenta's distribution for over 3 years of unapproved Bt10 under the name of approved Bt11 is one consequence of EPA's failure to adequately inspect production facilities. CFS is not familiar enough with the details of

[3] USDA AMS (2006). "Cotton Varieties Planted: 2006 Crop," U.S. Dept. of Agriculture, Agricultural Marketing Service, Cotton Program, August 2006.
http://www.ams.usda.gov/cottonrpts/MNXLS/mp_cn833.xls.
[4] "Adoption of Genetically Engineered Crops in the U.S.," http://www.ers.usda.gov/Data/BiotechCrops/.

this episode to know precisely how it occurred, or what specific changes to the PIP Rule, or EPA's implementation of it, would be necessary to prevent similar episodes in the future.

With conventional pesticides, farmers - the end users - read legally enforceable instructions on the label of the can of pesticide. If they fail to follow the instructions, EPA, and through delegation, state agencies, can and do take legal action against them. This ensures that the pesticides are used as intended. In contrast, farmers get no legally enforceable label with plant-incorporated pesticides. The manufacturer is supposed to ensure that farmers receive an "instruction sheet." It is the manufacturer which holds the enforceable label. If a farmer in Iowa or any other state fails to follow instructions, no state or local EPA office can take action against him/her. Instead, enforcement authority is delegated to the manufacturer, which is supposed to enforce "grower agreements." Thus, companies with a financial interest in selling their seeds are in effect appointed as officers to enforce restrictions – such as refugia rules – which often make their seeds less desirable. This clearly puts them in a conflict of interest situation, in which their interest in selling seeds conflicts with their delegated duty to ensure that sometimes burdensome rules are enforced.

There is abundant evidence that this system does not work. For instance, an industry survey revealed that only 70% of growers comply with refugia requirements. Given the fact that this survey was conducted by a consortium of companies, these data on degree of compliance are suspect. True compliance rates are probably even lower. A still clearer example of the failure of this system is the StarLink contamination debacle. Here, Aventis CropScience and its seed dealers, notably Garst Seed Company, not only failed to inform many farmers of the restrictions imposed by "grower agreement" on the cultivation and sale of StarLink (mandatory buffer strip, sale only for animal feed or industrial uses), but there is also solid evidence that Aventis and/or its dealers deliberately misled farmers with seed bag tags which explicitly stated that StarLink was suitable for food use. Although it might be argued that the EPA can exert pressure on the registrant to enforce these grower agreements, this is no substitution for direct enforcement authority in the field. In the case of StarLink, for example, it was revealed that the EPA knew of StarLink corn entering the food supply months before Friends of the Earth and Genetically Engineered Food Alert first revealed contamination of the food supply with StarLink on September 18, 2000. The lack of direct enforcement authority on the part of the EPA may well have contributed to the Agency's failure to take prompt action to keep the potentially allergenic Cry9C protein out of the food supply.

V. Need to Regulate Pest-Resistant Crops in Addition to the PIPs They Produce

CFS urges EPA to revise the PIP Rule to extend its authority beyond the PIP produced in the GE crop to encompass the entire plant. The regulated entity should be the "pesticidal plant" rather than the "plant-incorporated pesticide." As noted above, EPA's regulation currently rests on the fiction that GE pest-resistant plants are equivalent to the conventional progenitor plus an added PIP. This is not the case. Unintended and

potentially hazardous effects of the genetic engineering process go completely ignored by the EPA. Since FDA provides only for "voluntary consultations" with GE crop developers, a PIP-containing crop could enter the market with no assessment for unintended effects whatsoever. Even in those cases where FDA does conduct a voluntary consultation, such assessments are demonstrably inadequate.

There are a growing number of studies and suggestive evidence that indicate the need for "whole crop" regulation vs. EPA's current narrow focus on PIPs. Two examples are discussed below.

1. Colony Collapse Disorder

Scientists involved in researching the causes of colony collapse disorder in honeybees are investigating high-fructose corn syrup (often fed to honeybees) derived from GE corn as one possible cause (Barrionuevo 2007; Dr. May Berenbaum, personal communication). Since the starch fraction of corn from which corn syrup is derived contains very low levels of protein, it would seem unlikely that Bt insecticidal proteins could be involved. However, unintended effects of the genetic engineering process could result in alterations to certain starch or sugar components, or other corn constituents that end up in cornstarch, that render them toxic to honeybees. Studies submitted to the EPA regarding non-target organism impacts are conducted with a surrogate version of the PIP that is actually produced in the plant (usually administered in sugar solution), and so would be of absolutely no value in detecting such potentially harmful unintended effects in GE corn-derived corn syrup. It should be noted here that the FDA, to the extremely limited extent that it considers unintended effects in the context of its voluntary consultation process, has no remit (or expertise) to examine harmful environmental effects of this nature.

2. Need for Whole Crop Feeding Trials with Toxicological Endpoints

A sub-chronic toxicity study involving 90-day feeding of whole MON863 to rats has shown evidence of hepatic and renal damage (Seralini 2007). EPA approved MON863 in the complete absence of feeding trials on well-characterized lab animals with toxicological endpoints. We note hear that "performance" feeding trials of GE crops to poultry or other animals that are designed merely to detect changes in weight gain or other readily observable effects are grossly inadequate, and can in no way substitute for feeding trials with toxicological endpoints. See Freese & Schubert (2004) for an outline of the sort of animal feeding trials that are needed.

The "acute toxicity" feeding trials of the type normally submitted to the EPA are grossly inadequate, as they ignore the potential for unintended effects; and also fail to detect even sub-chronic or longer-term effects of the PIP itself (falsely assuming that protein toxicity is only acute in nature), and are in any case conducted with bacterial surrogates that often differ from the plant-produced pesticides they are meant to substitute for. To the limited extent that such trials are useful at all, EPA should demand that the test substance equivalence criteria recommended in SAP (2001) before allowing use of bacterial surrogates for testing purposes.

VI. Conclusion

We note that in the ANPMR, EPA tentatively suggests that PIPs pose lesser risk than conventional chemical pesticides: "In general, EPA's experience with PIPs is that they present different and ***potentially lower risk*** situations compared to chemical pesticides" (emphasis added).

We strongly disagree that there is an adequate evidentiary basis for making general statements about the magnitude of risks posed by PIPs as a class vs. chemical pesticides as a class. Above, we discussed evidence demonstrating that data as basic as PIP expression levels are quite uncertain, highly variable, and in at least one instance (MON810) deviate considerably from company-supplied figures that form the basis for EPA risk assessments. We have also presented suggestive evidence of harm from PIPs and/or the pest-resistant crops that contain them, evidence that argues strongly for assessment of the whole crop rather than merely the PIP.

Therefore, we request that EPA not make any revisions that weaken the PIP Rule on the unjustified assumption that pest-resistant crops and PIPs pose less risk than chemical pesticides. CFS urges EPA to give the "outcome-oriented" recommendations presented above careful consideration in any potential revisions it makes to the PIP Rule.

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