December 3, 2013

Comments for

FIFRA Scientific Advisory Panel
Scientific Uncertainties Associated with Corn Rootworm Resistance Monitoring for Bt Corn Plant Incorporated Protectants (PIPs)
Docket: EPA-HQ-OPP-2013-0490

by Center for Food Safety

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Summary of Comments

CFS generally agrees with EPA's proposed changes to corn rootworm (CRW) resistance monitoring. However, such changes will not significantly deter further emergence of Bt-resistant CRW unless they are accompanied by a substantial strengthening of the resistance ***prevention*** components of insect resistance management (IRM).

Monitoring has revealed declines in susceptibility to all of the commercial rootworm toxins since 2005; and escalating emergence of Cry3Bb1-resistant CRW since no later than 2009. First identified by independent scientists in Iowa and Illinois, resistant CRW are likely present in multiple regions of 11 states based on reports of unexpected damage to Bt corn reviewed by EPA (see section II.A). This rapid emergence of resistance is attributable to several factors:

1) Increased continuous corn cultivation that has been facilitated by Bt corn and encouraged by its developers (see II.D);

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2) Sharply reduced availability and planting of conventional (or non-Bt) corn seed, a key IRM measure (see II.C);

3) The rise of resistance-promoting, volunteer Bt corn as a weed, made more difficult to control when stacked with herbicide-resistance traits (see II.E); and

4) Most importantly, EPA's irresponsible reductions in refuge size requirements to levels much lower than are needed to dilute resistance genes and deter resistance (see II.B).

EPA's failure to stem resistance in CRW can be explained in several ways (see generally IV). First, there has been misplaced application of IRM for lepidopteran Bt corn to the very different resistance challenges presented by rootworm-active Bt corn. Second, an overly stringent definition of resistance has resulted in numerous false negative findings and thus delayed effective remedial action for years (I: Questions 4 and 6). Finally, EPA has relied excessively on industry views and assessments that are skewed by financial self-interest; and rejected the unbiased analysis and recommendations of independent experts, as seen most clearly in refugia requirements that are much too low to dilute resistance genes and forestall resistance (II.B).

CFS recommends that EPA:

1) Make publically available the monitoring data reported to EPA re: unexpected damage to Bt corn, and/or provide complete descriptions of it in relevant documents released to the public (II.A)

2) Establish a simple, single-criterion definition of resistance along the lines discussed in section I, Question 4

3) Increase refuge requirements for all rootworm-active Bt corn events to 50% for single-toxin Bt corn and 20% for pyramids (II.B)

4) Establish mandatory IRM involving rotation away from rootworm Bt corn (IV)

5) Increase the role of independent scientists and reduce that of seed firms in every aspect of IRM in light of industry's failure to successfully detect and notify EPA of the emergence of resistant CRW (IV)

Comments

Center for Food Safety (CFS) appreciates the opportunity to comment on the growing resistance of corn rootworm to Bt toxins and EPA's proposals to improve monitoring for resistance and remedial action.

CFS generally agrees with EPA's proposed changes to corn rootworm (CRW) resistance monitoring. However, while these changes would perhaps deliver marginal improvements, they would not significantly deter further rapid emergence of Bt toxin-resistant CRW. To achieve this would require more thoroughgoing reform of the insect resistance management plans. In these comments, we first address the specific charge questions, followed by a discussion of issues not addressed by EPA and of measures that do have the potential to significantly deter further emergence of CRW resistance.

I. Comments on Charge Questions

Question 1: Annual Corn Rootworm Sampling to Assess Bt Susceptibility

CFS agrees with EPA that IRM monitoring should involve more intensive and focused sampling. This approach would seem to be more consistent with the primarily short-distance dispersal patterns of CRW adults, as well as the observed emergence of resistant CRW populations primarily in localized hot spots. However, corn rootworm has shown the capacity for fairly rapid dispersal over long distances. First, CRW expanded eastward across the Corn Belt in the 1960s and 1970s at rates ranging from 20 to 200 km/year, depending in part on the direction of prevailing winds and storm fronts. Second, rotation-resistant CRW has expanded its range from its origins in eastern Illinois in 1987 to infest parts of seven states in 2007, just 20 years later. Finally, CRW first discovered in Europe near Belgrade in 1992 was found in 20 European countries just 15 years later in 2007[1] (Gray et al 2009, see maps below). Thus, EPA must not neglect the potential for longer-distance dispersal of resistant CRW from numerous hot spots, which is likely already leading to rapid emergence of area-wide resistance. Random sampling is better suited to detect emergence of area-wide resistance, and should remain part of annual monitoring together with more intensive and focused sampling.

Current monitoring involves random sampling of just 12-15 populations each year in three states. Clearly, many more populations will have to be sampled with incorporation of the intensive, focused sampling approach. The number of CRW populations that are sampled should increase in proportion to the number of unexpected Bt damage reports, and intensive sampling should be focused in those areas.

[1] CRW's expansion in Europe is due to some combination of multiple introductions from the U.S. (at least 3) and subsequent range expansion from these foci.

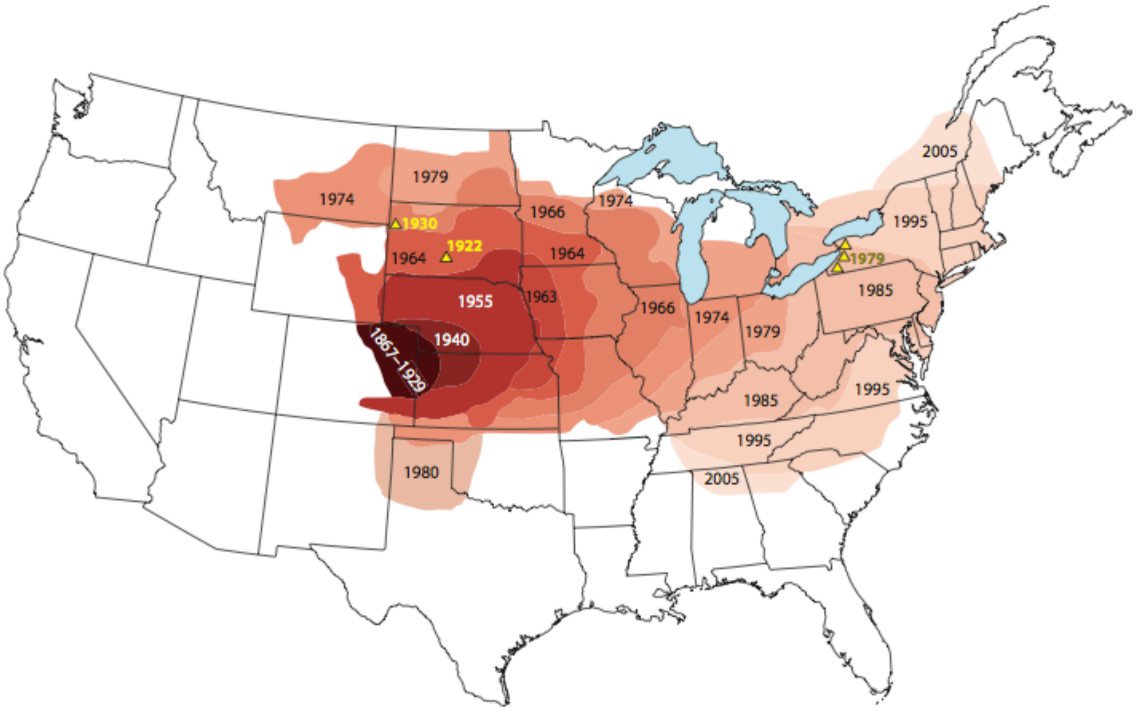

Figure 1

Reconstruction of western corn rootworm, *Diabrotica virgifera virgifera* LeConte, range expansion from central Great Plains across North America from 1867 to 2005, based on data or reports in the literature (25, 39, 48, 49, 64, 67, 68, 69, 70, 110, 115, 116, 123). Distribution boundaries are approximate and do not include distributions in areas to the west of the indicated expansion boundaries (see References 48, 114 for western distributions). Triangles mark reports of *D. v. virgifera* far ahead of the established distribution in the years indicated.

Source: Gray et al (2009)

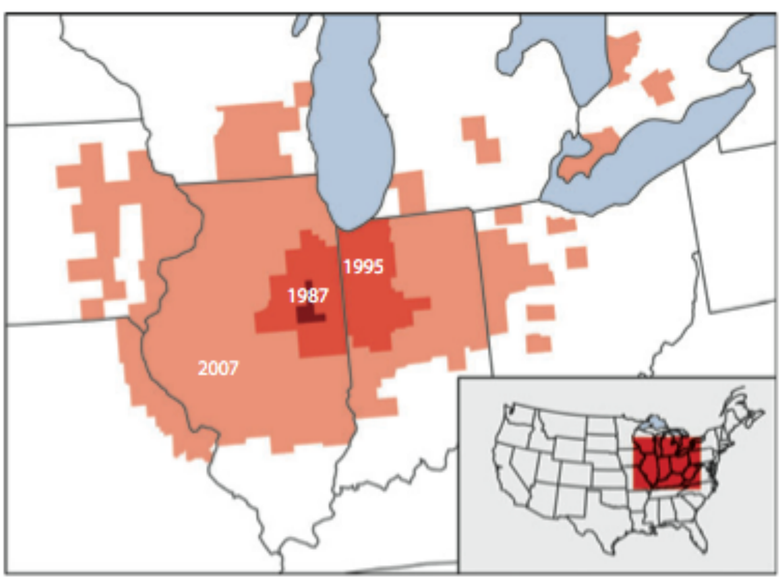

Figure 4

Range expansion of the variant western corn rootworm, *Diabrotica virgifera virgifera* LeConte, in the United States Corn Belt through 2007.

Source: Gray et al (2009)

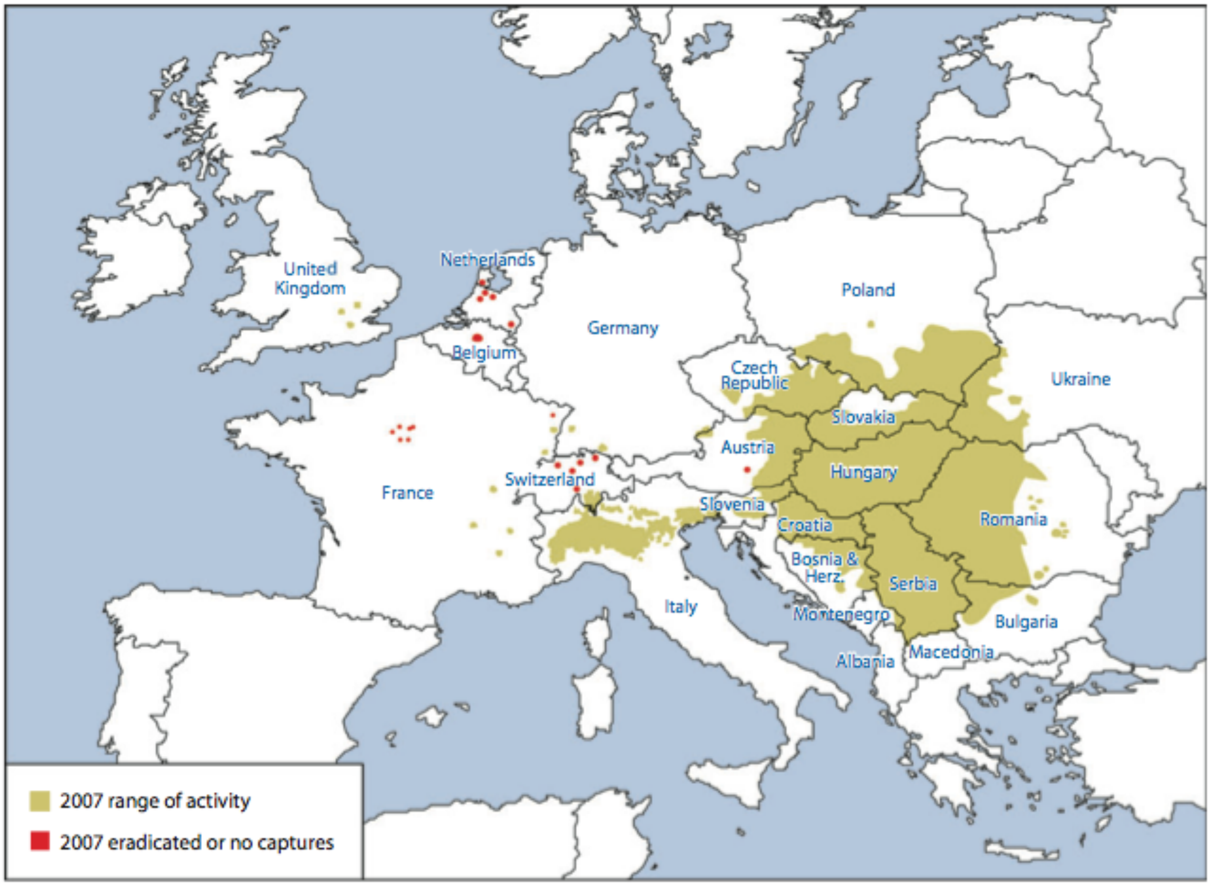

Figure 2

Western corn rootworm, *Diabrotica virgifera virgifera* LeConte, distribution in Europe through 2007 (with permission of C.R. Edwards, Purdue University).

Source: Gray et al (2009).

Question 2: Corn Rootworm Sampling in Response to Damaged Bt Fields

EPA recommends use of field damage ratings based on root node injury for investigations of CRW populations causing damage to Bt corn. The triggers suggested by EPA are: 1.0 for single-toxin Bt products and 0.5 for pyramided Bt products. CFS recommends that EPA utilize the 0.5 rating for both categories. This would be consistent with the expert recommendation of the 2002 Scientific Advisory Panel (SAP) that advised EPA on insect resistance management for Cry3Bb1-expressing MON863 corn. This SAP advised that CRW root damage "approaching a 0.5 (node-injury scale)" on MON863 roots, coupled with a history of MON863 cultivation, was sufficient to regard a CRW population as "suspected resistant" (SAP 2002, pdf p. 65[2]).

It is unclear why greater damage should be needed to deem a CRW population resistant or suspected resistant in the case of single-toxin plants. For example, at present Cry34/35Ab1

[2] Pdf page numbers (e.g. page 65 of 71) are cited for this SAP report because it does not have printed page numbers.

appears to be the only commercial rootworm PIP that remains largely uncompromised by resistant CRW, in light of the strong evidence for cross-resistance between Cry3Bb1 and mCry3A (BPPD 2013c, p 24). It is thus extremely important that its efficacy be preserved; and its effectiveness must be safeguarded as fully when deployed in a single-toxin plant as when deployed in a pyramid (e.g. SmartStax corn). This is true not only for Cry34/35Ab1; it applies more generally. EPA should establish the same damage trigger – 0.5 node injury – for single-toxin and pyramided seeds in resistance assessments.

In the charge question, EPA notes that some unidentified party or parties has raised a concern that sampling for adult CRW directly in damaged Bt fields, specifically in the vicinity of the damage, "may be biased relative to surrounding areas and not representative of the overall CRW population." Some such concern may well have been well have been what motivated Monsanto to propose a sampling plan in response to damage reports in which CRW were collected as far as one to two miles from failed fields (BPPD 2011, p. 2).

This concern, however, is entirely misplaced, based on a misunderstanding of the nature of CRW resistance and the purpose of this part of the monitoring program.

First, because CRW resistance to Bt toxins is likely to arise (at least initially) in numerous confined areas, collecting CRW samples far away from damaged Bt corn would introduce a clear bias tending towards false negative results. As EPA noted with respect to the Monsanto plan mentioned above: "this proposal is insufficient if the goal is to determine whether Bt failure is due to resistance of the CRW population" (BPPD 2011, p. 2). CFS agrees.

Second, the primary purpose of sampling in response to damage reports is damage control – rapid assessment of probable resistance, followed by strong and effective remedial action to contain and extirpate it, as needed. The purpose is not – as it has been with annual sampling – to provide early indications of evolving resistance on an area-wide basis, in which case broader sampling would make more sense. However, as discussed above, CFS agrees with EPA that annual monitoring should incorporate more intensive and focused sampling.

For both of these reasons, sampling of CRW adults in response to unexpected damage should be focused directly in the damaged area of Bt fields and the immediate vicinity as much as possible.

Question 3: Diagnostic Assays

CFS supports EPA's recommendation that diagnostic on-plant assays be the primary resistance detection tool for corn rootworm. CFS recommends use of the Gassmann assay, which has proven itself capable of detecting resistance where diet bioassays have (perhaps) failed.[3] As EPA notes in its white paper, neither the instar development nor body

[3] We say "perhaps failed" because in EPA's white paper (page 16), it is stated that field populations of CRW that meet a key resistance criterion (LC50s exceeding the upper limit of the 95% confidence interval of the control population) have been identified with use of diet bioassays, apparently for all three CRW Bt toxins,

size criteria employed in the sublethal seedling assays (e.g. Nowatzki et al 2008) has been validated as a reliable marker of resistance.

> "BPPD notes there is no evidence demonstrating that resistant corn rootworm need to have greater body mass or head capsule widths for development than their susceptible counterparts. Hence, ***this significance criterion is likely too stringent and would potentially result in false negatives***." (White paper, p. 17)

Whenever diagnostic assays involve comparisons to susceptible CRW populations (whether contemporary or historical data), care should be taken to ensure that the susceptible standard of comparison represents truly susceptible CRW prior to any selection pressure from exposure to Bt rootworm toxins. EPA notes that "[i]n some cases, lower susceptibility has been observed in field populations relative to the laboratory colonies" (White Paper, p. 15); and similarly: "CRW populations in the field have experienced selection to Bt corn over the past decade and likely have obtained some degree of tolerance to the toxins (Cry3Bb1, mCry3A, and Cry34/35)" (White paper, 29). Use of "less susceptible" or partially tolerant CRW for control purposes in resistance assessments is to be avoided whenever possible; or if not avoidable, accounted for in resistance assessments by, for example, reducing the resistance ratio or other comparative metric required for diagnosis of resistance.

Question 4: Defining Resistance

EPA's ostensible goal is to make resistance monitoring proactive rather than reactive. To that end, the Agency recognizes that resistance must be defined such that an "actionable threshold" is met before resistance is widespread (White paper, p. 22). If resistance is not defined in this way; if timely regulatory action is not possible due to an excessively stringent definition of resistance; then IRM completely fails to serve its intended purpose; the Bt toxin's value is lost or eroded; and chemical insecticide use rises, with associated toxicity to human health and the environment. In EPA's terms, "population suppression (e.g. chemical insecticide use) may be the only alternative for managing resistance" (White paper, p. 22).

Results of a prospective survey conducted by University of Illinois entomologist Michael Gray show that in 2013, nearly 50% of Illinois corn growers expected to use both Bt corn with rootworm-active toxin(s) AND chemical insecticides (Jongeneel 2013). University of Minnesota entomologist Ken Ostlie expected similarly high use of insecticides, both on continuous corn and rotated corn:

> "At winter meetings with ag professionals, they indicated more than 50 percent of corn-on-corn would end up with an insecticide overlay of traits,"

"although none of the populations have been deemed resistant by registrants… [p]resumably … due to the difficulty of interpreting and obtaining accurate LC50 values." Thus, the problem may lie less with the type of assay than with how it is interpreted, and who is doing the interpreting. Below, we discuss how corporate financial interests may be skewing the science and regulation of IRM.

says Ostlie. "About 25 to 30 percent of rotated corn with no threat of resistance was expected to receive an overlay. I suspect final percentages of both were higher." (Ruen 2013)

This evidence shows that resistance[4] is already prevalent enough to be driving up the use of insecticides substantially.

Despite EPA's goal to make IRM proactive, however, its current and proposed definitions of resistance ensure its continuing failure for corn rootworm. As EPA itself concedes:

> "All of the proposed procedures are likely to detect resistance only if it is complete (i.e., CRW develop and survive on Bt corn at the same levels as isoline corn). Comparisons of field populations on Bt and non-Bt corn require statistical equivalence to make a positive resistance determination. This statistical approach would exclude cases of incomplete resistance, in which a field population is more fit than a control colony on Bt plants but not as fit as a population with complete resistance." (White Paper, p. 29)

The definition of resistance must be revised to encompass partial resistance. This is particularly important given the ongoing emergence of resistant CRW populations under the more stringent definitions used hitherto. Because more stringent definitions of resistance have demonstrably enabled resistant CRW to emerge without triggering remedial action plans, these definitions must be loosened to enable more timely response at earlier stages of resistance. Otherwise, IRM has little chance of stemming the tide of resistant CRW.

To this end, criteria that require demonstration of complete resistance should be eliminated. CFS supports the first criterion of the Single On-Plant Assay Option 2 (White paper, p. 28) as a fully sufficient definition of confirmed resistance.

> "Using a single on-plant assay (e.g., Gassmann et al. 2011 or similar methods), a corn rootworm population is said to be resistant when: The percent survival observed of the field population on Bt corn exceeds the percent survival of the susceptible population on Bt corn (statistically significant; P-value <0.05)."

The second criterion relates to average weight: "The average weight of the survivors from the field population on Bt corn is equal to (no statistically significant difference) or greater than the average weight of the susceptible colony on isoline corn."

This second criterion should be eliminated for several reasons. First, as noted by EPA, it is not independent from the first (White paper, 28-29). Second, average larval weight has not

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[4] More accurately, one should say some unknown mix of actual resistance and fear of resistance, with use of chemical insecticides to either control resistant CRW or as a prophylactic measure to forestall or prevent the spread of resistance.

been validated as a measure of resistance (Ibid, p. 17). Finally, to the extent that weight does prove to correlate with percent survival, the criterion demands a showing of complete resistance, when as argued above the definition must include incomplete resistance.

If EPA does choose to use either instar development or body size/weight as a criterion in resistance definitions, it should only be used as a possible ***alternative*** measure to survival, not as an independent criterion. This is how it appears to function in the first criterion of the proposed On-Plant Assay Option 1:

> "A statistically significant difference in measures of ***either*** lethality/mortality ***or*** sublethal effects (growth/development) between the field population and the control population on Bt corn" (White paper, p. 28, emphasis added).

In a similar context, EPA's BPPD IRM team recommended a definition of confirmed resistance to Cry3Bb1 based on a single criterion (survival):

> "On-plant assays with "suspected resistant" field populations demonstrate increased survival of field populations on Bt compared to non-selected lab colonies." (BPPD 2012, p. 20).

Likewise, when presented with a possible definition of resistance that involved meeting both of two independent criteria (LC50 and proportion of root nodes destroyed), the 2002 SAP mentioned above, which included leading experts on Bt resistance, recommended that meeting a single criterion sufficed for confirmation of resistance:

> "The Panel also agreed that rather than require both clauses, either clause would be sufficient to demonstrate confirmed resistance." (SAP 2002, pdf p. 66)

Question 5: Determining Remedial Action Areas

No comment.

Question 6: Containment/Mitigation of Resistance

The most effective measures to mitigate resistant CRW populations will be those that deny CRW a food source. It is well known that CRW infestations are much more likely – and more severe when they occur – in continuous corn. Indeed, one of many benefits of rotating corn (e.g. with soybeans) is to forestall CRW infestations.[5] Thus, rotating away from corn to a non-CRW host crop is clearly the most effective mitigation measure, and is especially important in view of the sharp rise in in acres planted to continuous corn over

[5] A corn/soybean rotation provides good protection against CRW in parts of the Corn Belt, but is of less value in areas (e.g. Illinois and Indiana) where a rotation-resistant variant has become prevalent. However, even in these areas entomologists have recommended that growers "continue rotating as a second line of defense" to soil insecticides and/or rootworm active Bt toxins (Michael Gray, as quoted in Ruen (2013)).

the past decade (addressed further below). EPA should consider mandating such crop rotations as part of remediation plans.

Any mitigation that involves continuous corn is of less value. But of measures that involve corn-on-corn, planting of non-Bt corn eliminates ***all*** selection pressure for evolution of resistance to ***any*** rootworm-active PIP and is thus the most desirable (Porter et al 2012). This is particularly true given the inadequate refuge size requirements for all corn rootworm-active PIPs (see section II.B below). Rotation to corn that expresses a different PIP or PIP combination should be the last recommendation.

CFS finds EPA's distinction between "hot spot" and "area-wide" resistance somewhat misleading (White paper, 34-36). While probably not intended by EPA, the labels suggest that the operative distinction is total area infested with CRW – little for "hot spot" resistance and much more for area-wide resistance – and that the former is thus less problematic and merits less intervention than the latter. This is not the case.

As EPA acknowledges, reports of unexpected CRW damage to Bt corn are rising dramatically, indicative of expanding resistance (see section II.A). EPA finds that the most likely scenario is evolution "in many different hot spots simultaneously from ubiquitous management practices favoring resistance" (scenario 2) rather than widespread dispersal of resistant CRW from one or a few hot spots (scenario 1). As EPA concedes, the end result of these two scenarios is not likely to be distinguishable; they are merely different paths to "area-wide resistance."

What distinguishes these scenarios is the relative importance of the ***evolution*** of resistance versus the ***spread*** of resistance, ***once evolved***, rather than the geographic extent of resistance. EPA is probably right that scenario 2 predominates. Resistance evolution is not a rare, but rather a frequent event, resulting in numerous "hot spots" due to "widespread agricultural practices employed across the Corn Belt (i.e. continual planting of corn for feed or ethanol production, lack of crop rotation, etc.) and the non-high dose nature of the rootworm Bt toxins" (White paper, p. 35). EPA leaves out one of the most important causative factors, however, which is its own setting of entirely inadequate refuge size requirements for all corn events expressing rootworm PIPs (see section II.B).

The "many little hot spots" mode of CRW resistance emergence has further implications not addressed by EPA. CRW adults are capable of sustained, high-altitude flight, and can take advantage of prevailing winds and storm fronts to move considerable distances (Isard et al 2004). Extreme weather is becoming more common with climate change. All other things being equal, the likelihood that storms will transport resistant CRW moderate to long distances increases with the geographic range and number of hot spots across the Corn Belt. It is greater with EPA's scenario 2 than scenario 1. To illustrate this, imagine just one large population of resistant CRW (scenario 1) vs. 50 hot spots scattered across the Corn Belt (scenario 2), where the total area occupied by resistant CRW is the same in both scenarios. The likelihood of unusual weather events spreading resistant CRW in scenario 1 is small, equivalent to the probability that such a weather event will occur (and occur at the appropriate CRW life stage) in just one area. In scenario 2, the probability of CRWtransporting weather events is much greater – somewhat less than the sum of the probabilities of occurrence in 50 different areas.[6]

Thus, some proportion of resistant CRW populations in numerous confined areas will spill beyond their local boundaries during extreme weather, an additional mode of resistance spread that EPA must consider. Most importantly, however, frequent emergence of resistance in numerous localized areas points directly to the glaring weaknesses in the resistance ***prevention*** component of EPA's IRM plans, to which we now turn.

II. Comments on Issues Not Addressed by EPA

A. Prevalence of CRW Resistance

EPA's white paper and charge questions focus narrowly on technical issues associated with monitoring for resistance and give no overall impression of the prevalence and seriousness of the problem, which 22 corn entomologists recently told EPA requires action "with a sense of some urgency" (Porter et al 2012). Corn rootworm resistance to Bt toxins has risen dramatically in the decade since the first rootworm-active Bt corn event was approved in 2003, but precise data are lacking.

EPA must make publically available much more complete resistance monitoring data so that farmers, extension agents, entomologists and the public are better informed about the extent of CRW resistance to Bt toxins. The BPPD's reviews of monitoring data (e.g. BBPD 2011) contain some useful information, but lack basic components such as total number of unexpected Bt corn damage reports each year, broken down by state and county. Fuller and standardized reporting of such data is necessary to keep stakeholders informed.[7]

Monitoring data provided by Monsanto to EPA shows a clear trend of declining susceptibility to Cry3Bb1 since 2005 (BPPD 2011, Tables 5 and 6). Entomologists in Nebraska have observed moderate to severe rootworm damage to Cry3Bb1 corn beginning no later than 2008, and in Minnesota since 2009 (Ibid, p. 5), likely indicative of resistance. CRW sampled from a damaged Bt field in Iowa in 2009 were confirmed as resistant in 2011 (Gassmann et al 2011), and resistant CRW have been confirmed in Illinois as well (Gray 2012).

Between 2009 and 2012, there were reports of heavy corn rootworm damage to Cry3Bb1 corn in at least 23 counties of 6 states in the Corn Belt (NE, IA, SD, MN, WI, IL) (BPPD 2012, p. 2). The BPPD IRM team believes that these damaged Cry3Bb1 fields may also be due to Cry3Bb1 resistance.

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[6] "Somewhat less than" because weather patterns in different regions of the Corn Belt are of course not entirely independent.

[7] Ironically, perhaps, University of Illinois entomologist Joseph Spencer expressed the hope ***that seed companies*** would provide this information to help farmers make planting decisions (see Smith 2013). Farmers and scientists should not be dependent on the good will of seed firms (which in some cases have denied resistance even exists, see Philpott 2011) for this information. It is EPA's responsibility to provide it.

Map showing Cry3Bb1 fields with heavy CRW damage and/or resistant corn rootworm populations reported to the US EPA (2009-2012)

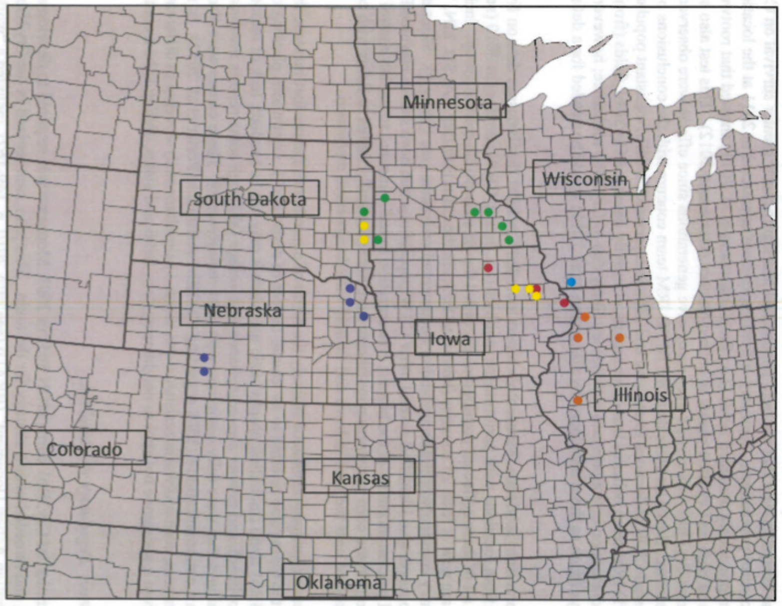

Figure 2. This map includes only field failures that were reported to the US EPA. Counties with unexpected Cry3Bb1 field failures had a history of corn-on-corn with Cry3Bb1, and many have had multi-year failures (2009-2012) as reported by academics; Monsanto's 2010 performance inquiries are included as well (● = Monsanto 2010 reports – crop history undetermined; ● = Gassmann 2009-2011 resistance reports; ● = Ostlie 2009-2012 field failure reports; ● = Hunt and Meinke 2011 report; ● = Gray 2011-2012 resistant and field failure reports; ● = Cullen 2012 field failure report).

Figure above excerpted from BPPD (2012), p. 17, report dated Oct. 11, 2012.

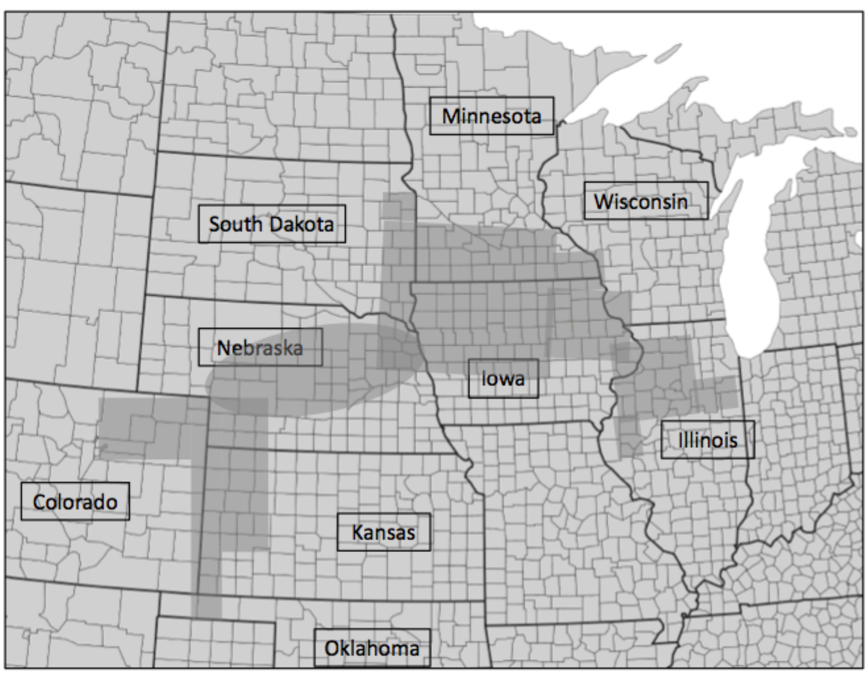

Figure 5. 2013 Updated map showing the general areas in the US Corn Belt that have had Cry3Bb1 fields with heavy damage and/or resistant western corn rootworm populations (2009-2012)

Figure above excerpted from BPPD (2013c), p. 21, report dated Sept. 26, 2013. New areas compared to Oct. 2012 map above include western KS, eastern CO, central NE, western 2/3 of Iowa, eastern Illinois and Oklahoma. As noted in text, heavy damage to Cry3Bb1 fields also reported in MI and MT (not shown on map).

An update to the aforementioned report one year later shows additional areas of heavy CRW damage to Cry3Bb1 corn in several new regions (central NE, the western 2/3 of Iowa, eastern Illinois and in two new states (CO and KS), for 8 states altogether (BPPD 2013c, Figure 5, p. 21). Additional though apparently less frequent reports of unexpected damage to Cry3Bb1 corn came from three additional states: Michigan, Montana and Oklahoma (BPPD 2013c, p. 16). Thus, CRW have caused heavy damage to Cry3Bb1 corn in at least 11 states, and most of these cases likely represent CRW that have evolved resistance to Cry3Bb1. On the preceding page, two maps are reproduced from the EPA reports cited above that portray this development.

And there are also signs of resistance evolving to the other two commercially available rootworm toxins – Cry34/35Ab1 and mCry3A – in the form of LC50 values in field populations that substantially exceed those of control populations:

> "A number of field-collected populations have shown LC_{50}s exceeding the upper limit of the 95% confidence interval of the control population (see data reviewed in BPPD 2011, 2012, 2013a, b, c), although none of the populations have been deemed resistant by registrants" (White paper, p. 16)[8]

The rapid emergence of Cry3Bb1-resistant corn rootworm throughout the Corn Belt, and signs of evolving resistance to the other toxins, raise several serious questions for EPA. First and most obviously, why are EPA's IRM plans for corn rootworm failing so dramatically and so rapidly?

B. Deficient Refuge Requirements

All of EPA's charge questions relate to changes in the monitoring program. Yet by far the most important reason for the expanding failure of IRM is to be found in the thoroughly inadequate refuge size that EPA has set for rootworm-active Bt corn events.

All Bt corn hybrids targeting corn rootworm produce relatively low doses of Bt toxin, violating EPA's preferred high-dose strategy that is met by all or most Bt events for major lepidopteran pests. EPA guidelines for a high dose require that such Bt plants kill ≥99.99% of susceptible target insects in the field (SAP 1998, pp. 4-5), equivalent to a survival rate of ≤0.01%. The various rootworm Bt events not only do not meet this standard, they do not even begin to approach it. The survival rate of susceptible CRW on corn expressing Cry3Bb1, averaged over three studies, is 2.6%, or 260-fold higher than the maximum 0.01% survival rate that defines high-dose Bt events. Similar CRW survival rates are found for corn expressing Cry34/35Ab1 (4.2%) and mCry3A (3.6%) (Tabashnik & Gould 2012, Figure 2).

[8] BPPD 2011, 2012 and 2013c are EPA reviews of monitoring data and field reports on unexpected damage to Cry3Bb1-expressing corn; BPPD 2013a and BPPD 2013b are similar reviews for Cry34/354Ab1 and mCry3A corn, respectively.

These high survival rates are indicative of nonrecessive inheritance of resistance, which is predicted to dramatically accelerate evolution of resistance relative to the recessive resistance to Bt toxins like Cry1Ab seen in lepidopteran pests such as European corn borer. In fact, survival rates in this range represent a worst-case scenario for resistance evolution (Tabashnik & Gould 2012, p. 769).

A large refuge is required to compensate for the resistance-promoting effects of the low doses of rootworm-active Bt toxins. Below, we focus on Cry3Bb1, as both the first rootworm Bt toxin and the one to which CRW resistance is most advanced. But similar considerations apply to the others as well given their similarly low doses.

In 2002, EPA convened a Scientific Advisory Panel (SAP) to advise it on insect resistance management for Cry3Bb1-expressing MON863, the first Bt corn event targeting corn rootworm. A clear majority of the SAP (11 of 14 members) recommended that at least a 50% refuge be mandated for MON863[9] (Knight 2003). This SAP, which included some of the world's leading experts on pest resistance to Bt toxins, found that "modeling suggested that a 50% refuge would net at least twice the time to resistance as the proposed 20% refuge" (SAP 2002). EPA ignored the SAP's recommendation and instead complied with Monsanto's request, establishing a 20% refuge (Knight 2003). It appears that EPA took this action on the basis of information submitted to it by Monsanto ***after*** the SAP meeting took place (Pollack 2003), information that was thus unavailable for critical review by the SAP.

In contrast to Bt resistance experts, EPA claimed then that its modeling projected that even if Cry3Bb1-producing corn were planted all over the U.S., it would take 7 to 16 years for resistance to become a problem (Knight 2003): that is, not until 2009 to 2018. With the much less extensive plantings projected by Monsanto, resistance would presumably take much longer to emerge. As it turned out, MON863 plantings in fact represented just 17% of aggregate corn plantings from its introduction in 2003 to 2009.[10] Despite this limited acreage, resistance emerged no later than 2009 (Gassmann et al 2011), the earliest date that EPA had predicted for its "worst-case" scenario of nationwide coverage with MON863.

EPA's ostensible reasons for acceding to Monsanto's request for a 20% refuge were:

1) The registration being considered was interim, lasting only one year with probable extension to three years (Pollack 2003); and even with a refuge as small as 20%, resistance was not likely to evolve in three years, after which time the refuge size requirement could be re-evaluated and changes made as necessary (Knight 2003);
2) Growers would be confused by, and not comply with, a refuge as large as 50%, while their familiarity with a 20% refuge (from Bt corn targeting European corn

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[9] A majority favored 50%; a couple of panel members supported a refuge of greater than 50% (Tabashnik & Gould 2012, p. 770).

[10] Based on Monsanto biotechnology trait acreage figures calculated from Monsanto (2009) and USDA NASS data on total corn plantings. Cry3Bb1-expressing corn comprised 1%, 2%, 5%, 13%, 22%, 35%, and 36% of U.S. corn plantings from 2003 to 2009, respectively.

borer) would increase compliance (SAP 2002, pdf p. 58, expressing the views of a minority of SAP members, 3 of 14).

In making these arguments, EPA essentially ignored the majority of its scientific advisers, who "concluded that there was no ***practical or scientific*** justification for establishing a precedent for a 20% refuge" for MON863 (SAP 2002, pdf p. 57, emphasis added).

As for EPA's first reason, the SAP warned that while the 20% refuge was not likely to result in field failures due to resistance during this three-year period:

> "[i]t could, particularly in local areas, lead to a significant increase in resistance allele frequencies over this time. This increased frequency would limit future options for resistance management relative to Cry3Bb1 and any other toxin for which there was cross-resistance with Cry3Bb1. Panel members indicated that the choice of a 20% refuge for the interim plan was likely to limit choices of refuge size in the future because farmers and companies would not desire to increase refuge size." (SAP 2002, pdf p. 57)

The SAP's majority was correct on both scientific and practical grounds. As noted above, CRW survival rates and/or the amount of toxin required to kill or impair growth have generally increased over time for all of the rootworm-active Bt toxins, including Cry3Bb1, indicating a rise in resistance allele frequency. A 50% refuge would have diluted resistance genes and delayed resistance much better than the unscientific 20% refuge that EPA actually implemented. As noted above, the SAP found that a 50% refuge would have at least doubled the time to emergence of resistance relative to the 20% refuge.

Neither did EPA (to the best of our knowledge) make any attempt to re-assess its interim decision or increase refuge size at any of the three decision points on extending the registration of Cry3Bb1-expressing corn (MON863 or its successor MON88017) in 2004, 2006 or 2010.[11]

EPA presented no empirical evidence in support of its second reason regarding grower compliance, while ignoring evidence that undermined it. First of all, in the five years preceding introduction of MON863, U.S. corn farmers applied insecticides to control CRW on just 14 to 18 million acres of corn each year, representing 18% to 23% of total corn acres (EPA 2005). If CRW infestations justified spraying on just one-fifth of national corn acres, it is difficult to understand how permitting 50% of corn (over twice as much) to be "treated" with Cry3Bb1 would result in massive non-compliance with a 50% refuge requirement.[12]

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[11] The EPA initially (2/24/03) issued a time-limited registration for MON863 corn that was renewed for two years on 4/23/04; then for four additional years on 7/27/06. In September 2010, the registration for MON863's successor, MON88017, was extended for five years and now expires on 9/30/15 (EPA 2010a, Regulatory History, pp. 9-18).

[12] While the proportion of corn acres sprayed for CRW would of course vary greatly at the on-farm level depending on CRW pressure in various regions, the fact that only 20% of corn acres were sprayed for CRW nationally suggests at least that the pest afflicts a clear minority of corn at economic injury levels in any given

Second, EPA completely ignored the precedent of insect resistant management (IRM) for Bt cotton in Australia, which was discussed and cited as a precedent by the SAP (SAP 2002, pdf pp. 57-58). There, government regulators successfully implemented, and farmers complied with, a comprehensive IRM plan that included a 50% refuge requirement and involved a host of other measures as well (Fitt 2004, Table 1 and p. 17):

1) Sliding cap on the proportion of national cotton acreage that could be planted to single-toxin (Cry1Ac) cotton, which increased in stages from just 8% in 1996/97 to a maximum of 30% in 2001/02;[13]
2) Refuge requirements stipulating that up to 50% of a Bt cotton farmer's fields be planted to non-Bt cotton;[14]
3) Defined planting window to avoid late planted cotton that could serve as host for *H. armigera* late in the season;
4) Mandatory cultivation of Bt cotton to destroy overwintering pupae of *H. armigera* and mandatory removal of volunteer Bt plants in subsequent seasons;
5) Three audits per year for each farm growing Bt cotton to check on compliance with refuges; among other requirements (Fitt 2004).

Australian regulators established this stringent IRM plan because, vis-a-vis the chief Australian cotton pest (*H. armigera*) "Inguard cotton varieties expressing a single Cry1Ac gene clearly do not express a high dose and heterozygote mortality is unlikely to be high except perhaps when plants are quite young..." (Fitt 2004). This mirrors precisely the situation EPA faced with MON863 and corn rootworm. While Australian regulators followed the science and have thus far succeeded admirably in forestalling resistance, EPA rejected the science in favor of entirely unfounded speculation about putative farmer non-compliance and thus set the stage for today's rapidly emerging CRW resistance.

As the reports of unexpected damage to Cry3Bb1 corn and hence the incidence of CRW resistance escalate, EPA has responded, incredibly, by sharply ***reducing*** the already inadequate 20% refuge requirement. EPA's rationales for doing so – refuge in a bag and pyramided Bt corn products – have no more scientific merit than its decision to set a 20% refuge.

Refuge in a bag (RIB) or blended refuge is a seed mixture in which the non-Bt seed[15] is mixed together with the Bt seed; the "refuge" is then comprised of the non-Bt corn plants

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year; and that constraining the minority of corn farmers with economic CRW infestations to plant half their fields to non-Cry3Bb1 corn would have been a reasonable requirement striking a scientifically sound balance between current benefits and long-term sustainability.

[13] Australian regulators worked with industry to orchestrate a planned transition from single-toxin Cry1Ac cotton to dual-toxin Bollgard II cotton, which took place in the 2003/04 season, the only season in which both single and dual-toxin varieties were planted. The national cap was eliminated at this time, though other IRM measures remained in effect.

[14] Refuge requirements varied by refuge crop and management practice. A refuge of 50% was required if the non-Bt cotton refuge was sprayed for CRW. Refugia could be smaller if unsprayed.

growing uniformly intermixed with the Bt plants. The other form of refuge is the block or structured refuge, where the non-Bt plants are planted together in a plot or plots adjacent to the Bt corn. EPA required block refugia for all Bt crop varieties until 2010, when it registered the first refuge in a bag product, Optimum AcreMax, which consisted of 90% Cry34/35Ab1 and 10% non-rootworm Bt corn (EPA 2010b). This 90:10 ratio for RIB represented half the refuge required for the same Cry34/35Ab1 corn in a structured context, where a 20% refuge is required.

Once again, EPA's decision was directly contrary to the recommendation of its expert advisors. A Scientific Advisory Panel convened to advise EPA on this very question was unequivocal: "The Panel generally agreed that data presented by Pioneer and data found in the public literature provide no compelling evidence to reduce the proportion of non-Bt plants (either as a seed blend or spatial refuge) from 20%...." (SAP 2009, p. 6). "[I]n fact, ***the Panel recommended that the proportion of non-Bt plants remain at 20% rather than be reduced to 10% as proposed by BPPD. The recommendation from a previous FIFRA Scientific Advisory Panel was for a 50% refuge.***" (SAP 2009, p. 21, emphasis added).

The experts on this Scientific Advisory Panel were not alone. Most agronomists and entomologists see refuge in a bag as a decidedly "mixed bag" that has some advantages over the traditional block refuge as well as some disadvantages. Thirteen agronomists who evaluated the issue found that "neither blocks nor mixtures are clearly superior" (Onstad et al 2011; see Table 1 from that paper, reproduced below), making it very unclear whether RIB justifies any reduction in refuge size at all. What is clear, however, is that any effect that RIB ***might*** have in delaying resistance should not be undercut by slashing the refuge size, given the continuing rapid emergence of CRW resistance throughout the U.S.

Pyramided Bt products incorporate two or more Bt toxins that act on the target pest(s) with differing modes of action, thereby reducing the likelihood of resistance evolving to either one. In 2009 and 2011, EPA registered Cry3Bb1 + Cry34/Cry35Ab1 corn and mCry3A + Cry34/Cry35Ab1 corn, respectively. For these products, EPA slashed the prevailing 20% refuge requirement for single-toxin Bt seed by 75%, from 20% to just 5% (Tabashnik & Gould 2012, Table 1).

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[15] As used here, "non-Bt seed" means seed that does not contain a rootworm-active Bt toxin; it may be either conventional seed or contain one or more Bt toxins targeting lepidopteran pests.

Table 1. Summary of IPM issues pertaining to choice of deployment of IRM refuges as seed mixtures or blocks

Issue	Seed mixture	Block
Pest monitoring	Difficult	Typical
Control of secondary pests	New approaches	Traditional
Biological control	New approaches	Traditional
Insecticide use	Less	More
Quality of refuge relative to Bt corn	Similar	Probably different
Effects on IRM of larval behavior	More risk	Less risk
Effects on IRM of adult behavior	Less risk	More risk
Adoption of PIP technology[a]	Higher	Lower
Compliance with IRM rules	Higher	Lower

[a] PIP, plant-incorporated pesticide.

Source: Onstad et al (2011).

Similar arguments apply here as to refuge in a bag (even though pyramids more clearly provide at least a modest resistance prevention boost versus RIB). With resistance to Cry3Bb1 on the rise due to a clearly inadequate 20% refuge, it was reckless of EPA to squander the resistance-fighting effects of the pyramid through a resistance-promoting reduction in refuge size. The first pyramid cited above acts as a single-toxin product for the large and growing number of CRW that are rapidly evolving resistance to Cry3Bb1 throughout the Corn Belt. In those resistance-ridden areas where this pyramid is most likely to be grown, there is next to no refuge corn (only 5%) to dilute the Cry34/35Ab1 resistance alleles that can be expected to rapidly accumulate in Cry3Bb1-resistant CRW. The expected result is rapid evolution of CRW resistant to both toxins.

The situation may be somewhat better for the second pyramid, but rather uncertain due to the close amino acid sequence similarity and likely cross-resistance between Cry3Bb1 and mCry3A. Only time will tell the magnitude of the cross-resistance risk. If it is small, then this pyramid has the potential to be more durable; if on the other hand resistance to Cry3Bb1 frequently confers resistance to mCry3A (and vice versa), then similarly to the first pyramid, an increasing number of CRW already resistant to the Cry3 toxins will experience intense selection pressure to evolve additional resistance to Cry34/35Ab1.

EPA's BPPD IRM team summarizes the situation well:

> "BPPD is concerned with these preliminary reports of cross-resistance between Cry3Bb1 and mCry3A and the planting of CRW pyramided corn expressing Cry3-Bt toxins in areas with Cry3Bb1 resistant corn rootworm populations. ***Such pyramids are effectively reduced to a single toxin product deployed with a much lower refuge (5%).*** There are currently four registered corn rootworm toxins, two of which (mCry3A and Cry3Bb1)

> would be ineffective in corn rootworm resistant areas. ***The selection pressure in these regions on the remaining toxin, Cry34/35, will be tremendous if deployed in a pyramid with Cry3Bb1 and a reduced refuge of 5%."*** (BPPD 2013c, p. 24, emphasis added)

It is also concerning that the Cry3Bb1 + Cry34/Cry35Ab1 pyramid (sold commercially as SmartStax) does not have anywhere near the lethality that one would expect if the two toxins acted independently. The predicted survival rate assuming independent action is just 0.145%; yet the observed survival rate is 12 times that, or 1.8%, ≥ 180 times the ≤0.01% survival rate that defines a high-dose event (Tabashnik & Gould 2012). The fact that the SmartStax pyramid delivers only a marginally higher dose than its constituent single-toxins, and is still a low-dose event, represents another argument against EPA's irresponsible reduction in refuge requirements to a miniscule 5%.

In light of these and similar considerations, two of the world's leading experts on Bt resistance, Drs. Bruce Tabashnik and Fred Gould, recently recommended that EPA establish a 50% refuge for all single-toxin Bt corn products, and a 20% refuge for pyramided products (Tabashnik & Gould 2012). These sensible recommendations – which logically propose that ***increasing*** CRW resistance be countered by ***strengthening*** IRM – is thoroughly at odds with EPA's inexplicable actions that dramatically ***weaken*** it. If short supplies of non-Bt seed make immediate establishment of these refugia requirements unworkable, increases in refuge percentage could be phased in over years to give seed firms time to multiply the needed seeds.

C. Declining Availability of High-Quality Conventional (Non-Bt) Corn Endangers IRM

The discussion above suggests that an adequate supply of high-quality, non-Bt corn seed is an indispensible element of any successful IRM plan. With a large majority of U.S. corn acreage planted to varieties with Bt toxins (76% in 2013),[16] refugia represent by far the biggest source of demand for non-Bt corn seed today. An indirect effect of EPA's reckless slashing of refuge requirements is a corresponding decline in demand for non-Bt corn seed, accompanied by a reduction in the diversity, quality and volume of non-Bt offerings. The paucity of non-Bt corn seed in turn undermines integrated pest management (IPM). Growers who would like to periodically grow conventional corn as part of their overall IPM strategy find it increasingly hard to do so. IRM is reduced to a dangerously narrow set of transgenic options: switching among different Bt modes of action or (more commonly) combining them in pyramids (Gray 2011).

Numerous agronomists have warned of these intertwined problems of declining availability of non-Bt seed and the demise of IPM. In a 2010 survey, University of Illinois

[16] Up sharply from 67% in 2012, likely reflecting the increased use of RIB with 5%-10% refuge requirements. See http://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-us.aspx#.Upyxd6VXaa4. Add figures for "insect-resistant" and "stacked" corn (stacked corn by definition includes traits for both herbicide- and insect-resistance).

entomologist Michael Gray found that fully 40% of Illinois corn farmers did not have access to elite varieties of non-Bt corn seed in 2009 (Gray 2011, Table 2). Onstad et al (2011) also find that the pool of nontransgenic corn hybrids is shrinking, giving growers fewer choices to eliminate selection pressure by growing conventional corn.

Twenty-two public sector corn entomologists, many with extension responsibilities and hence familiarity with the challenges farmers face, warned EPA that declining availability of high-yielding non-Bt corn varieties leads to prophylactic or entirely superfluous deployment of Bt toxins, and hence needless selection pressure for resistance. This in turn erodes an essential tool in the fight against further evolution of CRW resistance to Bt toxins:

> "Rootworm-protected Bt corn is being ***used prophylactically in areas with little or no need for it.*** This ***unwarranted use*** occurs in part because genes to produce rootworm Bt toxins (and toxins active against Lepidoptera) are incorporated into elite germplasm with the highest yield potential. Thus growers often have few options other than to plant stacks and pyramids if they wish to use the hybrids with best yield potential. When growers do not want to use Bt corn, many report increasing difficulty in obtaining non-transgenic seed. ***Scarcity of non-Bt seed may become more acute as the seed industry transitions to a refuge "in the bag" approach for resistance management.***
>
> ***Planting non-Bt corn can be profitable and should be one of the IPM tools to maintain susceptibility to rootworm-protected transgenic corn.*** After all, whether used in conjunction with soil-applied insecticides or not, conventional hybrids cause no selection for resistance to any Bt toxin. It is ironic that ***the decreasing availability of non-Bt hybrids erodes the ability of producers to move to a more integrated system of corn rootworm management, one that protects the value of Bt hybrids***. As a component of effective IPM for corn rootworms, attention should be given to increasing the supply of elite hybrids that do not contain Bt" (Porter et al 2012, emphasis added)

It is noteworthy that "refuge in a bag," an innovation that EPA has used to justify the refuge reductions (e.g. 20% block to 10% RIB for Cry34/35Ab1 corn) desired by industry, is cited by these corn entomologists as a prime driver of non-Bt corn scarcity, and hence superfluous selection pressure that accelerates CRW resistance to rootworm toxins. Gray (2011) makes a similar point.

Thus, EPA's unjustified reductions in refuge requirements exacerbate rootworm resistance in two ways: 1) Directly, by shrinking the pool of susceptible insects for dilution of resistance alleles; and 2) Indirectly, by reducing demand for non-Bt corn, which leads to declining availability and planting of non-Bt seeds that are urgently needed to lessen selection pressure for rootworm resistance to Bt toxins.

Monsanto wanted a 20% rather than a 50% refuge requirement because its makes more profit selling biotech vs. conventional seeds; and seeds with more vs. fewer traits. Related to this, the 20% refuge requirement matched the existing one for Bt corn targeting lepidopteran pests. Having the same refuge requirements for rootworm and lepidopteran Bt corn greatly facilitated Monsanto's profit-driven "biotech trait penetration" strategy of combining both Bt traits in the great majority of their corn varieties, and sharply reducing single Bt offerings of either sort. This trend is reflected in Monsanto's biotechnology trait acreage figures, which show that U.S. acreage planted to Monsanto single-Bt corn (of either sort) peaked at 34 million acres in 2004, declining to 7.9 million acres by 2009; while plantings of Bt corn targeting both CRW and lepidopteran pests increased from 0 to 31.3 million acres over the same period (Monsanto 2009).

If EPA had followed the science and established a 50% refuge requirement, it would not only have dramatically slowed evolution of resistance. It would have had the additional beneficial effects of encouraging Monsanto (and other seed firms) to offer more conventional and/or more single-toxin-Bt corn lines.[17] This increased diversity of seed offerings would have better met farmers' needs and reduced the "unwarranted use" of Bt toxins mentioned above by farmers who are presently constrained to buy them even though they have no agronomic need for them.

Industry and EPA often place the blame for resistance on farmers for not always complying with refuge requirements. The analysis presented above suggests that seed firms are as or more culpable. Farmer non-compliance with refuge requirements is at least partly attributable to the dearth of locally adapted, high-yielding conventional (non-Bt) varieties on offer.[18]

D. Increasing Corn Monoculture

U.S. corn acreage has increased a substantial 31% since 1990, to a near historical high of 96.9 million acres in 2012. The 19% increase in corn acreage since the year 2005 in particular is attributable largely to ethanol demand, which has driven up corn prices and made corn more profitable to grow than most other crops. The portion of U.S. corn production utilized for ethanol rose from just 14% in 2005 to roughly 40% in 2012. This rise in overall corn acreage has meant more acres planted to corn continuously, year after year.

A recent assessment that utilized satellite imagery to determine cropping patterns in the central U.S. found that corn monoculture has increased sharply over the past decade (Plourde et al 2013). From 2003 to 2010, the land area planted to corn two years in a row increased by 22%. Still more striking, the amount of corn in quadruple planting (four years of corn in a row) doubled – from 4% to 8% of total corn acres – from the first half of the period 2003-2006 to the second half of the 2007-2010 time period.

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[17] Especially single-toxin Bt for lepidopteran pests, since these could be used to meet the 50% refuge requirement and would be more profitable than conventional lines.

[18] A related reason for non-compliance has been farmer anticipation of refuge-in-a-bag, which led many to believe that structured refuge requirements (and hence compliance with them) were of little importance, since soon to be replaced by RIB (Gray 2011).

Cultivation of corn continuously on the same fields over years is associated with several adverse impacts relative to corn grown in rotation (e.g. with soybeans): lower yield; higher per acre fertilizer use in an attempt to compensate for reduced yield; greater disease pressure; corn rootworm infestations; and, if the corn expresses a rootworm-active Bt toxin, accelerated evolution of resistance.

Nearly all reports of Cry3Bb1-resistant CRW have been in fields planted continuously to Cry3Bb1-producing corn. For instance, the first published paper on resistant CRW (collected in 2009) noted that all fields harboring them had been planted to Cry3Bb1 corn for at least three consecutive years:

> "In all cases, fields experiencing severe rootworm feeding contained Cry3Bb1 maize. Interviews with farmers indicated that Cry3Bb1 maize had been grown in those fields for at least three consecutive years. There was a significant positive correlation between the number of years Cry3Bb1 maize had been grown in a field and the survival of rootworm populations on Cry3Bb1 maize in bioassays." (Gassmann et al 2011)

The same team found that 2010 CRW populations determined to be resistant "came from fields with a history of continuous maize production and between 3 and 7 years of Cry3Bb1 maize cultivation" (Gassmann et al 2012).

While continuous corn is nothing new, it has always represented a minority of corn acres. Most farmers have been reluctant to plant corn in successive years because of the heightened risk of rootworm infestations and the other problems mentioned above: reduced yield, greater fertilizer use, and disease issues. Bt corn targeting corn rootworm has been a major factor in eroding that reluctance, and thus an important factor facilitating the rise of corn-on-corn discussed above.[19] Understanding this dynamic, seed firms have actively promoted Bt corn for this use.

According to Wyffels Seed Company:

> "With the advent of seed technology that puts rootworm protection in the plant, growing corn-on-corn has become much easier. Selecting hybrids with Agrisure® 3000GT, Herculex® XTRA, Genuity® SmartStax®, Genuity® VT Triple PRO® or YieldGard VT Triple® technologies is a great way to go."[20] (Wyffels Hybrids undated)

Monsanto goes so far as to offer farmers "Corn-On-Corn Clinics," which it describes as follows:

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[19] While ethanol is ***driving*** the demand for more corn and hence more continuous corn by driving up corn prices, some and perhaps many farmers who did in fact transition to "corn-on-corn" would not have done so because of the associated risk of major losses from CRW infestations if they had not had access to a tool (Bt corn for rootworm) that for a time at least prevented those losses.

[20] http://www.wyffels.com/agronomy/continuous-corn/, last visited 12/3/13.

> "The Corn-On-Corn Clinics are a series of events across the country featuring a panel of industry experts, academics and local growers speaking on a variety of corn topics, including fertility management, insect management, disease management and residue management. ***Control pests in your corn-on-corn acres with the help of Genuity® SmartStax® RIB Complete™" corn blend."*** (emphasis added)[21]

Monsanto understands that most growers have reservations about continuous corn. Those reservations are eroded by holding "clinics" in which experts from Monsanto and academia persuade these farmers that with proper "scientific" management, corn-on-corn can be good or at least acceptable agronomic practice, when of course there are few practices more agronomically or environmentally detrimental.[22] The chief facilitator of continuous corn is Bt seed – in this case, SmartStax, which is Monsanto's most expensive and profitable product. Monsanto even entices farmers to attend its "Corn-On-Corn Clinics" by offering attendees the chance at a $500 gift card.

Interestingly, Monsanto's 2012 "corn-on-corn clinics" were all held in areas where CRW resistance to Monsanto's Cry3Bb1 is prevalent (see map on next page), and thus where SmartStax often acts as a single-toxin product with a paltry 5% refuge. There is no better recipe for rapid evolution of resistance to the sole Bt toxin that (at present) remains largely uncompromised (Cry34/35Ab1).

[21] http://www.genuity.com/corn/Pages/Corn-on-Corn-Clinics.aspx, last visited 12/3/13.

[22] Aside from fostering CRW, increased acreage planted to continuous corn is likely a major factor in the record rates of inorganic nitrogen fertilizer applied to corn, since as noted above N use is normally boosted in continuous corn to compensate for reduced yield relative to corn in a corn/soybean rotation. In 2010, the last year for which USDA data are available, an average of 140 lbs./acre of nitrogen fertilizer were applied to corn, the highest rate since 1964 (although matched in 1985). See "Table 10. Nitrogen used on corn, rate per fertilized acre receiving nitrogen, selected States," accessible from: http://www.ers.usda.gov/data-products/fertilizer-use-and-price.aspx#.Up40LqVXaa4.n. Corn is by far the biggest N using crop, and N runoff generates dead zones in coastal waters while N fertilizer also contributes substantially to global warming through conversion to nitrous oxides, potent greenhouse gases.

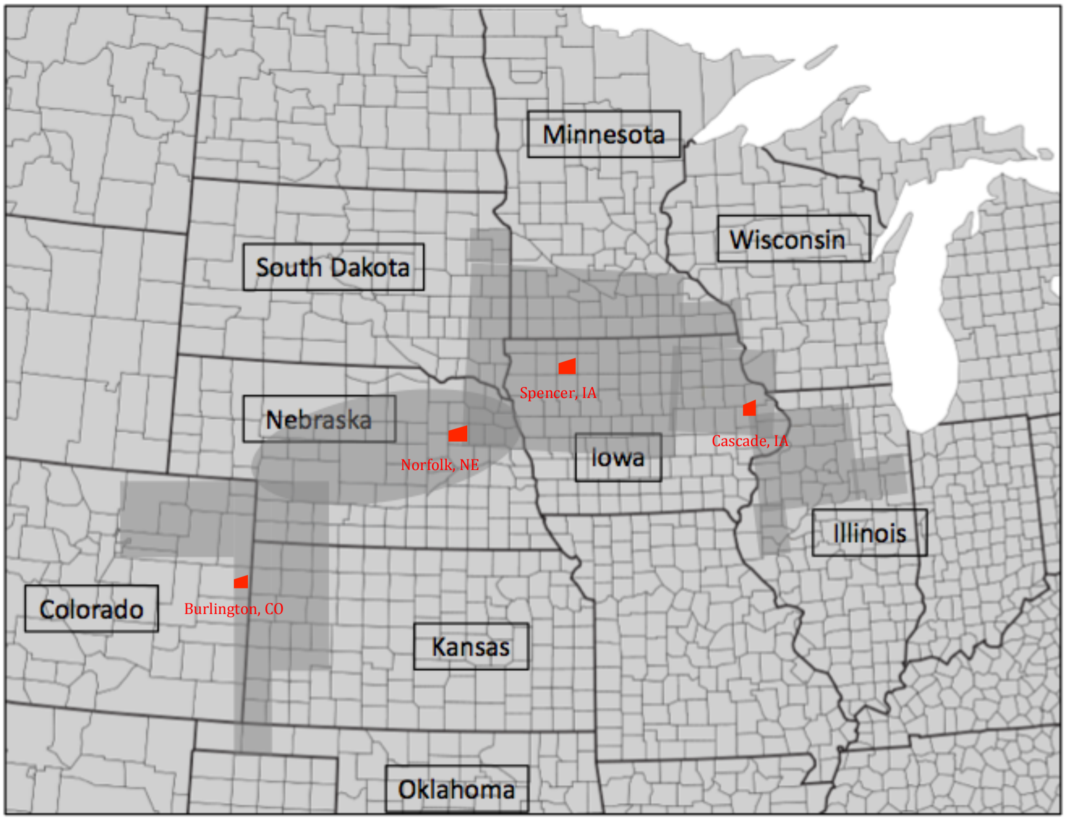

Figure 5. 2013 Updated map showing the general areas in the US Corn Belt that have had Cry3Bb1 fields with heavy damage and/or resistant western corn rootworm populations (2009-2012). Map excerpted from BPPD (2013c). CFS has amended EPA's map to show (in red) towns in which Monsanto gave "corn-on-corn clinics" in the summer of 2012. See http://www.genuity.com/corn/Pages/Corn-on-Corn-Clinics.aspx.

E. Volunteer Herbicide-Resistant Corn

Volunteers are crop plants that sprout from unharvested seed to infest the following season's crop grown on the same field. Harvesting equipment always leaves some proportion of the crop seed in the field. For instance, storms and plant disease often cause corn plants to topple, leading to ears of corn on or near the ground that are then missed by harvesters. Some proportion of this seed will find conducive conditions to sprout, so some level of volunteer presence is an inescapable fact of farming. Corn volunteers can be a troublesome weed in the following season's crop, especially soybeans, dry beans, sugar beets and subsequent corn crops (Bernards et al, 2010; Davis, 2009; Johnson et al, 2010; Stewart, 2011). Two to four volunteer corn plants per square meter can reduce yields in soybeans by 20% (Morrison 2012).

Volunteer corn not only reduces yields, it can act as a host plant for corn rootworm in years when corn is not grown. In the common corn/soybean rotation, volunteer corn provides a bridge for rootworm populations to persist in the soybean years. If the volunteer corn is Bt for CRW, it could also accelerate the evolution of resistance, especially when stacked with an herbicide resistance trait.

Krupke et al (2009) examined volunteers of stacked glyphosate-resistant/insect-resistant corn emerging in follow-on glyphosate-resistant soybeans. They found that 65% of the volunteers tested positive for Cry3Bb1, and that 60% tested positive for both glyphosate-resistance and Cry3Bb1. Surprisingly, Cry3Bb1-positive corn volunteers exhibited the same degree of root damage from larval rootworm feeding as volunteers that tested negative for the Cry3Bb1. They hypothesized that these volunteers produce lower, non-lethal levels of Cry3Bb1 due to deficient nitrogen in soybean fields that are not amended with this nutrient (as corn fields are). Whatever the reason, exposure of corn rootworm to low levels of Cry3Bb1 in corn volunteers has likely accelerated evolution of resistance and helped undermine insect resistance management efforts.

Corn volunteers have become an increasingly problematic weed in their research area (Indiana) and throughout the Corn Belt because glyphosate-only weed control programs with Roundup Ready soybeans fail to control glyphosate-resistant/Bt corn volunteers in common soy/corn rotations. Krupke et al conclude that "weedy volunteer corn plants stacked with GR [glyphosate-resistance] and Bt traits may accelerate the development of Bt-resistant WCR [western corn rootworm] populations, circumventing the current [Bt insect-resistance] management plans." In continuous GR/Bt corn managed with glyphosate, GR/Bt corn volunteers producing lower, resistance-promoting levels of rootworm toxin would be still more likely to escape control than in soybeans, since harder to distinguish as volunteers in a field of corn.

In 2013, only 5% of U.S. corn acres were Bt only, versus 71% stacked with both Bt and herbicide resistance,[23] giving a sense of the scope of this problem. And the CRW resistance risks posed by volunteer corn will only increase with the introduction of multiple herbicide-resistant/Bt corn varieties that are still more difficult to control than those with the Roundup Ready trait alone. Already, SmartStax corn volunteers (which incorporate both glyphosate and glufosinate resistance) have been noted as more problematic weeds than GR corn volunteers, especially in corn-on-corn rotations (Brooks 2012, Morrison 2012). Recommended control practices for such dual-HR corn volunteers are a pre-emergence application of a paraquat-atrazine mixture, or post-emergence use of inter-row cultivation (USDA APHIS 2013, p. 37). Neither paraquat (applied to just 1% of corn acres in 2010[24]) nor inter-row cultivation are used much in corn; thus many growers would likely leave such volunteers uncontrolled.

Dow AgrosSciences is awaiting deregulation of GE corn resistant to 2,4-D and "fops" grass herbicides, which would be stacked with glyphosate-resistance.[25] Monsanto is developing

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[23] See http://www.ers.usda.gov/data-products/fertilizer-use-and-price.aspx#.Up40LqVXaa4.
[24] USDA National Agricultural Statistics Service data, accessible at http://www.nass.usda.gov/Data_and_Statistics/Pre-Defined_Queries/2010_Corn_Upland_Cotton_Fall_Potatoes/index.asp.
[25] Dow's corn is engineered to produce an aryloxyalkanoate dioxygenase-1 enzyme (AAD-1) that confers high-level resistance to both phenoxy auxin herbicides like 2,4-D as well as the aryloxyphenoxyproprionate

corn resistant to the herbicides dicamba, glufosinate and glyphosate, as well as "FOPS-Tolerant corn" that would also be resistant to glyphosate.[26] "Fops" herbicides like quizalofop are often used to kill volunteer corn in soybeans; that option would be eliminated with these new multi-herbicide-resistant crops. Big Biotech firms frequently cross-license their traits, which could easily lead to corn, and hence volunteer corn, with resistance to four or more different classes of herbicide. For example, USDA recently deregulated a DuPont-Pioneer GE corn with dual resistance to glyphosate and glufosinate. DuPont-Pioneer suggested it might be combined with Dow's 2,4-D and "fops" resistance for quad-resistant corn (DuPont-Pioneer 2012, pp. 78-79). A patent awarded to DuPont envisions corn and other crops resistant to seven or more different classes of herbicide (DuPont-Pioneer 2009, par. 33).

Volunteer corn control options diminish as the number of herbicide-resistance traits rises. Corn volunteers with multiple resistance to glyphosate, glufosinate, dicamba, "fops" and/or other herbicides would be more likely to survive, and if stacked with rootworm Bt, select for CRW resistance to the Bt toxin. While Krupke's work involved Bt corn expressing Monsanto's Cry3Bb1, it is quite possible volunteers of other HR/Bt corn types would express similarly low levels of rootworm toxin and also foster resistance.

III. Conclusion

EPA is rightly proud of the mandatory insect resistance management plans it established for cultivation of Bt crops targeting lepidopteran pests. The Agency heeded the warnings and recommendations of independent entomologists, and prevailed over considerable opposition from industry. IRM for Bt crops represented the first time, to our knowledge, that EPA imposed constraints on the use of a class of less harmful pesticides to preserve their efficacy and so forestall the use of more toxic pesticides that would ensue in the event that resistance to the former emerges. Because IRM for this class of Bt crops has been scientifically sound, it has succeeded in largely forestalling any significant resistance in above-ground pests.

In contrast, EPA's IRM for rootworm Bt has been thoroughly ineffective. CFS sees several reasons for EPA's failure.

The IRM concepts and modeling that EPA and entomologists developed for lepidopteran Bt are in many respects inapplicable to rootworm Bt, yet EPA appears unwilling to fully accept the implications. Lepidopteran Bt corn delivers a high dose to kill over 99.99% of pests that exhibit recessive, high-level resistance to Bt toxins. Corn rootworm Bt delivers a low dose to kill a relatively low percentage of pests that exhibit non-recessive, lower-level

("fops") class of ACCase inhibitor herbicides, such as quizalofop and cyhaolfop. For more on this crop, see CFS comments to EPA at http://www.centerforfoodsafety.org/files/cfs-24-d-comments-to-epa-final-6-22-12.pdf. Dow's corn is pending deregulation (approval for commercial cultivation) by USDA. See petition 09-233-01p at http://www.aphis.usda.gov/biotechnology/petitions_table_pending.shtml

[26] See http://www.monsanto.com/products/Pages/corn-pipeline.aspx, last visited 12/3/13.

resistance to Bt toxins. While the difference between resistance and susceptibility to Bt toxins is a "bright line" in European corn borer, the distinction is muddier for CRW. Industry has exploited the less clear-cut nature of Bt resistance in CRW to deny the obvious fact that it has developed (Philpott 2011), and so avoid serious remedial actions that might involve reduced sales of its products.

EPA must adopt a more expansive definition of resistance that aims foremost at reducing the current high rate of false negative resistance assessments that are in large part responsible for emerging resistance. The definition must include "partially resistant" CRW. We remind EPA that with its current IRM plans, it has failed to stem resistance; and so failed to fulfill its statutory mandate of preventing the unreasonable adverse effects on the environment that are caused by sharply increased use of organophosphate insecticides to kill Bt-resistant CRW.

EPA's failure is due in large part to undue reliance on industry. In contrast to its formulation of IRM plans for lepidopteran Bt corn, EPA has consistently privileged industry assessments and views over independent science in developing IRM for corn rootworm. As noted above, on at least two occasions EPA has explicitly rejected the recommendations of Scientific Advisory Panels (SAP 2002, SAP 2009) and instead allowed itself to be led by faulty industry assessments biased by self interest (in setting deficient refuge requirements). EPA has also flaccidly accepted industry's "blame-the-farmer" excuses for resistance. EPA made a major regulatory blunder (20% refuge for Cry3Bb1 corn) based in part on industry-inspired speculation that farmers wouldn't comply with a 50% refuge, and like industry has often used putative farmer "non-compliance" as an excuse for rejecting scientific IRM in favor of expedient but ineffective IRM plans.

EPA must fully comprehend that seed firms have not been good-faith partners in IRM efforts, and act accordingly. Since effective IRM must involve reducing selection pressure, which entails reduced product deployment, sales and hence profits, industry's financial self-interest is directly opposed to IRM. This self-interest skews industry science, making it unreliable as the basis for regulatory decision-making. This is demonstrated by the bottom line measure of rapidly emerging resistance that has occurred with use of industry-fashioned IRM plans. One may also refer to the lengthy critique of Lefko et al (2008) – a study by DuPont-Pioneer scientists that formed the basis of DuPont's request for, and EPA's grant of, reduced refuge requirements for an RIB version of Cry34/35Ab1 corn – by independent scientists in SAP (2009). Neither have seed firms proven reliable in terms of IRM practice, as evidenced by the many deficiencies in Monsanto' resistance monitoring (BPPD 2011). EPA should return to its former course of accepting and following the recommendations of its independent experts.

Bt corn developers have consistently opposed and weakened resistance ***prevention*** efforts, but have understandably proven much more willing to engage in profitable forms of resistance ***management***. For instance, Monsanto prevailed upon EPA to set a thoroughly inadequate 20% refuge for MON863, substantially accelerating evolution of Cry3Bb1 resistance in CRW. Now that resistance has emerged, Monsanto is eagerly exploiting it as an opportunity to market SmartStax corn, particularly as a tool to facilitate the resistance-promoting and generally detrimental agronomic practice of corn-on-corn; continuous SmartStax corn, however, will accelerate the evolution of additional resistance (to Cry34/35Ab1). While eager to promote these profitable forms of short-term resistance management, industry makes less profitable but more effective tactics (e.g. periodic use of non-Bt corn) much more difficult for farmers to implement by slashing their offerings of high-quality conventional corn seed. Resistance ***prevention*** must take center stage as EPA moves to reform IRM.

None of this is inevitable. While biotech-seed firms (like most others) will normally act to maximize their financial self-interest, it is not inconceivable that they might pursue more responsible paths that sacrifice some profit if prodded by proactive regulators. In this context, seed firms should implement a mandatory resistance management plan for all low-dose rootworm-active Bt corn events (which includes today's pyramids) as part of the technology use agreement that farmers sign upon seed purchase. The IRM plan would require that farmers grow the Bt corn in rotation with another crop (e.g. soybeans) or with non-Bt corn. The Bt corn would have to be rotated every other year, or perhaps (to permit greater flexibility) planted no more than two years of every four. Seed firms should also drop their efforts to zero out refuge requirements, and scale up production of high-quality conventional seeds.

There is precedent for such an approach. As part of its stewardship program for its herbicide-resistant, Clearfield wheat, BASF requires that growers abstain from growing it, and from applying the associated herbicides (imidazolinones), more than two of every four years (OSU 2010). The goal is to deter the emergence of resistant weeds and so prolong the effective life of the herbicide-resistance trait through restraints on its use[27] – precisely analogous to the purpose of IRM for Bt crops.

There is also precedent for a proactive regulatory stance by EPA. One model is the comprehensive IRM program for Bt cotton that was successfully implemented by Australian regulators in collaboration with industry. With more respect for science and law, and the requisite political will, EPA could even now redress the huge deficiencies in its IRM program. If decisive action is not taken soon, however, EPA and industry will have squandered the valuable resource of rootworm-active Bt toxins.

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[27] This example should not be misconstrued as CFS endorsement of Clearfield wheat, only the concept of reducing selection pressure for resistance through restraints on use. CFS opposes herbicide-resistant crops (however they are developed, via genetic engineering, mutagenesis or conventional breeding) because they foster greater use of and dependence on often harmful pesticides, and increase selection pressure for resistant weeds. In the case of Clearfield wheat, one clear harm of the associated class of herbicides (imidazolinones) is an increased risk of bladder and colon cancer in farmers exposed to them (Koutros et al 2009).

IV. Recommendations

1) Establish a simple, single-criterion definition of resistance along the lines discussed above (comments on Question 4) that reduces as much as possible the potential for false negative resistance assessments

2) Increase refuge requirements for all rootworm-active Bt corn events as recommended by Tabashnik & Gould (2012) – 50% for single-toxin Bt corn and 20% for pyramids – with phase-in as needed allow for seed firms to multiply sufficient quantities of needed seeds

3) Mandatory IRM involving rotation ***away*** from rootworm Bt corn

4) EPA should increase the role of independent scientists and reduce that of seed firms in every aspect of IRM – for instance, resistance monitoring, diagnostic assays, definition of resistance, and setting of refuge size requirements – in light of seed firms' failure to successfully detect and notify EPA of the emergence of resistant CRW.

5) EPA should make publically available the resistance monitoring data reported to it by industry, and/or provide complete and standardized descriptions of it in relevant documents released to the public, in particular the number of unexpected damage/resistance reports broken down by state and county.

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