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September 21, 2009

Office of Pesticide Programs
OPP Regulatory Public Docket (7502P)
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

RE: Registration Review; Glyphosate Docket Opened for Review and Comment.
Docket Number: EPA–HQ–OPP–2009–0361

To Whom It May Concern:

The Center for Food Safety appreciates the opportunity to submit comments re: the docket listed above.

I. Introduction

The purpose of the registration review program is to assess the risks that pesticides pose to human health and the environment in the light of new scientific information, enhanced ability to detect risks, changes in pesticide policy, and alterations in pesticide usage practices.

Since the EPA last reregistered glyphosate in 1993, there have been profound changes in the usage patterns of this pesticide. Overall and agricultural use of numerous glyphosate formulations has grown tremendously; the advent of transgenic glyphosate-resistant crops has permitted previously infeasible "over-the-top" application, raising novel food, feed, environmental and agronomic concerns; the unprecedented degree of reliance on this single weed control chemical in conjuction with the glyphosate-resistant crop system has fostered an epidemic of resistant weeds; animal and human exposure to glyphosate residues has increased sharply with a spate of new registrations as well as new and often greatly increased tolerances; and finally, rising use of glyphosate correlates to some degree with profound alterations in farming practices, in particular increasing use of conservation tillage/no-till.

The strong and still growing dependence of U.S. and world farmers on glyphosate is no doubt one important factor driving intense scientific study of this chemical. This scientific study has revealed much new evidence that glyphosate and its formulations (especially those with the surfactant POEA) poses serious risks to human health and the environment, including the agricultural environment. We note that in general, any risks posed by a particular pesticide will be amplified and exacerbated with increasing use, and that it is only rational to take full account of this factor in risk assessments. On the policy front, EPA has played an important role in facilitating increased glyphosate use by issuing new registrations and new and increased tolerances, and by failing to establish resistance management regulations or even guidelines to stem the epidemic of glyphosate-resistant weeds.

In these comments, we will first describe the profound changes in glyphosate use patterns, including a prospective assessment of further changes to be expected in the near future. We will then describe new evidence of ecological/agronomic risks and human health risks.

II. Glyphosate Usage Trends: Past and Prospective

The EPA rightly emphasizes the importance of assessing changes in the usage patterns of a pesticide in its registration review (Summary Document, p. 4). Though the Agency does not explain why this is important, the rationale should be clear. A pesticide with adverse effects will obviously have adverse impacts that correlate with its use – greater and more widespread usage means greater impacts. Thus, a highly toxic pesticide that is very little used may well have much less overall adverse impact than a heavily-used pesticide that is less toxic. It is equally clear that suggestive evidence of harm from a pesticide (i.e. not fully confirmed) should be given greater weight in the risk assessment process in rough proportion to the prevalence and level of use of that pesticide. The history of pesticides, drugs and other chemicals is filled with examples of hazardous substances whose widespread use was allowed to continue for decades in the face of strong suggestive evidence of harm that was eventually confirmed, resulting in massive human suffering and ecological degradation that could have been avoided had appropriate restrictions been enacted before definitive conclusions were reached. Dioxin-containing pesticides and other chemicals, indiscriminate use of DDT, PCBs, and lead in paint and gasoline are a few of many such examples.

Yet surprisingly, none of the Agency's review documents in Docket EPA-HQ-OPP-2009-0361 makes any reference to changes in the usage of glyphosate over the past 15 years, much less gives a prospective assessment of future trends. This is especially concerning in light of the accumulating evidence of the adverse impacts of glyphosate and its formulations, and the fact that over this period, ***glyphosate has become by far the most widely used pesticide in the history of agriculture***. This is a serious failing in the Agency's work plan that we hope will be remedied as the registration review proceeds.

We begin by describing the reasons for and the magnitude of the explosive growth in glyphosate's use. Glyphosate was first registered in 1974. By 1987, its agricultural usage was still limited mainly to orchards, and with an estimated 6 to 8 million lbs. active ingredient ranked just 17th among pesticides in terms of quantity applied for U.S. agricultural crop production (see Figure 1). Three major developments in agriculture have expanded its use.

1) Glyphosate for Burndown Use

First, increasing adoption of conservation tillage/no-till cultivation practices in major field crops, especially in soybeans, drove greatly increased applications of glyphosate for burndown use in the late 1980s and the 1990s. In no-till cultivation, crops are killed chemically (burnt down) at the end of the season, and the following year's seeds are drilled through crop stubble, rather than the traditional plowing under of crop residues. Glyphosate quickly became the herbicide of choice for such applications, facilitating its rapid adoption in field crop cultivation. This is the main factor driving the four- to six-fold increase in agricultural use of glyphosate from 1987 (6 to 8 million lbs.) to 1997 (34 to 38 million lbs.) (Figure 1).

2) Glyphosate Use with Glyphosate-Resistant Crops

a) *Roundup Ready Soybeans and Cotton*

The second major factor driving increased glyphosate use has been the widespread adoption of transgenic, glyphosate-resistant soybeans, cotton, and corn by farmers beginning in 1996, 1997 and 1998, respectively. While glyphosate had previously been restricted mainly to orchard use and burndown applications in field crops, glyphosate-resistance facilitated "over-the-top" or in-field application of this broad-spectrum herbicide that had previously been infeasible. Glyphosate-resistant (GR) varieties of soybeans and cotton were rapidly adopted, rising to comprise 75% of the soybean acres (USDA NASS figure) and 72%[1] of the cotton acres planted in 2002. Figure 2 shows that Roundup Ready (RR) crops, planted on just 1.2 million acres in 1996 (all RR soybeans), covered a massive 78.7 million acres just six years later in 2002 (Figure 2).[2] This huge growth in RR crop acreage coincides with, and was undoubtedly the chief factor driving, a substantial acceleration in the growth rate of glyphosate use. In the decade from 1987 to 1997 (largely prior to the advent of RR crops), agricultural glyphosate use rose by an average of 2.9 million lbs. a.i. per year. In the four years from 1997 to 2001, the average annual growth rate had more than quadrupled, to 12.9 million lbs. per year (i.e. 36 to 87.5 million lbs.).[3] Figures 1 and 2 illustrate clearly that glyphosate use associated with RR soybeans is the most important factor driving the overall increase in agricultural glyphosate use during this period. Thus, it is no surprise to find EPA figures showing that by 2001, glyphosate had surpassed atrazine to become the most heavily used agricultural pesticide in the nation (EPA 2004, Table 3.6).

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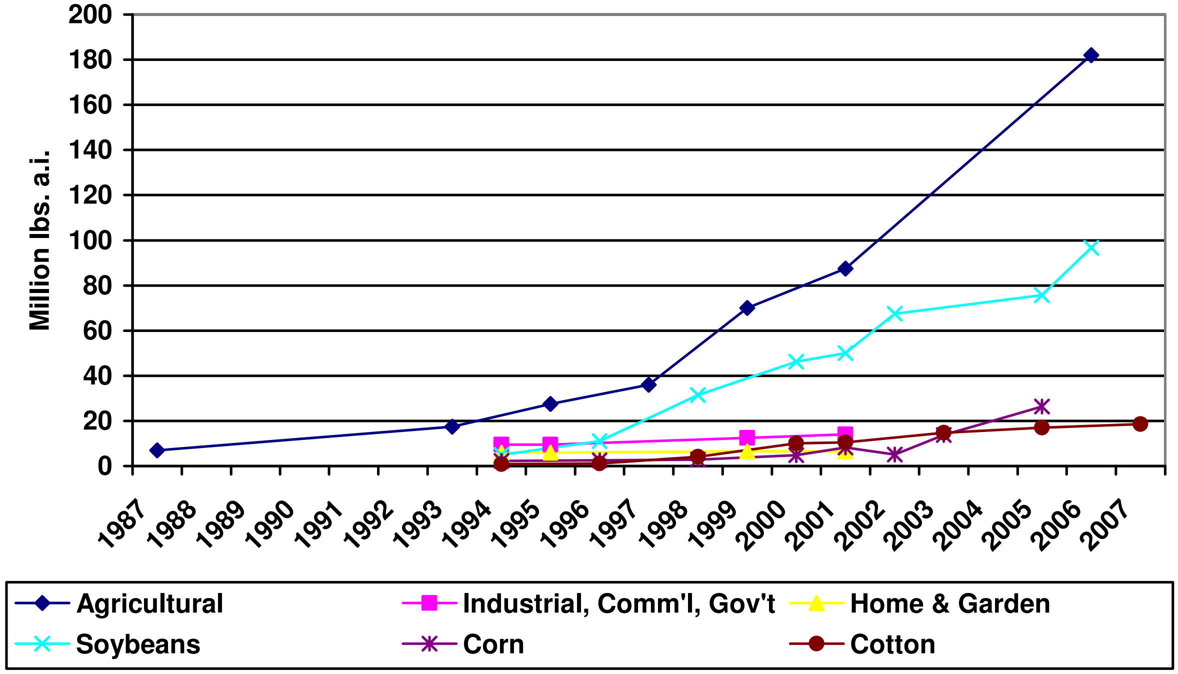
[1] May, O.L., F.M. Bourland and R.L. Nichols (2003). "Challenges in Testing Transgenic and Nontransgenic Cotton Cultivars," *Crop Science* 43: 1594-1601, Table 1. http://crop.scijournals.org/cgi/reprint/43/5/1594.pdf. Note that May et al cite USDA AMS figures for cotton that are more reliable than USDA NASS re: GE crop adoption.

[2] Based on Monsanto's figures. The breakdown is RR soybeans (60 million acres), RR cotton (10 million), RR corn (7.8 million) and RR canola (0.9 million). Since canola is a relatively minor crop for which consistent data are lacking re: glyphosate use, we exclude it from the subsequent discussion.

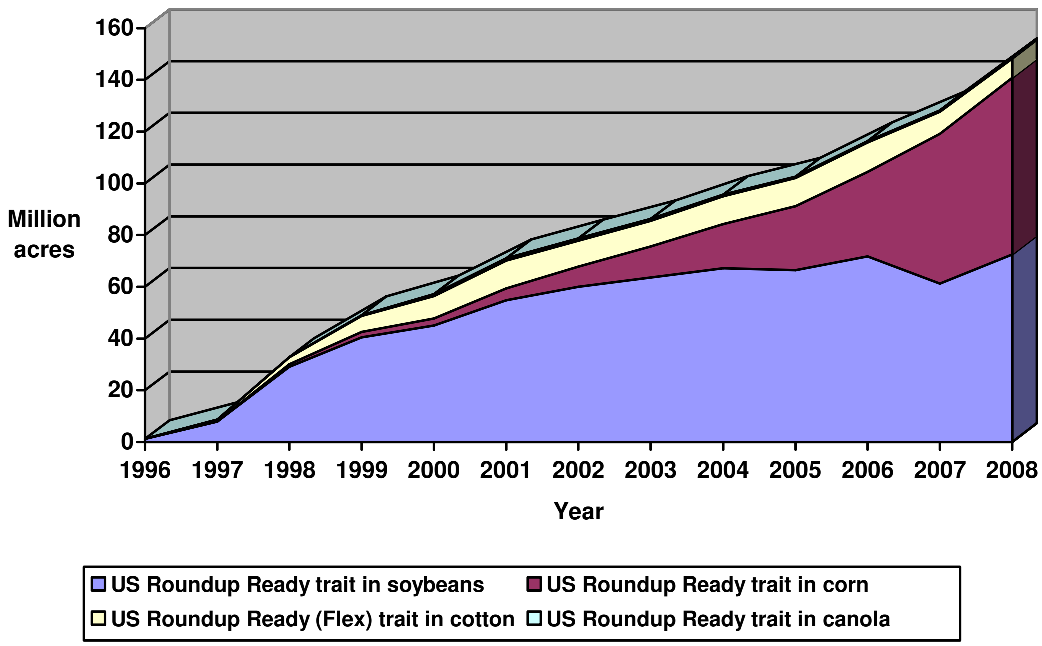
[3] Note that EPA figures for glyphosate use are given in ranges: e.g. 34 to 38 million lbs. (1997) and 85 to 90 million lbs. (2001). We have used the midpoint of these ranges for simplicity's sake.

Figure 1: Use of Glyphosate in the U.S. by Category and Field Crop: 1987 to 2005-2007



EPA figures 1987 to 1995 from EPA (1997). "Pesticides Industry Sales and Usage: 1994 and 1995 Market Estimates," EPA, August 1997, Tables 8 & 9; EPA figures 1997, 1999 & 2001 from EPA (2004). "Pesticides Industry Sales and Usage: 2000 and 2001 Market Estimates," EPA, May 2004, Tables 3.6 to 3.8. Each data point is the midpoint of the range (e.g. 27.5 for 25-30 million) given in EPA (1997) and EPA (2004). EPA figure for 2006 derived from EPA (2009). "Glyphosate Summary Document Registration Review: Initial Docket," June 2009, p. 12, which states that 135 million lbs. glyphosate acid equivalents are applied annually to agricultural crops, based on data from Screening Level Estimates of Agricultural Uses of the Case Glyphosate, 11/26/08. Acid equivalents converted to the most common salt of glyphosate (isopropylamine) using 0.74 conversion factor to arrive at the equivalent figure for the isopropylamine salt of glyphosate (182 million lbs.) to facilitate comparison to prior years. EPA leaves unclear in which year this estimated 135 a.e./182 a.i. million lbs. of glyphosate were applied. Comparison of EPA's figures for soybeans, corn and cotton in the Screening Level Estimates with the latest available from USDA NASS for soybeans (2006), corn (2005) and cotton (2007) suggests that EPA relied primarily on these USDA NASS data. We choose 2006 as the midpoint of this three year (2005-2007) range, and because soybeans, surveyed in 2006, receive the most glyphosate. See text for explanation as to why this figure likely underestimates actual glyphosate use, which CFS estimates at 210-220 million lbs. a.i. (iso.). Glyphosate use figures for soybeans, corn and cotton derived from USDA NASS Agricultural Chemical Usage reports for respective years, adjusted to reflect usage on 100% of crop acreage.

Figure 2: U.S. Acreage Planted to Crops with Roundup Ready Trait: 1996 to 2008



Source: Monsanto Biotechnology Trait Acreage: 1996-2008, Oct. 8, 2008.

b) Roundup Ready Corn

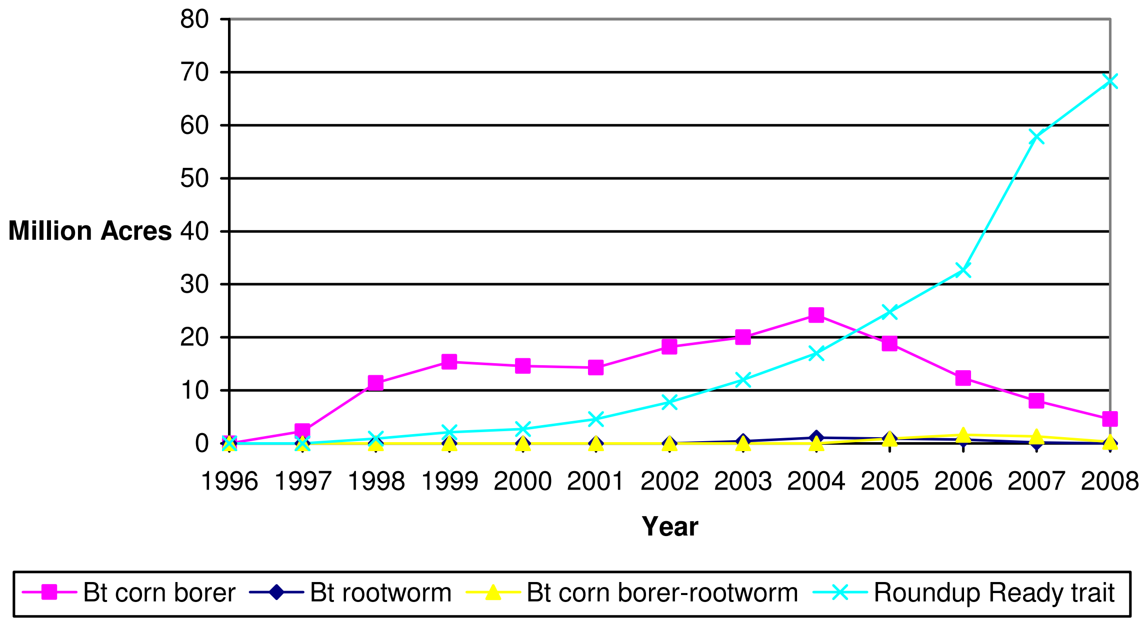
Despite this extremely rapid and accelerated rise in glyphosate use from 1997 to 2001, the years ***since*** 2001 have seen not only continued growth, but ***a substantial acceleration in the rate at which agricultural glyphosate use has increased***. Based on EPA's figures, agricultural use of glyphosate rose from 87.5 million lbs. in 2001 to 182 million lbs. by 2006,[4] an average annual growth rate of 18.9 million lbs. over this period (Figure 1). The major factors driving this accelerated use are glyphosate usage associated with increasing adoption of Roundup Ready corn, and the rapid emergence of weeds tolerant or resistant to glyphosate.

Figure 3 shows that adoption of RR corn was relatively slow through 2002, but has accelerated ever more rapidly since that time through 2007, with a slightly less pronounced increase from 2007 to 2008. The 68.3 million acres planted to corn containing the Roundup Ready trait in 2008 represents nearly a nine-fold increase over the 7.8 million RR trait-containing acres in 2002, and a more than 3-fold increase over the 24.8 million acres of RR corn in 2005. This huge increase in RR corn acres has been accompanied by a corresponding rise in glyphosate use. For instance, USDA NASS data show a more than five-fold increase

[4] For conversion of 135 million lbs. glyphosate a.e. to 182 million lbs a.i. (isopropylamine salt), see caption to Figure 1. As explained further below, we believe this 182 million lbs. a.i. figure is a substantial underestimate attributable to a large underestimate of glyphosate use on corn.

in glyphosate use on all U.S. corn from 2002 (5.1 million lbs.) to 2005 (26.3 million lbs.). It is interesting to note that glyphosate use on corn rose considerably faster (five-fold) than RR corn acres (3-fold) from 2002 to 2005.

Figure 3: Area in U.S. Planted to Monsanto GM Corn with Bt Trait(s) Alone vs. Varieties with Roundup Ready Trait: 1996-2008



Source: Monsanto Biotechnology Trait Acreage: 1996-2008, Oct. 8, 2008.

Since 2005, RR corn adoption has risen still more rapidly, nearly tripling from 24.8 to 68.3 million acres. Unfortunately, USDA NASS has not collected pesticide usage data for corn since 2005, so we do not know how much more glyphosate use is associated with the rapid rise in RR corn adoption. A conservative estimate would have glyphosate use on corn rising by the same factor as RR corn acres (recall that from 2002 to 2005, glyphosate use rose much more rapidly than RR corn acres). Multiplying 26.3 million lbs. (2005 glyphosate use on corn) by 2.75 (the factorial rise in RR corn acres from 2005-2008, 68.3/24.8) gives an estimated 72 million lbs. of glyphosate use on corn in 2008. This is more than double EPA's figure for glyphosate use on corn in the Screening Level Estimates of 30.4 million lbs. a.i.[5] EPA's substantial underestimate of glyphosate use on corn is likely due to reliance on the USDA NASS figure for 2005 (the latest available), when much less RR corn was grown, and perhaps to EPA's failure to adjust USDA NASS survey figures to account for glyphosate applied to 100% of crop acreage. EPA is urged to reevaluate its estimate for glyphosate use

[5] 30.4 million lbs. is derived by converting the cited glyphosate acid equivalent figure of 22.5 million lbs. to lbs. of active ingredient in the most common salt form of glyphosate (isopropylamine) using the conversion factor for the isopropylamine salt, 0.74.

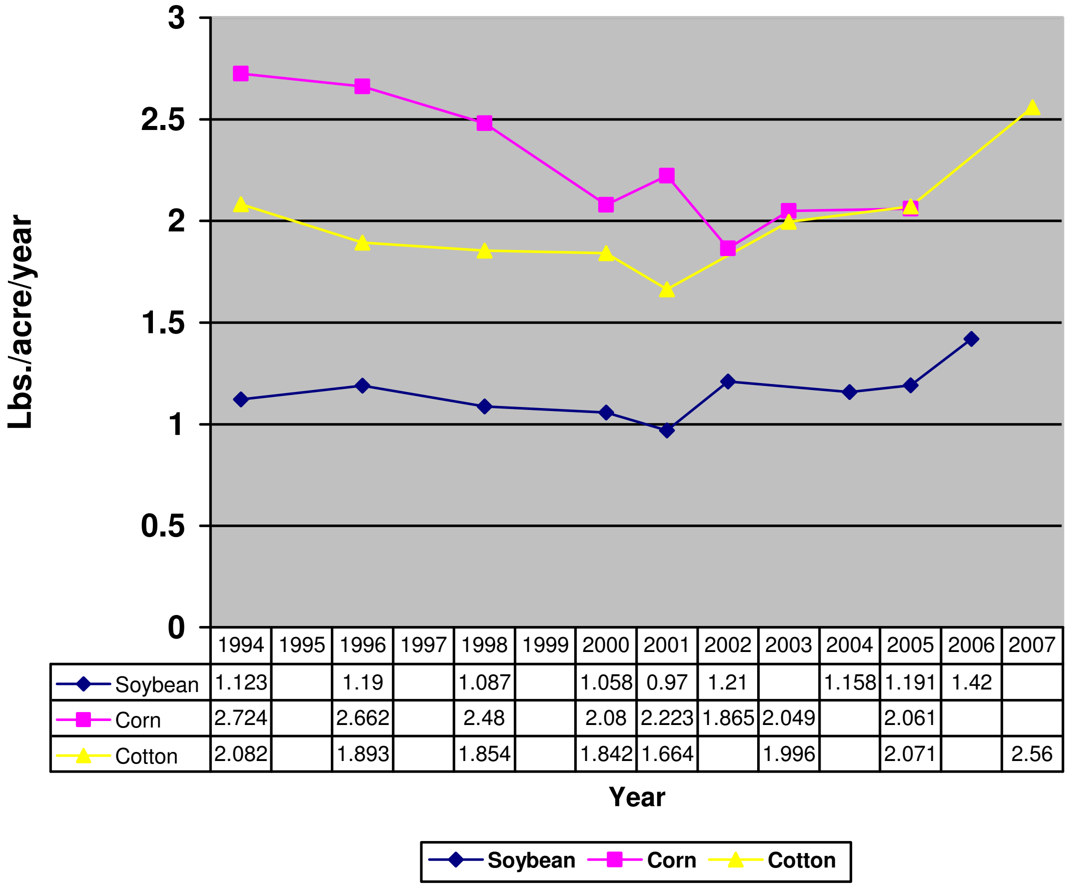
on corn to account for the dramatic rise in RR corn acres since 2005. Using the revised estimate suggested above for glyphosate use on corn of roughly 70 million lbs. a.i., overall agricultural glyphosate use would now stand at approximately 220 million lbs. a.i. rather than the EPA's estimated 182 million lbs a.i.

3) Glyphosate Use Fosters Weed Shifts and Glyphosate-Resistant Weeds

An even more important factor in the continuing rise in glyphosate use is the rapid emergence of glyphosate-resistant and glyphosate-tolerant weeds (from weed shifts) since the year 2000. For more on weed shifts and glyphosate-resistant weeds and how they have driven increased glyphosate (and overall herbicide) use, see Appendix 1. Here, we note merely that overall herbicide usage rates (lbs./acre/year) have risen dramatically on soybeans and cotton, the crops most infested with GR weeds, since GR weeds exploded onto the scene in 2000-2001 (Figure 4). In the case of soybeans, average herbicide intensity has risen by 46% from 2001 (0.97 lbs./acre/year) to 2006 (1.42 lbs./acre/year), while in cotton there has been a 54% increase in herbicide intensity from 2001 to 2007 (1.66 lbs/acre/year to 2.56 lbs./acre/year).

Closer analysis of the data reveals that these substantially higher herbicide usage rates for soybeans and especially cotton since 2001 are comprised of increased glyphosate usage rates and roughly constant rates for the category of non-glyphosate herbicides. Based on these observations with soybeans and cotton, the pattern of herbicide use with increasing adoption of glyphosate-resistant crops is: first, displacement of other herbicides by glyphosate until RR versions become predominant (roughly 75% of overall crop acreage); then, continuing large increases in glyphosate use with constant use (overall) of non-glyphosate herbicides, as the growing number of farmers plagued by GR weeds and glyphosate-induced weed shifts lead to increased annual glyphosate usage rates (chiefly increased number of applications per year, but rising rates per application as well). We note that as of 2009, RR corn still comprises "only" about 60% of all corn acreage. If this pattern is repeated with corn, as seems likely, the near-term future will see continuing substantial rises in glyphosate use.

Figure 4: Herbicide Use on Major Field Crops in the U.S.: 1994 - 2007



	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Soybean	1.123		1.19		1.087		1.058	0.97	1.21		1.158	1.191	1.42	
Corn	2.724		2.662		2.48		2.08	2.223	1.865	2.049		2.061		
Cotton	2.082		1.893		1.854		1.842	1.664		1.996		2.071		2.56

Notes: Herbicide use rates began rising in 2002 for soybeans and cotton, as GE herbicide-resistant versions of these crops became prevalent (reaching 75% and 74% of overall crop acreage, respectively, in 2002). Herbicide use on corn rose slightly in 2003, but no trends apparent as of 2005, the last year for which we have data.

Sources: "Agricultural Chemical Usage: Field Crops Summary," USDA National Agricultural Statistics Service, for the respective years. See: http://usda.mannlib.cornell.edu/MannUsda/viewDocumentInfo.do?documentID=1560. The figures represent total herbicide use on the respective crop in the "Program States" included in USDA's survey, divided by the number of acres planted to that crop in the Program States. The Program States surveyed by USDA represent a high percentage of nationwide acreage planted to the crop (usually more than 80%, often more than 90%). The only assumption made here is that the amount of herbicides applied per acre covered by the survey is equal to that applied on acres not included in the survey. This is accepted practice for calculation of pesticide usage rates. For instance, compare Table 3.3.3 in Section 3.3: "Biotechnology and Agriculture," in: "Agricultural Resources and Environmental Indicators, 2006 Edition," USDA Economic Research Service, Economic Information Bulletin 16, July 2006, accessible from: http://www.ers.usda.gov/Publications/AREI/EIB16/. In this 2006 report, USDA for some unexplained reason plotted pesticide use on major field crops only up through 2001 or 2002, despite the availability of data for later years.

4) Prospective Assessment of Glyphosate Use

A prospective assessment of glyphosate usage patterns must take several factors into consideration, including: a) Potential for increased glyphosate use with expanded acreage of GR crops; and b) Potential for increased glyphosate usage rates (i.e. lbs./acre/year) from introduction of newer GR varieties with enhanced glyphosate-resistance and/or broadened application windows, and in response to weed shifts to more glyphosate tolerant weed species and continued evolution of GR weeds.

a) GR crop acreage and associated glyphosate use will continue to rise

High adoption rates of glyphosate-tolerant soybeans and cotton (>=90%) suggest modest, but not negligible, potential for increased glyphosate use from expansion in acreage planted to GR versions of these crops. GR corn adoption, however, was "only" roughly 60% of U.S. corn acres in 2009, and will likely continue to rise in the near future. Introduction of GR alfalfa (4th most widely planted crop in the U.S.), which is presently pending deregulation by USDA, would add considerably to overall GR crop acreage and increase glyphosate use correspondingly. Introduction of GR wheat (3rd most widely planted crop in U.S.) would spur glyphosate use still more, as would the pending deregulation of GR bentgrass. Any significant GR adoption rate of these widely planted crops and grass would add considerably to overall glyphosate use.

Another factor to consider in any near-term assessment of glyphosate use patterns is the spate of new GR crops developed by Monsanto's competitors. DuPont-Pioneer obtained deregulated status for its glyphosate-resistant Optimum GAT soybeans, while GR Optimum GAT corn is pending deregulation with USDA. Bayer has obtained deregulated status for its GR Glytol cotton, and a new version of GR corn from Stine Seeds is pending deregulation. Expanded marketplace offerings of GR crops by Monsanto's competitors may well drive increased adoption, even in crops with already-high adoption rates (soybeans, cotton). We note that such GR crop adoption rate increases could be partly demand-driven, but will also likely be in part supply-driven. Supply-driven increases in GR crop adoption rates are attributable to the "trait penetration" strategy of Monsanto and other biotech seed suppliers. Trait penetration is the profit-driven strategy of loading as many traits as possible into seed varieties, and retiring or cutting back supplies of conventional seeds and seeds with fewer traits. It is beyond the scope of these comments to discuss this matter in any detail, but there is considerable evidence to suggest that trait penetration is currently focused chiefly on introducing the glyphosate-resistance trait into corn. The steep rise in RR trait-containing corn acres over the past four years is at least partly the result of Monsanto's implementation of this strategy (Figure 3). Even farmers who "unwillingly" purchase a variety of corn seed with glyphosate resistance (due to lack of desirable/suitable varieties without the GR trait) may well make use of the GR trait through "over-the-top" use of glyphosate.

The medium- to long-term projection of glyphosate use associated with expanded GR crop acreage is more difficult. Some evidence for such an assessment can be gleaned from USDA's database of field trial permits for genetically engineered crops. CFS undertook an analysis of this database on April 7, 2009.[6] As of that date, there were 812 active permits issued by USDA for GE crop field trials; 283 or 35% involved herbicide-resistant (HR) crops (some of these permits authorized field-testing of other traits in addition to herbicide resistance). Since some field trial permits authorized field testing of various single-trait HR plants each resistant to different herbicides (e.g. some glyphosate-resistant, others dicamba-resistant), the total number of HR phenotypes was 327. Still other permits involved combinations of 2 or 3 HR traits in the same plant (23 and 4 permits, respectively); when these HR traits are counted separately, the total number of HR traits comes to 358. Of these 358 HR traits, 164 (46%) were glyphosate-resistance, and included GR alfalfa, corn, onion, canola/rapeseed and soybeans. There are no deregulated GR versions of either alfalfa or onion. In the case of field trials of herbicide-resistant creeping bentgrass and tobacco, one or more permits did not specify the herbicide to which the crop is resistant, thus these may also involve glyphosate-resistance.[7] Thus, two and perhaps as many as four glyphosate-resistant crops for which no GR versions are currently deregulated are currently undergoing field tests. This indicates at least modest medium- to long-term potential for increased glyphosate use associated with the introduction of new GR crops.

b) Enhanced resistance to glyphosate

A more important factor driving increased glyphosate use is the introduction of GR crops with increased levels of glyphosate-resistance and/or broader application windows for application of glyphosate. This development is being driven by the rapid expansion of glyphosate-tolerant and glyphosate-resistant weeds (which can still often be controlled, in the short term, by increased application rates of glyphosate and additional glyphosate applications). To our knowledge, this was first seen with the 2006 introduction of Monsanto's Roundup Ready Flex cotton, the successor to its original RR cotton.[8] The label for Roundup Ready Flex cotton recommends 1.5 times the application rate of that applied to original RR cotton (32 ounces/acre for Flex vs. 22 ounces/acre for original RR cotton).[9] With original RR cotton, the CP4 EPSPS enzyme (RR trait) was not expressed in reproductive tissues, limiting the "application window" to the immature plant. RR Flex cotton expresses the enzyme in reproductive tissues, permitting application of glyphosate to mature plants as well. With RR Flex cotton, farmers are enabled to wait until weeds become larger before applying glyphosate; larger weeds require higher application rates to kill, and are also more likely to flower and set seed. Any glyphosate-resistant weeds that are allowed to flower and set seed can then spread the resistance trait in two ways: 1) Spatially, through

[6] Two searches conducted at http://www.isb.vt.edu/cfdocs/fieldtests1.cfm. All active permits for GE crop field trials determined on 4/7/09 by checking the "phenotype category" on first page, then selecting all phenotype categories and "field test permits currently in effect" and "short record" on the next page. For active HT crop field trials, search conducted on 4/5/09 by checking "phenotype category" on first page and "herbicide-tolerance," "field test permits currently in effect" and "full record" on the next webpage. Permits with "status" of "withdrawn" or "denied" were excluded from the analysis of both total active field trials and active HT crop field trials.

[7] For some unexplained reason, fully 29% (105) of the HT traits being tested in field trials of GE crops as of April 7, 2009 were not specified in USDA's database. These traits were either labeled CBI ("confidential business information") or simply not specified.

[8] Bennett, D. (2005). "A look at Roundup Ready Flex cotton," *Delta Farm Press*, 2/24/05, http://deltafarmpress.com/news/050224-roundup-flex/.

[9] See Monsanto 2008 Technology Use Guide, pdf pages 31 and 34.

cross-pollination with susceptible weeds; and 2) Over time, by leaving weed seeds bearing the resistance trait in the seed bank to sprout in subsequent seasons. Introduction of RR Flex cotton may well have contributed to the steep (24%) increase in herbicide use on cotton from 2005 to 2007 (see Figure 4).

USDA's APHIS recently deregulated Bayer CropScience's GlyTol cotton (event GHB614), which incorporates still another new mechanism of glyphosate resistance.[10] Bayer informed APHIS that the company did not request a glyphosate label change with EPA and is using the current label application rate of glyphosate on their GHB614 product.[11] However, Cheminova, Inc., a manufacturer of glyphosate and other pesticides based in Denmark, applied for and recently obtained from EPA a tolerance increase for residues of glyphosate on cotton gin byproducts (from 175 to 210 ppm) that was specifically linked to introduction of GlyTol cotton.

> "Cheminova, Inc. has requested a Section 3 registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for application glyphosate to glyphosate-tolerant cotton including Bayer GHB614 cotton (GlyTol cotton), a genetically modified cotton being commercialized by Bayer Crop Science. As a result, the petitioner has requested that the current tolerance for cotton, gin byproducts be increased to 210 ppm."[12]

In this same FR notice, EPA also refers to an Agency review entitled "Glyphosate Label Amendment to Permit Application of Glyphosate to Bayer's Glyphosate-Tolerant Cotton GHB614."[13] Thus, it appears that introduction of Bayer's GlyTol cotton requires both a tolerance increase and a glyphosate label amendment, suggesting that higher rates of glyphosate will be applied to this glyphosate-tolerant cotton; otherwise, there would seem to be little reason to seek and obtain a tolerance increase. The preexisting glyphosate tolerance for cotton gin byproducts was 175 ppm, which itself represents an increase from the corresponding tolerance prevailing in 2000 of 100 pm.

The increased glyphosate application rates and tolerances associated with GR cotton are consistent with the fact that GR weeds have posed a particular threat to cotton-growing areas in the U.S. Soybeans and corn are also increasingly infested with GR and glyphosate-tolerant weeds.

DuPont-Pioneer's Optimum GAT soybeans and corn (the former already deregulated, the latter pending deregulation by USDA)[14] contain a new mechanism of glyphosate resistance,

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[10] See USDA website listed above, petition 06-332-01p. For CFS comments, see: http://www.centerforfoodsafety.org/pubs/Bayer%20GlyTol%20Cotton%20Comments%20-%20CFS%20FINAL%208-18-08.pdf.

[11] APHIS (2009). "Determination of Non-regulated Status for Glyphosate-Tolerant (GlyTol) Cotton, Gossypoium hirsutum, event GHB614: Final Environmental Assessment, April 15, 2009, Response to Comments section, p. 24.

[12] EPA (2009). "Glyphosate; Pesticide Tolerances," FR Vol. 24, No. 120, June 24, 2009, pp. 29963-29996.

[13] Id., p. 29964.

[14] USDA Petitions for Nonregulated Status and any (draft) environmental assessments (EA) by USDA's APHIS are listed at http://www.aphis.usda.gov/brs/not_reg.html. DuPont-Pioneer's corn is petition 07-152-01p. For fuller discussion of this dual-HR corn, see also: "Comments to USDA APHIS on Environmental Assessment for the Determination of Nonregulated Status for Pioneer Hi-Bred International, Inc. Herbicide Tolerant 98140 Corn,"

different than Roundup Ready. GAT stands for glyphosate acetyltransferase, which inactivates glyphosate by adding an acetyl group to it. One report by DuPont scientists suggests that GAT corn may survive six times the normal dose of glyphosate "with no adverse symptoms."[15] This would permit higher doses of glyphosate (whether officially permitted by the label or not).

In a patent, DuPont-Pioneer proposes to "stack" GAT with one or both of Monsanto's mechanisms of glyphosate-resistance (CP4 EPSPS and GOX [glyphosate oxidoreductase]) in order to enhance tolerance to glyphosate still more and so enable applications of higher rates to kill increasingly resistant weeds.

> "A transgenic plant or transgenic plant explant having ***an enhanced tolerance to glyphosate***, wherein the plant or plant explant expresses a polypeptide with glyphosate-N-acetyltransferase activity… and ***at least one polypeptide imparting glyphosate tolerance by an additional mechanism***."[16] (emphasis added)

In a second patent issued to DuPont-Pioneer, the authors cite two examples of glyphosate application to soybeans incorporating dual glyphosate resistance comprising both DuPont-Pioneer's GAT mechanism and Monsanto's CP4 EPSPS mechanism. Glyphosate application totalled roughly 3 lbs. a.i. per acre per season in two applications in Example 1; and 4 lbs. a.i. per acre per season in one application in Example 2.[17] These application rates represent more than double to triple the average amount of glyphosate applied to glyphosate-treated soybeans in the U.S. in 2006 (1.33 lbs./acre/year, the figure for most the commonly used isopropylamine salt), according to USDA NASS's Agricultural Chemical Usage Report for that year. This 2006 figure already represents a huge increase over the average glyphosate usage rate prevailing before GR soybeans were first introduced (e.g. 0.52 lbs./acre/year in 1994).

Likewise, a biotech startup company in North Carolina, Athenix, is also developing a bacterial gene to confer enhanced glyphosate tolerance in crops.[18]

These examples show clearly the strong near-term potential for greatly increased glyphosate use associated with enhanced glyphosate tolerance in cotton, soybeans and corn, a development being driven by the rapid expansion of glyphosate-tolerant and –resistant weeds fostered by current GR crop systems.

Center for Food Safety, February 6, 2009, http://www.centerforfoodsafety.org/pubs/CFS%20comments%20on%20Pioneer%20HT%2098140%20corn%20EA_final_2_6_09-FINAL.pdf.

[15] Castle et al (2004). "Discovery and directed evolution of a glyphosate tolerance gene," *Science* 304: 1151-54. For discussion, see CFS comments cited in last footnote.

[16] "Novel Glyphosate-N-Acetyltransferase (GAT) Genes," U.S. Patent 2005/0246798, issued Nov. 3, 2005, assigned to: Verdia, Inc. and Pioneer Hi-Bred International, see claim 111, p. 89.

[17] "Novel Glyphosate-N-Acetyltransferase (GAT) Genes," U.S. Patent Application Publication, Pub. No. US 2009/0011938 A1, January 8, 2009, paragraphs 0152 & 0154. In Example 1, glyphosate was applied as follows: 840 grams a.e./ha 24 days post-plant and 1680 grams a.e./ha 44 days post-plant, for a total of 2520 grams. In Example 2, glyphosate was applied at 3360 grams a.e./ha 31 days post-plant. Conversion made from grams a.e. per hectare to pounds a.i. (isopropylamine salt) per acre in each case.

[18] Service, R.F. (2008). "A growing threat down on the farm," *Science* 316: 1114-1117.

The medium- to long-term potential for increased glyphosate use associated with enhanced glyphosate resistance is suggested by the predominance of glyphosate resistance among active GE HR crop field trial permits. As noted above, nearly half (46%) of HT crop traits in active field trial permit listings are glyphosate resistance. It is likely that some or most of these GR crop traits involve enhanced glyphosate resistance.

5) Glyphosate Usage Patterns: Summing Up

Glyphosate use has been driven by burndown use associated with no-till crop production, widespread introduction of glyphosate-resistant crop systems, and a growing epidemic of glyphosate-tolerant (weed shifts) and glyphosate-resistant weeds. Already the most heavily used pesticide in the U.S. by 2001, agricultural glyphosate use has not only grown further since then, but its rate of increase has actually increased since 2001. Today, it is by far the most widely used pesticide in the history of agriculture. Present use patterns are clearly unsustainable, yet a prospective assessment suggests continued growth in glyphosate use in the near- and medium-term future – driven by increased acreage of GR crops and even more importantly by the intertwined phenomena of shifts to more glyphosate-tolerant weed species and continued rapid evolution of GR weeds, on the one hand, and the development and introduction of newer GR crops with enhanced glyphosate resistance in response, on the other.

CFS urges EPA to fully describe glyphosate usage patterns since the last reregistration in 1993, and offer a prospective assessment as well. Specifically, the Agency should:

1) Include quantitative assessments of home and garden as well as commercial, industrial and government uses of glyphosate, which are totally absent in EPA's background documents

2) Revise its estimate of agricultural glyphosate use, through:
   a) Use of USDA NASS figures adjusted for 100% of crop acreage, rather than simply citing the glyphosate applied to surveyed acres;[19]
   b) Revision of the estimate of glyphosate use on corn, taking account of the glyphosate use increase driven by the substantial increase in RR corn acreage since 2005; as explained above, glyphosate use on corn is likely at least double (60-70 million lbs. a.i. (iso.)) that estimated by EPA;
   c) Express all glyphosate usage figures in lbs. of active ingredient, using the most common salt of glyphosate (isopropylamine), rather than acid equivalents. The conflicting usage of acid equivalents for the Screening Level Estimates and the total amount of glyphosate used, versus use of active ingredient (salt) figures for all other references (e.g. Appendix A of the Registration Review – Preliminary Problem Formulation for the Ecological Risk and Drinking Water Exposure Assessments for Glyphosate and its Salts) gives rise to needless confusion.

[19] In "Screening Level Estimates of Agricultural Uses of The Case Glyphosate," EPA inexplicably excludes glyphosate use on acres not surveyed, which can give rise to substantial underestimates, and is contrary to accept practice, which is to assume that the average use on surveyed acres applies to non-surveyed acres.

III. Ecological Threats Posed by Glyphosate

1) Toxicity of Glyphosate Formulations, Especially to Amphibians

The Center for Food Safety welcomes EPA's plan to examine more data on glyphosate formulations, especially those containing the surfactant polyethoxylated tallow amine (POEA), with respect to ecological risks. However, we urge the Agency to expand this assessment in several ways. First, the Agency should give full consideration to the numerous existing studies demonstrating substantial mortality of several species of amphibians (aquatic and terrestial phase) following exposure to glyphosate formulations containing POEA in outdoor mecocosms at field-relevant usage rates.[20] Rick Relyea's research team is just one of several that have found serious adverse impacts of Roundup on amphibians at environmentally relevant concentrations, as evidenced by the studies listed in the excerpt below from a letter to *Ecological Adapations*:[21]

> For example, Chen et al. (2004:828)[22] studied zooplankton and tadpoles and concluded, ''concentrations equal to and less than the EEC [expected environmental concentrations] were significantly toxic to both species. This suggests that both groups may be at risk of direct mortality at environmentally relevant concentrations.'' Edginton et al. (2004:821)[23] state, ''We concluded that, at EEC levels, there was an appreciable concern of adverse effects to larval amphibians in neutral to alkaline wetlands. The finding that the mean pH of Northern Ontario wetlands is 7.0 further compounds this concern.'' Even Thompson et al. (2004:848)[24] conclude that, ''Overall, results of this tiered research program confirm that amphibian larvae are particularly sensitive to Vision [i.e., Roundup] herbicide and that these effects may be exacerbated by high pH or concomitant exposure with other environmental stressors.'' Howe et al. (2004:1933)[25] state, ''The present results indicate that formulations of the pesticide glyphosate that include the surfactant POEA at environmentally relevant concentrations found in ponds after field applications can be toxic to the tadpole stages of common North American amphibians.'' My experiments concur with the conclusion that Roundup with POEA can be highly lethal to tadpoles at environmentally relevant concentrations.

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[20] For instance, see: Relyea, R.A. (2005a). "The lethal impact of Roundup on aquatic and terrestial amphibians," *Ecological Applications* 15(4): 1118–1124; Relyea et al (2005). "Pesticides and amphibians: The importance of community context," *Ecological Adaptations* 15: 1125-1134; Relyea, R.A. (2005b). "The letal impacts of Roundup and predatory stress on six species of North American tadpoles," *Archives of Environmental Contamination and Toxicology* 48: 351-57

[21] Relyea, R.A. (2006) in: *Ecological Adaptations* 16(5): 2027-2034.

[22] Chen, C. Y., K. M. Hathaway, and C. L. Folt (2004). "Multiple stress effects of Visiont herbicide, pH, and food on zooplankton and larval amphibian species from forest wetlands," *Environmental Toxicology and Chemistry* 23: 823–831.

[23] Edginton, A. N., P. M. Sheridan, G. R. Stephenson, D. G. Thompson, and H. J. Boermans (2004). "Comparative effects of pH and Vision herbicide on two life stages of four anuran amphibian species," *Environmental Toxicology and Chemistry* 23: 815–822.

[24] Thompson, D. G., B. F. Wojtaszek, B. Staznik, D. T. Chartrand, and G. R. Stephenson (2004). "Chemical and biomonitoring to assess potential acute effects of Vision herbicide on native amphibian larvae in forest wetlands," *Environmental Contamination and Toxicology* 23: 843–849.

[25] Howe, C. M.,M. Berrill, B. D. Pauli, C. C. Helbring, K.Werry, and N. Veldhoen (2004). "Toxicity of glyphosate-cased pesticides to four North American frog species," *Environmental Toxicology and Chemistry* 23: 1928–1938.

The need for EPA to thoroughly investigate Roundup's risk to amphibians and take appropriate actions is especially urgent give the lack of data on Roundup's risk to amphibians in the Agency's 1993 risk assessment; the vastly increased use of glyphosate/Roundup since 1993, as documented above; the possible link between glyphosate/Roundup use and the global amphibian crisis that has developed over the past 15 years; and finally, the Agency's own recent determination under the Endangered Species Act that use of glyphosate as currently registered is likely to adversely affect both the terrestial and aquatic phases of one endangered amphibian species, the California red-legged frog (Summary document, pp. 5-6). We note that the Agency does not list a single study of the effects of glyphosate or its formulations on frogs or other amphibians (either aquatic or terrestial phase) in Tables 5 to 11 of the Ecological Risk background document. This is a serious flaw in the Agency's work plan that must be remedied as the registration review proceeds.

Second, the EPA should expand its ecological risk assessment to include glyphosate formulations that include non-POEA surfactants based on the Agency's finding that "only a few ecological effects studies have been conducted" with non-POEA formulations, and that there are "some non-POEA formulations that appear to be quite a bit more toxic than the technical material" (Ecological Risk background document, p. 19).

Third, the EPA should remove whatever internal impediments may exist to full consideration of high-quality research in the peer-reviewed literature regarding the ecological risks of glyphosate and its formulations. There is a surprising lack of references to any independent peer-reviewed scientific literature in the Ecological Risk background document, while the Agency specifically cites a Monsanto-prepared publication on the subject (Ecological Risk document, p. 6). The Agency states that it consults "open literature studies" (Ecological Risk, p. 17), but fails to present any evidence in the way of concrete references that it does so. EPA should not artificially limit its consultation of peer-reviewed scientific literature by overly restrictive screening procedures for "consistency," such as may be associated with acceptance into its ECOTOX database (Ibid). Excessive concern for consistency should not blind the Agency to high-quality data that has been generated by independent scientists and published in the peer-reviewed literature. Studies conducted by independent scientists and published in peer-reviewed journals are almost always of higher quality than registrant-conducted or commissioned studies.

Fourth, the EPA should make a priority of collecting full data on the surfactants contained in every glyphosate formulation, whether registered as a formulated product or not. EPA states: "For most formulations, we have no data. There is an uncertainty associated with formulations registered for aquatic uses and whether or not they contain POEA-type surfactants or other surfactants that are more toxic than technical glyphosate" (Ecological Risk document, p. 19). "There are many formulated products for glyphosate and the surfactants used in these products that must first be identified" (Ibid, p. 31). EPA should demand data on the specific surfactants in every glyphosate formulation that is employed in the field as a condition of FIFRA registration. In those cases where a company seeks registration of a glyphosate product that does not contain, but is invariably used with, surfactants (such as Rodeo), the formulations actually employed in the field including their corresponding surfactants should be subject to mandatory registration under FIFRA. EPA's admirable intent to collect data on the ecological risks posed by glyphosate formulations is seriously hampered by these data gaps.

Fifth, the Agency should not limit its assessment of the ecological toxicity of glyphosate formulations (with POEA or non-POEA surfactants) to those registered for direct application to water (as suggested in Ibid, p. 31). In Appendix A, aerial application is listed as permitted for fully 37 uses of glyphosate, including such large-scale agricultural applications as soybeans, corn, cotton, canola/rapeseed, wheat, alfalfa, agricultural fallow, non-food use crops and forestry. Glyphosate overspray of, and drift onto, wetlands and small bodies of water will be especially common with aerial applications over the vast acreages represented by such uses, and wetlands are the prime breeding ground for at-risk amphibian species such as frogs. Thus, EPA must expand its ecological effects testing requirements for glyphosate formulations to those registered for non-aquatic uses.

Sixth, the Agency should collect direct data on the ecological impacts of all glyphosate formulations, and not rely on separate analysis of surfactants' toxicity, either through collection of data from direct tests of the surfactants alone, or analysis of structure-activity relationships to extrapolate from the toxicity of known surfactants to those of similar structure (as suggested in Ecological Risks document, pp. 31-32). First, while some authors suggest that surfactants such as POEA are primarily responsible for ecological risks of glyphosate formulations (e.g. Relyea 2005a, cited above), others stress the importance of assessing formulations given the potential for additive or synergistic effects between active ingredient and surfactant(s).[26] When direct testing of formulations is not possible, toxicity testing of surfactants should be preferred to predictions from similarities in structure among surfactants.

CFS notes that EPA's review should also include further study of the toxicity of glyphosate formulations to freshwater aquatic plants, especially given the moderate to high toxicity found to duckweed and diatom, respectively (Ecological Risks, Table 6, p. 19; we note that EPA should fill in the "toxicity category" column for these two studies, with "Moderately toxic" (duckweed) and "Highly toxic" (freshwater diatom).

2) Glyphosate Use Adversely Affects Soil Biota, Linked to Plant Disease, Mineral Deficiencies and Reduced Yield

Transgenic glyphosate resistance facilitates the previously infeasible "over-the-top" application of glyphosate formulations to crops, raising novel food, feed, ecological and agronomic concerns. GR crops (e.g. corn, soybeans) are increasingly grown in rotation, meaning that each year, more prime cropland is sprayed more frequently with glyphosate, with increasing rates applied in many areas to control resistant weeds. While glyphosate is generally regarded as less toxic than many weed killers, a growing body of research suggests that continual use of this chemical may make RR plants more susceptible to disease and prone to mineral deficiencies than conventional crops, as well as reducing their yields. Some of these agronomic impacts are mediated through the impact of glyphosate on soil biota, an ecological effect that the EPA must consider in its ecological risk assessment.

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[26] Diamond, G.L. & Durkin, P.R. (1997). "Effects of surfactants on the toxicity of glyphosate, with specific reference to RODEO," Syracuse Environmental Research Associates, submitted to USDA's APHIS, Feb. 6, 1997.

When Roundup is sprayed on RR crops, much of the herbicide ends up on the surface of the soil, where it is degraded by microorganisms. However, some is absorbed by the plant and distributed throughout its tissues. Small amounts of glyphosate are exuded from the roots of RR plants and spread throughout the surrounding soil.[27] This rhizosphere is home to diverse soil organisms, such as bacteria and fungi, that play critical roles in plant health and disease; and it is also where the roots absorb essential nutrients from the soil, often with the help of microorganisms.

The presence of glyphosate in the root zone of RR crops can have several effects. First, it promotes the growth of certain plant disease organisms that reside in the soil, such as *Fusarium* fungi.[28] Even non-RR crops planted in fields previously treated with glyphosate are more likely to be damaged by fungal diseases such as Fusarium head blight, as has been demonstrated with wheat and barley in Canada.[29] This research suggests that glyphosate has long-term effects that persist even after its use has been discontinued. Second, glyphosate can alter the community of soil microorganisms, interfering with the plant's absorption of important nutrients. For instance, glyphosate's toxicity to nitrogen-fixing bacteria in the soil can depress the absorption of nitrogen by RR soybeans under certain conditions, such as water deficiency, and thereby reduce yield.[30] Glyphosate-treated GR soybeans also have lower levels of manganese-reducing microorganisms in the rhizosphere,[31] inhibiting uptake of this essential nutrient and resulting in lower leaf levels of manganese.[32] Glyphosate treatment of GR sunflower reduces uptake and transport of both manganese and iron.[33] Glyphosate absorbed into GR crop plant tissues may also bind minerals and make them unavailable to the plant.[34] Finally, studies simulating low level glyphosate spray drift to non-transgenic soybean cultivars have demonstrated reduced leaf concentrations of calcium, manganese and magnesium, as well as reduced soybean seed concentrations of calcium, magnesium, iron and manganese.[35] Glyphosate treatment can foster increased disease

[27] Motavalli, P.P. et al. (2004). "Impact of genetically modified crops and their management on soil microbially mediated plant nutrient transformations," *J. Environ. Qual.* 33:816-824; Kremer, R.J. et al. (2005). "Glyphosate affects soybean root exudation and rhizosphere microorganisms," *International J. Analytical Environ. Chem.* 85:1165-1174; Neumann, G. et al. (2006). "Relevance of glyphosate transfer to non-target plants via the rhizosphere," *Journal of Plant Diseases and Protection* 20:963-969.

[28] Kremer, R.J & Means, N.E. (2009). "Glyphosate and glyphosate-resistant crop interactions with rhizosphere microorganisms," *European Journal of Agronomy,* doi:10.1016/j.eja.2009.06.004; Kremer et al (2005), *op. cit.*

[29] Fernandez, J.R. et al (2009). "Glyphosate associations with cereal diseases caused by *Fusarium* spp. in the Canadian Prairies," *Eur. J. Agron.*, doi:10.1016/j.eja.2009.07.003; Fernandez, M.R., F. Selles, D. Gehl, R. M. DePauw and R.P. Zentner (2005). "Crop production factors associated with Fusarium Head Blight in spring wheat in Eastern Saskatchewan," *Crop Science* 45:1908-1916. http://crop.scijournals.org/cgi/content/abstract/45/5/1908.

[30] King, A.C., L.C. Purcell and E.D. Vories (2001). "Plant growth and nitrogenase activity of glyphosate-tolerant soybean in response to foliar glyphosate applications," *Agronomy Journal* 93:179-186.

[31] Kremer et al (2009), op. cit.

[32] Gordon, B. (2007). "Manganese nutrition of glyphosate-resistant and conventional soybeans," *Better Crops*, Vol. 91, No. 4: 12-13.

[33] Eker, S., Ozturk, L., Yazici, A., Erenoglu, B., Roemheld, V., Cakmak, I. (2006). "Foliar applied glyphosate substantially reduced uptake and transport of iron and manganese in sunflower (*Helianthus annuus L.*) plants. *J. Agric. Food Chem.* 54: 10019–10025.

[34] Bernards, M.L. et al (2005). "Glyphosate interaction with manganese in tank mixtures and its effect on glyphosate absorption and translocation," *Weed Science* 53: 787-794.

[35] Cakmak, I, Yazici, A., Tutus, U. and Ozturk, L. (2009). "Glyphosate reduced seed and leaf concentrations of calcium, manganese, magnesium and iron in non-glyphosate resistant soybean," *Eur. J. Agron.* Doi:10.1016/j.eja.2009.07.001.

susceptibility through fostering the growth of disease microorganisms, through inhibiting the production of plant defense compounds, and through reduced uptake of minerals essential to plant health and disease resistance.[36]

No ecological risk assessment would be complete without thorough data collection and analysis of these intertwined issues of glyphosate's impact on soil microbiota, nutrient deficiences and plant disease. These are not merely agronomic issues, but rather ecological issues involving soil biota that have important implications for American agriculture, particularly in view of the 150+ million plus acres planted to glyphosate-resistant crops and the roughly 200 million lbs. of glyphosate applied agriculturally in the U.S. each year.

IV. Assessment of Human Health Impacts of Glyphosate and its Formulations

CFS endorses the excellent discussion of the adverse impacts of glyphosate and its formulations on human health in comments submitted to this docket by Beyond Pesticides and Pesticide Action Network North America.

We would add the following additional comments. As with the ecological risk assessment, EPA states that it has "conducted an open search to look for new literature relevant to the human health risk assessment" (Human Health Scoping document, p. 3). Yet there is practically no reference in the scoping document to the many peer-reviewed studies suggesting harm from glyphosate exposure, especially occupational exposure. In the case of cancer, EPA's basis for classing glyphosate as a "Group E" chemical (evidence for non-carcinogenicity for humans) is studies in mice and rats. Case-controlled studies suggesting increased incidence of non-Hodgkin's lymphoma and hairy-cell leukemia in Roundup applicators go completely unmentioned.[37] EPA states that it has selected no endpoints for dermal or inhalational occupational exposure (Human Health Scoping document, p. 12), yet dermal, ocular and upper respiratory complaints figure prominently (2nd, 3rd and 4th most frequently reported categories) in the IDS database. Overall, the IDS database contains "a moderately large number of case reports" (Human Health Scoping document, p. 33), many of them considered possibly or probably related to glyphosate exposure. EPA should carefully and independently examine other such incidents in the TESS, NIOSH SENSOR and California databases, and search for correlations among them and its IDS database.

EPA should rescind its 2006 decision to waive the Food Quality Protection Act's stipulation of the 10x safety factor in view of the growing evidence that glyphosate and its formulations

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[36] Johal, G.S. & Huber, D.M. (2009). "Glyphosate effects on diseases of plants," *Eur. J. Agron.,* doi:10.1016/j.eja.2009.04.004; Benbrook, C. (2001). "Troubled Times Amid Commercial Success for Roundup Ready Soybeans: Glyphosate Efficacy is Slipping and Unstable Transgene Expression Erodes Plant Defenses and Yields," AgBioTech InfoNet Technical Paper No. 4, May 2001.

[37] Hardell, L., & Eriksson, M. (1999). "A Case-Controlled Study of Non-Hodgkin's Lymphoma and Exposure to Pesticides," *Cancer*, 85(6), 1353–1360; Hardell L, Eriksson M, & Nordstrom M. (2002). "Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies," *Leuk Lymphoma*, 43(5), 1043-1049; De Roos, et al. (2003). "Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men," *Occup Environ Med*, 60(9).

adversely affect embryonic, placental and umbilical cord cells.[38] This decision should also be revisited in light of the lack of chronic and subchronic neurotoxicity studies on glyphosate and its formulations, and the fact that neurological symptoms are the most frequently reported category of effects reported in EPA's IDS database (Human Health scoping document, Table 1, pp. 13-14). Impacts of glyphosate and its formulations on steroidogenesis have also been identified.[39]

EPA must correct several faulty tolerance listings in its Table 6 (Attachment 4). The Agency has apparently been raising glyphosate tolerances for various crops so frequently that its listing in Table 6 is already outdated. CFS has identified the following errors. The listing for Cotton, gin byproducts, is 210 ppm, not 175 ppm; Grain, aspirated fractions is 310 ppm, not 100 ppm; Poultry, meat is 4.0 ppm, not 0.1 ppm; and Soybean, hulls is 120 ppm, not 100 ppm.

In general, we note that the in part vastly increased tolerances since reregistration in 1993 (most to facilitate the introduction of glyphosate-resistant crops) have already resulted in substantially increased glyphosate exposure to the general population from increased glyphosate residues on crops and in meat products and byproducts.

V. Conclusion

CFS urges EPA to conduct a thorough and careful analysis of glyphosate's many adverse impacts on the environment and human health as outlined above. The unprecedented level of usage of this pesticide – far greater than any pesticide in the history of agriculture – demands an especially strict analysis.

Sincerely,

Bill Freese, Science Policy Analyst
Center for Food Safety

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[38] Benachour, N. & Seralini, G.-E. (2008). "Glyphosate formulation induce apoptosis and necrosis in human umbilical, embryonic and placental cells," *Chemica Research in Toxicology* 22(1): 97-105; Richard, S. et al (2005). "Differential effects of glyphosate and Roundup on human placental cells and aromatase," *Environmental Health Perspective* 113(6): 716-720.

[39] Walsh, O.P. et al (2000). "Roundup inhibits steroidogenesis by disrupting steroidogenic actue regulatory (StAR) protein expression," *Environmental Health Perspectives* 108: 769-776.

Appendix 1

Herbicide-Resistant Crops and Weeds

(Excerpted from CFS comments to USDA APHIS,
Docket No. APHIS 2008-0023,
June 29, 2009)

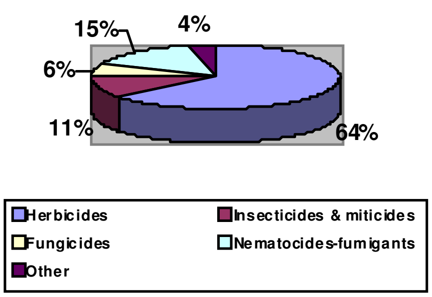
In past comments to the USDA on this rulemaking as well as on individual deregulation decisions, CFS has presented detailed arguments and evidence demonstrating that the unregulated use of genetically engineered, herbicide-tolerant (HT) crop systems – defined as an HT crop and use of its associated herbicide(s) – can have substantial negative impacts on U.S. agriculture, the environment and public health. These negative impacts include accelerated evolution of herbicide-resistant (HR) weeds; greater use of toxic herbicides to control HR weeds, and associated harm to the environment and public health; reduced yields as resistant weeds compete with crop plants for limited resources; increased soil erosion from greater use of mechanical tillage to control resistant weeds; increased costs to growers from herbicide-resistant weed control measures; and adverse health impacts on farmers from increased use of toxic herbicides to control resistant weeds. CFS has also urged USDA to exercize its noxious weed authority under the Plant Protection Act to mitigate these impacts, and make corresponding provisions in the proposed rule to this end. Below, we present new information and analysis to further support the need for regulation in this area. In brief:

1) The costs of (resistant) weeds to U.S. agriculture
   a) The pesticide treadmill
   b) Overview of herbicide use and herbicide-resistant weeds
   c) Herbicide-tolerant crop systems accelerate the pesticide treadmill
2) Acreage infested with glyphosate-resistant (GR) weeds continues to expand
   a) GR Palmer amaranth
   b) GR horseweed
   c) GR giant ragweed
3) Consequences of glyphosate-resistant weeds
4) The future of herbicide-tolerant crops: enhanced glyphosate-tolerance and tolerance to multiple herbicides
   a) Enhanced tolerance to glyphosate
   b) Multiple herbicide-tolerant crops
   c) Ongoing field tests involving herbicide-tolerant crops
5) Consequences of enhanced glyphosate and multiple herbicide-tolerant crop systems
6) Health consequences of herbcide-tolerant crop systems
7) Recommendations for APHIS regulation with respect to HT crop systems

1) The costs of (resistant) weeds to U.S. agriculture

Weeds compete with crops for limited supplies of nutrients and water, and can also shade crop plants, reducing yields. Weeds represent one of the biggest constraints on US crop production, costing an estimated $33 billion in lost crop productivity each year.[40] Since US food and fiber production is valued at over $115 billion annually,[41] weed competition reduces the production and value of US agricultural commodities by roughly 20% ($33 billion/($115+$33 billion). This huge loss in crop productivity attributable to weeds occurs despite the fact that US farmers apply over 400 million lbs. of herbicides annually,[42] at a cost of $7 billion.[43] While comprehensive lists are difficult to find, one source lists 287 herbicide active ingredients in use today in many more herbicide formulations (which often contain two or more active ingredients in various combinations).[44]

Figure 1: Agricultural Pesticide Use in the U.S. by Type: 2001



Herbicides comprise by far the largest category of pesticides, defined as any chemical used to kill plant, insect or disease-causing pests. In 2001, the last year for which the Environmental Protection Agency has published comprehensive data, weedkillers (herbicides) accounted for 433 million lbs. of the 675 million lbs. of chemical pesticides used in U.S. agriculture, nearly six-fold more than the insecticides that many associate with the term "pesticide." Source: "Pesticides Industry Sales and Usage: 2000 and 2001 Market Estimates," U.S. Environmental Protection Agency, 2004, Table 3.4. http://www.epa.gov/oppbead1/pestsales/01pestsales/market_estimates2001.pdf.

The pesticide treadmill

One reason farmers purchase and apply so many and such large quantities of herbicide is the growing problem of herbicide-resistant weeds. It is now generally acknowledged by agronomists that chemical-intensive pest (including weed) control methods can be counter-productive. This counter-intuitive notion – that greater reliance on pesticides exacerbates the problem it is meant to solve – is based primarily on two ecological insights: 1) Pesticides often kill not only pests, but natural predators of the pests that would otherwise help keep these pests in check (this applies mainly to insecticides/insects); and 2) Overreliance on particular pesticides generates enormous selection pressure that favors the survival of those rare individual pests that possess (genetically-endowed) natural resistance to the chemical(s). Over time, the resistant individuals gradually come to dominate the pest population. This applies to weeds as well as

40 USDA ARS IWMU-1. Agricultural Research Service, Invasive Weed Management Unit, http://arsweeds.cropsci.illinois.edu/.

41 USDA ARS Action Plan. "National Program 304: Crop Protection and Quarantine Action Plan 2008-2013," p. 1. http://www.ars.usda.gov/SP2UserFiles/Program/304/ActionPlan2008-2013/NP304ActionPlanwithCover2008-2013.pdf.

42 $433 million lbs. in 2001, the latest year for which comprehensive data are available. See: EPA (2004). "Pesticides Industry Sales and Usage: 2000 and 2001 Market Estimates," U.S. Environmental Protection Agency, May 2004, Table 3.4. http://www.epa.gov/oppbead1/pestsales/01pestsales/market_estimates2001.pdf.

43 USDA ARS IWMU-1, op. cit.

44 Compiled by CFS from information available at http://www.weedscience.org/summary/ChemFamilySum.asp.

insects. In a related phenomenon known as "weed shifts," weed species with naturally greater tolerance to overused weedkillers gradually displace more susceptible species.

Resistant pests require higher doses to control, and/or the application of other pesticides still able to kill them. Together, these two phenomena have been dubbed the "pesticide treadmill." In the short term, as pests evolve higher levels of resistance to a particular pesticide, farmers can often apply more of it (run faster) to achieve the same killing effect. When resistance exceeds a certain threshold, however, it becomes more economical to switch over to a new pesticide. In the longer term, then, the pesticide treadmill is the sequential "burnout" of overused pesticides, followed by application of different and/or newer chemicals that in turn become ineffective.[45]

Seen in this light, the large number and quantity of herbicides used each year by American farmers is both a response to existing weed problems, as well as a causal factor leading to still greater reliance on herbicide use thanks to the evolution of resistance in weeds.[46]

USDA's Agricultural Research Service (ARS) estimates that up to 25% of annual US pest (weed and insect) control expenditures are attributable to pesticide resistance management.[47] This suggests that efforts to forestall and control herbicide-resistant weeds cost farmers roughly $1.7 billion each year (25% of $7 billion), and also helps explains why major components of USDA ARS's Action Plan: 2008-2013 (cited above) are devoted to ameliorating pesticide resistance, including herbicide-resistance in weeds.

Overview of herbicide use and herbicide-resistant weeds

Since World War II, weedkilling pesticides (herbicides) have become the major tool employed by U.S. farmers to combat weeds. From 1964 to 1997, overall herbicide use on major crops (corn, soybeans, wheat, cotton, potatoes, vegetables, fruits and berries) increased from 48.2 to 366.4 million lbs., a dramatic 7.6-fold increase. By 1997, weedkilling chemicals were applied to well over 90% of national acres planted to corn, soybeans and cotton.[48] In 2001, the U.S. accounted for a substantial 30% of all herbicides used in the world.[49]

This rapidly escalating use of herbicides beginning in the 1960s was followed by the emergence of herbicide-resistant weeds in the 1970s. Figure 2 below shows how rapidly herbicide-resistant

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[45] This simplified description glosses over nuances. For instance, those herbicide resistance mechanisms that endow weeds with high levels of resistance lead more quickly to burnout and switching to new herbicides (e.g. weed resistance to ALS inhibitor herbicides). In other cases (glyphosate resistance), increasing the dosage is a more feasible response, at least for a time. In many cases, both strategies are applied at once – increased dosage of the herbicide to which weeds have developed moderate resistance, together with application of other herbicides.

[46] One complicating factor is the historical trend towards development and use of more potent pesticides (i.e. effective at lower doses). When lower-dose pesticides replace higher-dose ones, overall pesticide use may well decline, even though the adverse impacts of pesticide use (resistance development, toxicity to the environment and/or human health) may not be reduced, and may even be exacerbated.

[47] USDA ARS Action Plan-App. II. "National Program 304: Crop Protection and Quarantine Action Plan 2008-2013," Appendix II, p. 2. http://www.ars.usda.gov/SP2UserFiles/Program/304/ActionPlan2008-2013/NP304CropProtectionandQuarantineApendixII.pdf.

[48] USDA ERS (2003). "Agricultural Resources and Environmental Indicators, 2003," USDA Economic Research Service, Chapter 4.3: Pest Management Practices, Tables 4.3.1 & 4.3.2. http://www.ers.usda.gov/publications/arei/ah722/arei4_3/AREI4_3pestmgt.pdf.

[49] EPA (2004), op. cit., Table 3.1, Figure 3.1.

biotypes have emerged. As of June 26, 2009, 330 resistant biotypes of 189 different weed species have been documented infesting over 300,000 fields in the world.[50] Just as the U.S. is the world's leader in herbicide use, so we have by far the most herbicide-resistant weeds, by several measures. The U.S. harbors 125 resistant biotypes of 68 different weed species that are documented in up to 213,000 fields covering up to 18 million acres.[51] The problem may well be worse, since these figures include only documented instances of resistant weeds collected in a passive reporting system. As discussed further below, weed scientists have reported many resistant weeds that have not been recorded on the WSSC-HRAC website cited above.

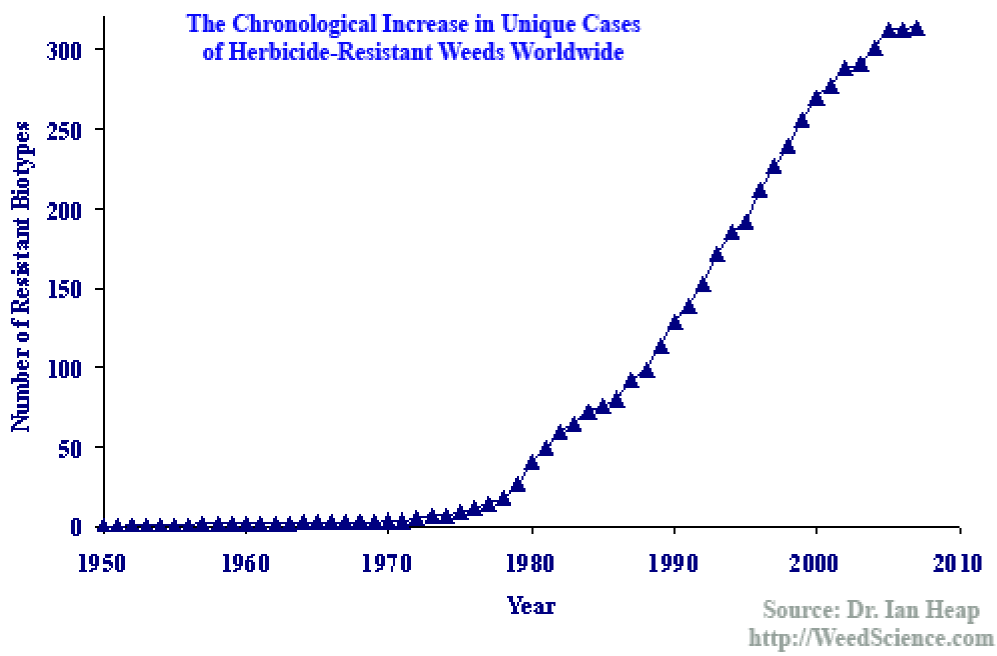

Figure 2: Source: "International Survey of Herbicide-Resistant Weeds," Weed Science Society of America and Herbicide-Resistance Action Committee. See link to "By Year 2007" chart at http://www.weedscience.org/In.asp. This chart has apparently not been updated since 2007.

The first major wave of herbicide resistant weeds in the U.S. that began in the 1970s involves 23 species of weeds resistant to atrazine and related herbicides of the photosystem II inhibitor class, which have been reported to infest up to 1.9 million acres of cropland in the U.S. The second

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[50] See WSSA-HRAC (2009). "International Survey of Herbicide-Resistant Weeds," a project of the Weed Science Society of America (WSSA), funded and supported by the Herbicide Resistance Action Committee (HRAC), a group comprised of pesticide manufacturers, at: www.weedscience.com, last accessed June 26, 2009. As recently as February 2, 2009, the number of resistant biotypes was seven fewer (323), and resistant species two fewer (187), a crude measure of how quickly herbicide-resistant weeds are evolving (2/2/09 figures cited in CFS's prior comments on the proposed rule).

[51] WSSA-HRAC (2009), op. cit. For 125 resistant biotypes, see http://www.weedscience.org/summary/CountrySummary.asp, last accessed 6/26/09. Note that Australia is a distant second to the U.S. with 53 resistant biotypes, less than half the number found in the U.S. 213,000 fields and 18 million acres represent upper-bound estimates, as compiled by CFS from WSSA-HRAC website data in November 2007, except for glyphosate-resistant weeds, for which figures were updated on February 2, 2009.

major wave began in the 1980s, and involves 37 species of weeds resistant to ALS inhibitors, which have been documented infesting up to 152,000 sites covering 9.9 million acres. The third wave involves weeds resistant to glyphosate (see Figure 4).

Herbicide-tolerant crop systems accelerate the "pesticide treadmill"

Herbicide-tolerant (HT) crops are engineered to withstand direct application of a broad-spectrum herbicide to permit herbicide spraying to control weeds after the crop seedling has sprouted. This method of weed control is called "post-emergence" or "in-crop" herbicide application, as distinguished from "pre-emergence" application of herbicides before the crop seed has sprouted or "emerged."[52] HT crops create a strong incentive for farmers to make preferential, and in some cases exclusive, use of the HT-crop associated herbicide. Thus, HT crops must be assessed in conjunction with use of that herbicide, as "herbicide-tolerant crop systems." By encouraging overreliance on a particular herbicide, HT crop systems are uniquely suited to foster the rapid evolution of resistant weeds, just as overused antibiotics foster the evolution of bacteria resistant to them.

At present, the predominant HT crop system involves tolerance to the herbicide glyphosate. Monsanto's brand name formulations of this herbicide are known as Roundup, and the crops are dubbed Roundup Ready. It should be noted that many other manufacturers produce generic versions of glyphosate, which may also be used on Roundup Ready crops. Figure 5 displays acreage planted to the four major Roundup Ready crops in the U.S. over time, which by 2008 had reached 148.7 million acres.[53] As of 2008, Roundup Ready soybeans, cotton and corn comprised 92%, 93% and roughly 60% of all US acres planted to soybeans, cotton and corn, respectively.

The rapid adoption of Roundup Ready crops has been matched by a huge increase in glyphosate use. USDA NASS data show that overall glyphosate use on soybeans, corn and cotton increased by over 15-fold from 1994 (7.9 million lbs.) shortly before the introduction of Roundup Ready crops, to 2005 (119.1 million lbs.), the last year for which we have data for all three crops (Appendix 1). USDA NASS data also show that overall herbicide use has increased sharply on soybeans and cotton since 2001, and modestly on corn since 2002 (Figure 6).

The huge increase in acreage infested with glyphosate-resistant weeds portrayed in Figure 4 is directly attributable to the widespread adoption of Roundup Ready crop systems, and the excessive reliance they foster on glyphosate. For further background on the intertwined issues of

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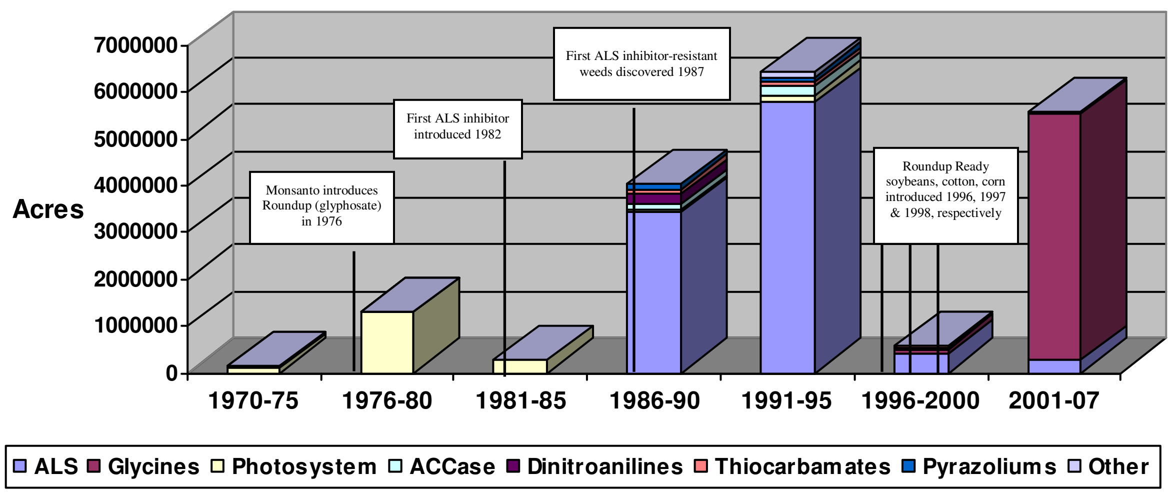
[52] Herbicides applied "pre-emergence" generally have "residual activity" of several days to weeks or longer, and are thus able to kill weeds that sprout subsequent to application.

[53] As APHIS has frequently noted, not all herbicide-tolerant crops are genetically engineered. Prior to development of transgenic techniques, companies used conventional breeding or mutagenic techniques to develop a number of herbicide-tolerant crops. However, it is important to note that the acreage planted to such varieties is a small fraction of that planted to genetically engineered (GE) HT crops. According to APHIS, conventionally-bred HT crops (mostly ALS inhibitor-resistant varieties: BASF's Clearfield corn, wheat, rice, canola and sunflower; DuPont-Pioneer's STS soybeans) were planted on roughly 6 million acres in 2007 (see APHIS (2008). "Finding of No Significant Impact on Petition for Nonregulated Status for Pioneer Soybean DP-356043-5," July 15, 2008, Response to Comments, p. 26. http://www.aphis.usda.gov/brs/aphisdocs2/06_27101p_com.pdf). This represents roughly 1/20th or 5% of the acreage planted to GE Roundup Ready soybeans, corn, cotton and canola in that year (128.2 million acres in the U.S. in 2007. See Figure 1 and Monsanto Biotechnology Trait Acreage: Fiscal Years 1996 to 2008, October 8, 2008. http://www.monsanto.com/pdf/investors/2008/q4_biotech_acres.pdf.)

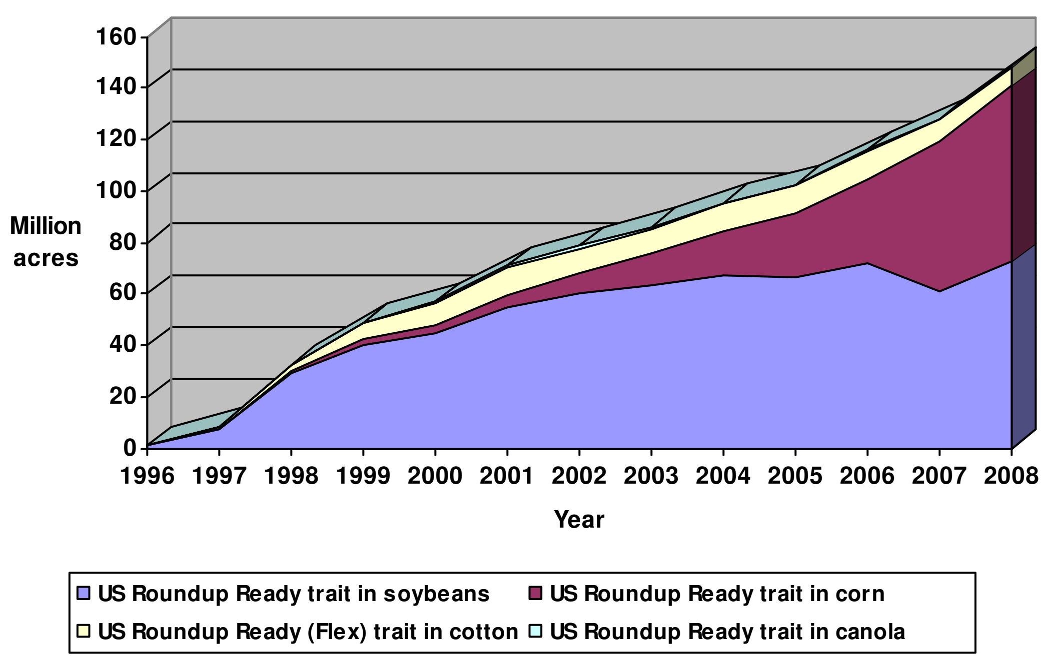
Roundup Ready crops, glyphosate use and glyphosate-resistant weeds, please refer to prior CFS comments to the USDA on the draft programmatic environmental impact statement, the

Figure 4: U.S. Crop Acreage Infested With Herbicide-Resistant Weeds by Class of Herbicide and Year Reported: 1970-2008



Compiled by CFS from WSSC-HRAC (2009), op. cit., last visited Feb. 3, 2009. Note that WSSC-HRAC report "acreage infested" figures in ranges due to the difficulty of determining the extent of a resistant weed population. The figures presented here represent aggregate upper-bound estimates. Note that glyphosate is the only member of the "glycines" class of herbicides.

Figure 5: U.S. Acreage Planted to Crops with Roundup Ready Trait: 1996 to 2008



Source: Monsanto Biotechnology Trait Acreage: Fiscal Years 1996 to 2008, October 8, 2008. http://www.monsanto.com/pdf/investors/2008/q4_biotech_acres.pdf.

proposed rule, and APHIS environmental assessements of various herbicide-tolerant crop deregulation petitions, which are incorporated here by reference. Below, we report recent findings on the continuing rapid expansion of glyphosate-resistant weeds.

2) Acreage Infested with Glyphosate-Resistant Weeds Continues to Expand

As Figure 4 illustrates, glyphosate-resistant (GR) weeds have evolved very rapidly in less than a decade. Today, WSSC-HRAC reports 41 documented GR biotypes of 9 different weed species in 19 states. Infestation with GR weeds continues to expand by both region of the country and overall acreage. For instance, weed scientists have recently reported GR weeds in South Dakota,[54] South Carolina and Alabama, though these reports have not (yet) been listed by WSSC-HRAC, bringing the total number of states with GR weeds up to at least 22. In addition, Canada recently reported its first suspected GR weed (giant ragweed).[55]

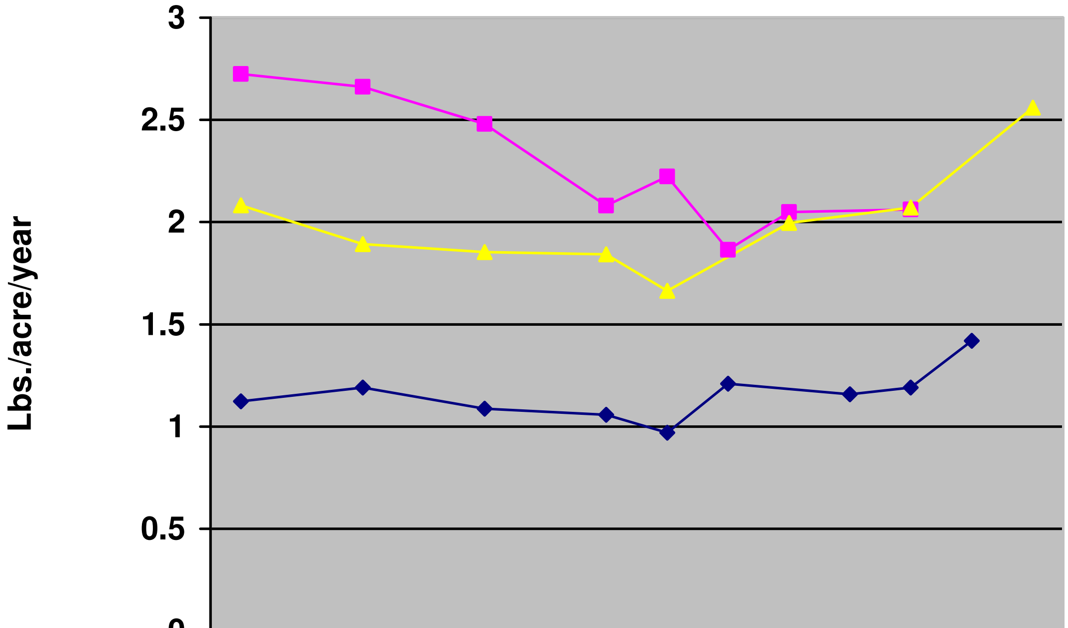
Except for isolated reports on the West Coast (California and Oregon), virtually all GR weeds have been linked to Roundup Ready cropping systems (soybeans, cotton and corn). Beginning in the year 2000 in Delaware, GR weeds first emerged in eastern and southern states, but were quickly found in states further west (e.g. Missouri, Kansas, Illinois). More recently, GR weeds have emerged in northern states (Minnesota, Michigan, South Dakota) as well as Canada.

More importantly, perhaps, is the dramatic increase in acreage infested with GR weeds. The reported extent of infestation in the U.S. has increased dramatically since just November of 2007, when GR populations of eight weed species were reported on no more than 3,251 sites covering up to 2.4 million acres. Today, GR weeds are reported on as many as 14,262 sites on up to 5.4 million acres.[56] In less than two years, then, the number of reported sites infested by GR weeds has increased by up to four-fold, while the maximum infested acreage has more than

[54] ArgusLeader (2008). "Report: Roundup-resistant weeds pose challenge for SD soybean farmers," ArgusLeader.com, August 11, 2008.
[55] University of Guelph (2009). Guelph researchers find super ragweed," University of Guelph News Service, May 7, 2009. http://news.guelphmercury.com/News/article/478286
[56] We stress "reported" acreage because there can be lags between the times that resistant weeds emerge, are discovered, confirmed and reported. This increase in acreage infested with GR weeds is obscured by the WSSC-HRAC's puzzling practice of entering new reports of GR weeds under old dates. For instance, CFS's visits to the WSSC-HRAC website on November 21, 2007 and again on July 16, 2008 revealed just three reports of GR Palmer amaranth: 2005 in Georgia (up to 500 acres); 2006 in Tennessee (up to 500 acres) and 2006 in Arkansas (acreage unknown). When CFS checked the website again on Feb. 2, 2009, there was a ***new*** entry for GR Palmer amaranth in North Carolina (up to 1 million acres), but for some reason it was listed as a 2005 report. In addition, the pre-existing 2005 Georgia entry had been changed from up to 500 acres to up to 1 million acres. Likewise, there were no reports of GR horseweed in Illinois in our 2007 and 2008 searches; yet on 2/2/09, we found a ***2005*** entry for GR horseweed in Illinois on up to 1 million acres. There are several more examples of the same sort (new 2005 entries for GR giant ragweed in Minnesota and Arkansas that first turned up only in our 2009 search). Accurate tracking of resistant weed dynamics clearly requires an improved monitoring and reporting system, one preferably run by USDA and university weed scientists. We note that while WSSC is comprised of academic weed scientists, the Herbicide Resistance Action Committee (HRAC) is funded by biotechnology/agrichemical companies, which may well have an interest in downplaying the magnitude of the resistant weed problem.

doubled. And there is a strong trend for further increases in the future. Of the 41 reports of GR weed biotypes, 32 were reported as expanding in acreage, only two were not expanding, while information was not available for seven reports.

Figure 6: Herbicide Use on Major Field Crops in the U.S.: 1994 - 2007



	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Soybean	1.123		1.19		1.087		1.058	0.97	1.21		1.158	1.191	1.42	
Corn	2.724		2.662		2.48		2.08	2.223	1.865	2.049		2.061		
Cotton	2.082		1.893		1.854		1.842	1.664		1.996		2.071		2.56

Year

Soybean — Corn — Cotton

Notes: Herbicide use rates began rising in 2002 for soybeans and cotton, as GE herbicide-tolerant versions of these crops became prevalent (reaching 75% and 74% of overall crop acreage, respectively, in 2002). Herbicide use on corn rose slightly in 2003, but no trends apparent as of 2005, the last year for which we have data. Note that adoption of HT corn has lagged behind that of soybeans and cotton, rising from 11% to 26% of overall corn acreage from 2002 to 2005. Thus, more recent herbicide use data on corn is needed to determine whether increasing HT corn adoption since 2005 will have a similar effect as it has had for soybeans and cotton.
Sources: "Agricultural Chemical Usage: Field Crops Summary," USDA National Agricultural Statistics Service, for the respective years. See: http://usda.mannlib.cornell.edu/MannUsda/viewDocumentInfo.do?documentID=1560. The figures represent total herbicide use on the respective crop in the "Program States" included in USDA's survey, divided by the number of acres planted to that crop in the Program States. The Program States surveyed by USDA represent a high percentage of nationwide acreage planted to the crop (usually more than 80%, often more than 90%). The only assumption made here is that the amount of herbicides applied per acre covered by the survey is equal to that applied on acres not included in the survey. This is accepted practice for calculation of pesticide usage rates. For instance, compare Table 3.3.3 in Section 3.3: "Biotechnology and Agriculture," in: "Agricultural Resources and Environmental Indicators, 2006 Edition," USDA Economic Research Service, Economic Information Bulletin 16, July 2006, accessible from: http://www.ers.usda.gov/Publications/AREI/EIB16/. In this 2006 report, USDA for some unexplained reason plotted pesticide use on major field crops only up through 2001 or 2002, despite the availability of data for later years.

The nine species of weeds with documented GR biotypes in the U.S. as reported by WSSC-HRAC are: Palmer amaranth, common waterhemp, common ragweed, giant ragweed, horseweed, Italian ryegrass, rigid ryegrass, hairy fleabane and Johnsongrass.[57] Unfortunately, nearly all of the additional acreage infested by GR weeds over the past two years involves two of the most damaging to agriculture: Palmer amaranth and horseweed.

Case study of glyphosate-resistant Palmer amaranth

Glyphosate-resistant Palmer amaranth (a pigweed) has spread very rapidly in cotton, soybean, and to a lesser extent corn fields of the South. As of November 2007, WSSC-HRAC listed GR Palmer amaranth on just 4-7 sites comprising up to 1,000 acres in 3 states. Less than two years later, GR Palmer amaranth had been reported on over 500 sites in 7 states on as many as 2.1 million acres. It has thus expanded to infest orders of magnitude more sites and acreage.

For instance, GR Palmer amaranth was first reported in 2004 in just one county in Georgia. It quickly spread to 2 more counties in 2005, 7 additional counties in 2006, 10 more counties in 2007, and at least 9 further counties in 2008.[58] Upper-bound estimates of Georgia cotton and soybean acreage infested rose from a mere 500 acres in 2005 to 1 million acres in 2009.[59] In Tennessee, GR Palmer amaranth was first reported by WSSC-HRAC on two to five sites covering up to 500 acres in 2006. By 2008, it had spread to hundreds of fields in 10 Tennessee counties.[60] In North Carolina, GR Palmer amaranth was first reported less than a year ago infesting up to 1 million acres of corn, soybean and cotton fields.[61] GR Palmer amaranth was initially reported on just 1 site in Arkansas in 2006, but is now widespread,[62] by one account present in 18 Arkansas counties as well as two counties in Mississippi, with suspected cases in Louisiana as well.[63]

GR Palmer amaranth is also spreading to states not documented on WSSC-HRAC's website. For instance, it has been reported in 130,000 acres in South Carolina[64] and in Barbour County, Alabama in 2008; Auburn University weed scientist Mike Patterson predicts that GR Palmer amaranth will spread across southern Alabama fields in the coming years.[65]

GR Palmer amaranth has several of the features that APHIS cited as characteristic of federally listed noxious weeds in its proposed rule: it is aggressively invasive, as demonstrated by its

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[57] http://www.weedscience.org/Summary/UspeciesMOA.asp?lstMOAID=12&FmHRACGroup=Go (last visited June 28, 2009).

[58] Culpepper and Kichler (2009), "University of Georgia Programs for Controlling Glyphosate-Resistant Palmer Amaranth in 2009 Cotton," University of Georgia Cooperative Extension, April 2009.

[59] http://www.weedscience.org/Case/Case.asp?ResistID=5256.

[60] Robinson, E. (2008a). "Pollen big factor in resistant pigweed spread," Southeast Farm Press, April 28, 2009. http://southeastfarmpress.com/cotton/herbicide-resistance-0428/.

[61] http://www.weedscience.org/Case/Case.asp?ResistID=5360, a 2005 report that first appeared on WSSC-HRAC website in 2009, see footnote above for discussion.

[62] Bennett, D. (2008). "Resistant pigweed 'blowing up' in Mid-South," Delta Farm Press, July 30, 2008. http://deltafarmpress.com/cotton/resistant-pigweed-0730/.

[63] Robinson, E. (2008a), op. cit.

[64] Robinson, E. (2008b). "Designing the perfect weed - Palmer amaranth," Delta Farm Press, 12/24/08. http://deltafarmpress.com/cotton/palmer-amaranth-1226/

[65] Hollis, P.L. (2009). "Resistant pigweed control programs updated," Southeast Farm Press, May 19, 2009. http://southeastfarmpress.com/cotton/weed-resistance-0519/

explosive spread described above; it has significant negative impacts; and it is extremely difficult to control.[66] The mature weed can easily exceed six feet in height, and has an extremely sturdy stalk that can be from 6-8 inches wide at its base.[67] The weed is so tough that it can damage cotton pickers,[68] and GR Palmer amaranth infestations can lead to abandonment of cropland, as it did with 10,000 acres of cotton in Georgia in 2007.[69] Just two Palmer amaranth plants per 20 row feet of cotton can reduce yields by 23% or more.

Difficulties in controlling GR Palmer amaranth are attributable to its fecundity, the many modes of propagation, and the paucity of weed control options. As to its fecundity, a single female plant can produce up 450,000 seeds. GR Palmer amaranth seed can become lodged in harvesting equipment, which unless thoroughly cleaned, can lead to propagation of the resistant seed to other fields; farmers' use of custom harvesters poses similar propagation risk.[70] In Louisiana, where at present there are suspected GR Palmer amaranth but no documented glyphosate-resistant weeds, experts even worry that farmers buying used soybean harvesting equipment from areas infested with GR weeds will inadvertently import the problem to the state.[71] Scientists in Arkansas and Tennessee believe that GR Palmer amaranth seed is spread via flooding as well, having noted that river counties have the most widespread resistance problems.[72] However, long-distance pollen flow is probably the most significant mode of propagation. In one experiment, a substantial 20% of the seeds of glyphosate-susceptible female plants at a distance of 300 meters from a pollinating resistant male plant produced glyphosate-resistant progeny.[73]

The multiple modes of propagation, especially long-distance pollen flow, help account for the GR weed's extremely rapid march across southern states in the past two years. Another key factor is the enormous selection pressure for GR biotypes from overreliance on glyphosate with Roundup Ready cotton, soybean and corn crop systems, which are often grown in rotation.

Glyphosate-resistance in this extremely damaging weed makes it all the more expensive and difficult to control. The difficulty in controlling a weed is a major factor that must be considered in assessments of whether it merits designation as "noxious." One facet is the increasing level of resistance. In both Georgia and Tennessee, resistance levels as measured by dose of glyphosate required to control GR Palmer amaranth have been rising. Initially in Tennessee, some GR Palmer amaranth could survive 44 ounces of Roundup, requiring 88 ounces for control (88 ounces exceeds the label rate); in 2008, resistant weeds were found that required an astronomical

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[66] USDA APHIS (2008), Proposed Rule, October 9, 2008, FR 73: 60008-46, at 60013.
[67] Roberson, R. (2008). "Herbicide-resistant weed problems spreading," Southeast Farm Press, May 14, 2008.
[68] Minor, E. (2006). "Herbicide-resistant weed worries farmers," *Associated Press*, 12/18/06, available at http://www.enn.com/top_stories/article/5679 (last visited Sept. 9, 2007).
[69] Robinson, E. (2008b), op. cit.
[70] Culpepper, S. and J. Kichler (2009), op. cit.; Robinson, E. (2008a). "Pollen big factor in resistant pigweed spread," Southeast Farm Press, April 28, 2009. http://southeastfarmpress.com/cotton/herbicide-resistance-0428/.
[71] Bennett, D. (2009). "Lousiana: sugarcane and soybeans," Delta Farm Press, June 3, 2009. http://deltafarmpress.com/soybeans/sugarcane-soybeans-0603/.
[72] Bennett, D. (2008), op. cit. "Resistant pigweed 'blowing up' in Mid-South," Delta Farm Press, July 30, 2008. http://deltafarmpress.com/cotton/resistant-pigweed-0730/.
[73] Robinson, E. (2008a), op. cit.

152 ounces of glyphosate to kill. ***In some cases, Palmer amaranth actually exhibits higher levels of resistance to glyphosate than the Roundup Ready soybeans in the field.***[74]

Rising levels of glyphosate resistance means that control of the weed is more expensive. Increasing costs of weed control to farmers is a significant negative impact of a weed that also deserves consideration in assessments of its noxious qualities. Larry Steckel, weed scientist at the University of Tennessee, estimated in 2006 that on average, glyphosate-resistant Palmer amaranth would cost cotton growers in the South an extra $40 or more per acre to control.[75] This represents a substantial burden, as cotton farmers' average expenditure on ***all*** pesticides (insecticides and herbicides) was $61 per acre in 2005.[76] Another expense is the need for increasing use of manual labor to remove GR Palmer amaranth. In both Arkansas and Tennessee, the use of "chopping crews" to remove this weed is sharply increasing.[77] The expansion of GR Palmer amaranth from mere hundreds of acres (when these reports were first made) to as many as 2 million acres of cotton, soybean and corn fields just a few years later means that the cost of controlling it has likewise risen dramatically.

Another facet of assessing the difficulty of weed control is the availability of alternative control methods. In this case, there are few economical options for dealing with GR Palmer amaranth, in part because many populations of Palmer amaranth are already resistant to other herbicides. Weed scientist Alan York and Cotton, Inc.'s Bob Nichols note that many populations of Palmer amaranth are already resistant to members of a widely used class of alternative herbicides known as ALS inhibitors, and are concerned that increasing reliance on a third class of herbicides, PPO inhibitors, will drive weed resistance to them as well. In fact, some populations are already resistant to glyphosate as well as ALS inhibitors. Palmer amaranth with dual resistance to glyphosate and ALS inhibitors has been reported in both Mississippi by WSSC-HRAC[78] and by Alan York in North Carolina.[79]

> "'But we also have a lot of ALS resistance in Palmer amaranth and we can't depend too much on that chemistry. We're also putting a lot of pressure on PPO inhibitors like Reflex, Valor, Blazer, Flexstar, and others. We cannot afford to lose those chemistries,' [said York]…."
>
> While York and Nichols are concerned about glyphosate resistance, growers should keep in mind that resistance to ALS herbicides such as Classic and Harmony is common ***and the potential to select for resistance to PPO-inhibiting herbicides such as Reflex, Valor, and Cobra certainly exists***.
>
> 'When we hear the term herbicide resistance, we automatically think glyphosate,' York said. 'I don't want to belittle glyphosate resistance. We know how much we depend on glyphosate, and it is a serious matter. But resistance is not unique to glyphosate.'

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74 Robinson, E. (2008a), op. cit., emphasis added.
75 Laws, F. (2006). "Glyphosate-resistant weeds more burden to growers' pocketbooks," *Delta Farm Press*, November 27, 2006, http://deltafarmpress.com/news/061127-glyphosate-weeds/
76 USDA ERS (2007b). Cost and return data for cotton production: 1997-2005. USDA Economic Research Service, last accessed January 12, 2007. http://www.ers.usda.gov/data/CostsandReturns/data/recent/Cott/R-USCott.xls.
77 Bennett, D. (2008), op. cit.
78 http://www.weedscience.org/Case/Case.asp?ResistID=5359.
79 Roberson, R. (2008), op. cit.

Nichols describes the Palmer pigweed situation as a 'serious economic threat to weed management in cotton. ***We need a general resistance management plan for the PPOs. PPOs are between us and the ability to do economic weed control in cotton and soybeans.***'"[80]

APHIS has frequently rejected CFS's call for USDA to take regulatory action on herbicide-tolerant crop systems and their propensity to foster herbicide-resistant weed populations by noting that herbicide-resistant weeds are not unique to GE crops, and that other weed control options are available when weeds evolve resistance to glyphosate or other herbicides. The second point is rapidly being proven false in the case of GR Palmer amaranth. The first point is simply irrelevant. It is equivalent to rejecting the need to take action on global warming by reference to damaging climatic events that have occurred throughout human history, before the advent of anthropogenic climate change. The point is not to split hairs about cause, but to tackle the problem at hand using all available regulatory tools. It is interesting to note that the weed scientist and cotton expert quoted above do NOT regard the prior evolution of herbicide-resistant weeds that are unrelated to GE herbicide-resistant crops (i.e. those resistant to ALS inhibitors) as grounds for inaction on the glyphosate-resistant weed epidemic, as APHIS does. On the contrary, they assess the GR weed threat in a comprehensive and cumulative manner, against the backdrop of pre-existing weed resistance problems (resistance to ALS inhibitors) and prospectively for its impacts on the viability of the few remaining chemical weed control options (PPO inhibitors).

GR Palmer amaranth is one of several factors that together pose a serious threat to the continued viability of the cotton industry in the United States. Already in 2006, North Carolina State University weed scientist Alan York described GR Palmer amaranth as "…potentially the worse threat [to cotton] since the boll weevil."[81]

Other weed scientists agree. According to Larry Steckel, speaking of GR Palmer amaranth:

> "One of the biggest concerns with this is, quite frankly, **it could run us out of cotton**. In soybeans, at least we have some options. In cotton those aren't there — once pigweed is up, it's safe.
>
> "**That's my greatest fear: losing cotton**. Between commodity prices, plant bug numbers appearing to pick up and this resistant-Palmer amaranth explosion, cotton is an increasingly tough sell."[82]

Clearly, the explosive spread of GR Palmer amaranth due to the unregulated use of Roundup Ready crop systems and the grave threat it poses to the cotton industry illustrates the need for APHIS to develop a comprehensive regulatory program to deal with the serious threats to the "interests of agriculture" posed by herbicide-tolerant crop systems and the resistant weeds they foster.

[80] Robinson, E. (2008b), op. cit.
[81] As quoted in Minor, E. (2006), op. cit.
[82] As quoted in: Bennett, D. (2008), op. cit., emphasis added.

Glyphosate-resistant horseweed

Glyphosate-resistant horseweed has also spread rapidly over the past two years. Since November 2007, it has been documented infesting up to 10,000 sites on as many as 1 million acres in Illinois,[83] the largest report since its discovery on over 2 million acres in 2001 in Tennessee.[84] An additional report of GR horseweed in Mississippi dated 2007 involves horseweed that is resistant to paraquat as well as glyphosate,[85] the first time WSSC-HRAC has documented multiple resistance to these two herbicides. Today, GR horseweed is the most widely dispersed GR weed, found in 16 states on up to 3.3 million acres.

GR horseweed is considered a "worst-case scenario" for glyphosate-tolerant crop systems because it is well adapted to no-tillage systems popular among GR crop growers, has a high level of fecundity (up to 200,000 seeds per plant), and its seeds disperse extremely long distances in the wind.[86] Left unchecked, horseweed can reduce cotton yields by 40-70%.[87] An Arkansas weed scientist estimated that Arkansas growers would have to spend as much as $9 million to combat glyphosate-resistant horseweed in 2004.[88] In 2005, Arkansas extension agent Mike Hamilton estimated that an uncontrolled outbreak of glyphosate-resistant horseweed in his state had the potential to cost Arkansas cotton and soybean producers nearly $500 million in losses, based on projected loss in yield of 50% in 900,000 acres of Arkansas cotton and a 25% yield loss in the over 3 million acres of Arkansas soybeans.[89] GR horseweed is even worse in Tennessee, reportedly infesting all cotton acres grown there. Larry Steckel reports that GR horseweed populations are becoming more dense in Tennessee; while 10 plants per square foot was considered heavy in 2004-2005, by 2006-07 bad infestations involved populations of from 20 to 25 plants per square foot.[90] In Tennessee, as well as Missouri, Arkansas, and Mississippi, GR horseweed is driving farmers to use mechanical tillage for control, reducing substantially the (cotton) acreage under conservation tillage.[91] This in turn can lead to increased soil erosion. As with Palmer amaranth, there are few good weed control options once a horseweed population has developed glyphosate resistance.[92]

Glyphosate-resistant giant ragweed

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[83] See http://www.weedscience.org/Case/Case.asp?ResistID=5276. As noted above, although this report is dated 2005, it was first listed by WSSC-HRAC in the past year.

[84] http://www.weedscience.org/Case/Case.asp?ResistID=5122.

[85] http://www.weedscience.org/Case/Case.asp?ResistID=5384.

[86] Owen, MDK (2008). "Weed species shifts in glyphosate-resistant crops," *Pest Management Science* 64: 377-387.

[87] Laws, F. (2006), op. cit.

[88] AP (2003). "Weed could cost farmers millions to fight," *Associated Press*, 6/4/03, http://www.biotech-info.net/millions_to_fight.html

[89] James, L. (2005). "Resistant weeds could be costly," Delta Farm Press, July 21, 2005. http://deltafarmpress.com/news/050721-resistant-weed/.

[90] Robinson, E. (2008c). "Weed control growing much more complex, new tools coming," Delta Farm Press, March 27, 2008.

[91] Steckel, L., S. Culpepper and K. Smith (2006). "The Impact of Glyphosate-Resistant Horseweed and Pigweed on Cotton Weed Management and Costs," Power Point presentation at Cotton Incorporated's "Crop Management Seminar," Memphis, 2006. http://www.cottoninc.com/CropManagementSeminar2006/SeminarProceedings/images/Steckle%20Larry.pdf; Laws, F. (2006), op. cit.

[92] Owen, MDK. (2008), op. cit.

Since just 2004, 6 reports of glyphosate-resistant giant ragweed have been reported in Ohio, Arkansas, Indiana, Minnesota, Kansas and Tennessee. Purdue University extension agents first confirmed a single population of glyphosate-resistant giant ragweed in Indiana in December of 2006;[93] just a year and half later, they announced GR giant ragweed in 14 counties in Indiana, and noted that some are also dual-resistant to ALS inhibitors as well.[94] Ohio State University researchers have reported giant ragweed with relatively high levels of resistance to both PPO and ALS inhibitor herbicides in three counties, and populations with lower levels of dual resistance in four other counties. They warn that although these weeds can be managed with glyphosate, "continuous use of this practice is likely to result in resistance to glyphosate as well."[95]

Giant ragweed is considered the most competitive broadleaf weed in Indiana soybean production. It can grow up to 15 feet tall, and 3 to 4 giant ragweed plants per square yard can reduce crop yields by as much as 70%.

3) Consequences of glyphosate-resistant weeds

Increased number and rate of glyphosate applications. Resistant/tolerant weeds can often still be killed by increased application rates, and farmers are in fact applying substantially more glyphosate to this end. For instance, USDA NASS data show that the average number of glyphosate applications per year on soybeans and cotton has risen from 1.0 for both soybeans in 1995 and for cotton in 1996 (the year before the introductions of RR soy and RR corn in 1996 and 1997, respectively) to 1.7 for soybeans (2006) and to 2.4 for cotton (2007). The average amount applied per application has also risen by 25% over this period for both crops. Thus, glyphosate use per acre per year on glyphosate-treated acres has more than doubled for soybeans (0.61 to 1.32 lbs) and nearly tripled for cotton (0.66 to 1.87 lbs.) over these time periods.

Health risks: Glyphosate is generally considered less toxic than many herbicides, yet certain Roundup formulations (especially those containing the adjuvant polyethoxylated tallowamine or POEA) have been found to pose greater risks to human health and the environment than glyphosate alone. Roundup use has been associated with increased risk of non-Hodgkin's lymphoma and hairy cell leukemia in pesticide applicators,[96] and increased risk of neurobehavioral disorders in children of Roundup applicators.[97] Roundup/glyphosate has been shown to inhibit steroidogenesis.[98] Both Roundup and glyphosate have been found to inhibit the aromatase enzyme involved in estrogen production, though Roundup was more potent.[99]

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[93] Johnson, B and Loux, M. (2006). "Glyphosate-resistant giant ragweed confirmed in Indiana, Ohio," Purdue University press release, 12/21/06.

[94] Johnson, B and G Nice (2008). "Lots of weedy soybean fields," Purdue Extension Weed Science, July 2008.

[95] Loux, M and J Stachler (2008). "Giant ragweed with resistance to PPO and ALS inhibiting herbicides," Crop Observation and Recommendation Network Newsletter 2008-11, 4/29 to 5/6/08.

[96] Hardell et al (2002). Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies," *Leuk. Lymphoma*, 43(5):1043-9.

[97] Garry et al (2002). "Birth Defects, Season of Conception, and Sex of Children Born to Pesticide Applicators Living in the Red River Valley of Minnesota, USA," *Environmental Health Perspectives,* 110, Suppl. 3, 441-449.

[98] Walsh et al (2000). "Roundup inhibits steroidogenesis by disrupting steroidogenic acute regulatory (StAR) protein expression," *Environmental Health Perspectives*, 108(8):769-76.

[99] Richard et al (2005). "Differential Effects of Glyphosate and Roundup on Human Placental Cells and Aromatase," *Environmental Health Perspectives*, 113: 716-720; for a comprehensive review of the adverse human

Glyphosate formulations have also been shown to cause cell death and necrosis in various human cell cultures at fairly low levels.[100]

Increased risks to amphibians: Certain formulations of Roundup have been found to be highly toxic to amphibians at field-relevant usage rates.[101]

Constant or rising use of other herbicides: Increasingly, weed scientists and Monsanto are advising farmers to employ non-glyphosate herbicides (preemergence, residual herbicides; tank mixes) to control and forestall the further spread of glyphosate-resistant weeds. For instance, paraquat and 2,4-D are recommended in addition to glyphosate to control GR horseweed and pigweed.[102]

4) The future of herbicide-tolerant crops: enhanced glyphosate-tolerance and tolerance to multiple herbicides

Thus far, we have discussed the threats posed by several glyphosate-resistant weeds, particularly GR Palmer amaranth. We have focused on GR weeds because their rise is intimately linked to the predominant HT cropping system. However, as discussed further below, biotech companies plan to introduce many more herbicide-tolerant crops, which represent their most active area of research and development. These crops are being developed in direct response to the glyphosate-resistant weed epidemic. In the programmatic EIS and proposed rule, APHIS keyed the revision of its regulation of GE crops to the in part different new risks presented by newer developments in agricultural biotechnology, such as pharmaceutical-producing crops and fitness-related traits. However, APHIS completely ignored significant new developments and associated risks in the HT crop arena, as evidenced by its extremely cursory and deficient treatment of the subject in the draft Programmatic Environmental Impact Statement (draft pEIS). In that document, APHIS provided absolutely no prospective assessment of this vigorous field of agricultural biotechnology research and development. In fact, the discussion did not even begin to address the existing problem of glyphosate-resistant weeds spawned by the currently dominant glyphosate-tolerant crop systems, failing to name, much less discuss, even one GR weed in the United States.[103] This serious deficiency must be remedied in the final rule. Below, we first

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and environmental impacts of glyphosate, see: FoE UK (2001). "Health and Environmental Impacts of Glyphosate," Friends of the Earth UK, July 2001. http://www.foe.co.uk/resource/reports/impacts_glyphosate.pdf.

[100] Benachour, N. & Seralini, G.E. (2009). "Glyphosate formulation induce apoptosis and necrosis in human umbilical, embryonic, and placental cells," *Chem. Res. Toxicol.* 22(1):97-105

[101] Relyea, R.A. (2005). "The lethal impact of Roundup on aquatic and terrestial amphibians," *Ecological Applications* 15(4): 1118-1124; Relyea, R.A., N.M Schoeppner & J.T. Hoverman (2005). "Pesticides and amphibians: the importance of community context," *Ecological Applications* 15(4): 1125-1134.

[102] Laws, F. (2006). "Glyphosate-resistant weeds more burden to growers' pocketbooks," *Delta Farm Press*, November 27, 2006, http://deltafarmpress.com/news/061127-glyphosate-weeds/. For an overview of recommendations by weed scientists and Monsanto for controlling and/or forestalling GR weeds, see: FoEI-CFS (2008). "Who Benefits from GM Crops? The Rise in Pesticide Use," Friends of the Earth International-Center for Food Safety, January 2008, Section 2.3. http://www.centerforfoodsafety.org/pubs/FoE%20I%20Who%20Benefits%202008%20-%20Exec%20Sum%20FINAL.pdf.

[103] USDA APHIS (2007). Introduction of Genetically Engineered Organisms, Draft Programmatic Environmental Impact Statement, July 2007. See pp. 119-121 for the thoroughly inadequate discussion of herbicide-tolerant crops, which fails to even name a single glyphosate-resistant weed population in the US.

describe some of these new developments, followed by an assessment of the potential risks they pose. Two themes emerge: crops with enhanced levels of glyphosate-tolerance, and crops with tolerance to multiple herbicides.

First, nearly half (6 of 14) of GM crops pending deregulation with USDA are herbicide-tolerant (see Table 1). This represents the near-term pipeline, and assuming they are approved, the near-term future of agricultural biotechnology.

Table 1: The 14 GM Crops Pending Deregulation (Commercial Approval) by USDA
(as of February 5, 2009)

Trait	No.	Notes
Tolerate 1 herbicide	5	Glyphosate-tolerant alfalfa and creeping bentgrass (Monsanto) Glyphosate-tolerant (1) and glufosinate-tolerant/insect-resistant (1) cotton (Bayer) ALS inhibitor-tolerant soybeans (BASF)
Tolerates 2 herbicides	1	Dual herbicide-tolerant corn tolerates glyphosate and imidazolinones (a class of ALS inhibitor herbicides) (DuPont-Pioneer)
Insect-resistant alone	2	Corn and cotton (Syngenta)
Virus-resistant	1	New version of old papaya trait (University of Florida)
Enzyme added	1	Corn w/ alpha-amylase enzyme derived from deep sea microorganisms for processing into ethanol. First GE industrial crop. Novel enzyme in corn has characteristics of food allergens, leading top U.S. food allergists to call for more careful evaluation of potential allergy-causing potential of this corn variety. South Africa has refused import clearance based in part on inadequate analysis of potential health impacts from consumption of this corn (Syngenta)
Sterile pollen, fertility altered	2	Corn with sterile pollen (DuPont-Pioneer); freeze-tolerant eucalyptus tree with altered fertility (ArborGen)
Oil alteration	1	High oleic acid soy for processing (DuPont-Pioneer)
Color alteration	1	Carnation (Florigene)

Source: USDA Petitions for Nonregulated Status Pending, February 5, 2009, at: http://www.aphis.usda.gov/brs/not_reg.html (last accessed February 9, 2009).

Enhanced resistance to glyphosate

There has been a trend to increase the level of glyphosate-tolerance in newer glyphosate-tolerant crops. This was first seen with the 2006 introduction of Monsanto's Roundup Ready Flex cotton, the successor to its original RR cotton.[104] The label for Roundup Ready Flex cotton recommends 1.5 times the application rate of that applied to original RR cotton (32 ounces/acre

[104] Bennett, D. (2005). "A look at Roundup Ready Flex cotton," *Delta Farm Press*, 2/24/05, http://deltafarmpress.com/news/050224-roundup-flex/.

for Flex vs. 22 ounces/acre for original RR cotton.[105] With original RR cotton, the CP4 EPSPS enzyme (RR trait) was not expressed in reproductive tissues, limiting the "application window" to the immature plant. RR Flex expresses the enzyme in reproductive tissues, permitting application of glyphosate to mature plants as well. With RR Flex cotton, farmers are enabled to wait until weeds become larger before applying glyphosate; larger weeds require higher application rates to kill, and are also more likely to flower and set seed. Any resistant individuals that are allowed to flower and set seed can then spread the resistance trait in two ways: 1) Spatially, through cross-pollination with susceptible weeds; and 2) Over time, by leaving weed seeds bearing the resistance trait in the seed bank to sprout in subsequent seasons. Introduction of RR Flex cotton may well have contributed to the steep (24%) increase in herbicide use on cotton from 2005 to 2007 (see Figure 6).

DuPont-Pioneer's Optimum GAT corn (pending approval by USDA)[106] contains a new mechanism of glyphosate resistance, different than Roundup Ready. GAT stands for glyphosate acetyltransferase, which inactivates glyphosate by adding an acetyl group to it. One report by DuPont scientists suggests that Optimum GAT corn may survive six times the normal dose of glyphosate "with no adverse symptoms."[107] This would permit higher doses of glyphosate application.

In a patent,[108] DuPont-Pioneer proposes to "stack" GAT with one or both of Monsanto's mechanisms of glyphosate-resistance (CP4 EPSPS and GOX [glyphosate oxidoreductase]) in order to enhance tolerance to glyphosate still more and so enable applications of higher rates to kill increasingly resistant weeds.

Likewise, a biotech startup company in North Carolina, Athenix, is also developing a bacterial gene to confer enhanced glyphosate tolerance in crops.[109]

Finally, APHIS recently deregulated Bayer CropScience's GlyTol cotton, which incorporates still another new mechanism of glyphosate resistance.[110] Bayer informed APHIS that the company did not request a glyphosate label change with EPA and is using the current label

[105] See Monsanto 2008 Technology Use Guide, pdf pages 31 and 34.
[106] USDA Petitions for Nonregulated Status and any (draft) environmental assessments (EA) by USDA's APHIS are listed at http://www.aphis.usda.gov/brs/not_reg.html. DuPont-Pioneer's corn is petition 07-152-01p. For fuller discussion of this dual-HR corn, see also: "Comments to USDA APHIS on Environmental Assessment for the Determination of Nonregulated Status for Pioneer Hi-Bred International, Inc. Herbicide Tolerant 98140 Corn," Center for Food Safety, February 6, 2009, http://www.centerforfoodsafety.org/pubs/CFS%20comments%20on%20Pioneer%20HT%2098140%20corn%20EA_final_2_6_09-FINAL.pdf.
[107] Castle et al (2004). "Discovery and directed evolution of a glyphosate tolerance gene," *Science* 304: 1151-54. For discussion, see CFS comments cited in last footnote.
[108] "Novel Glyphosate-N-Acetyltransferase (GAT) Genes," U.S. Patent 2005/0246798, issued Nov. 3, 2005, assigned to: Verdia, Inc. and Pioneer Hi-Bred International.
[109] Service, R.F. (2008). "A growing threat down on the farm," *Science* 316: 1114-1117.
[110] See USDA website listed above, petition 06-332-01p. For CFS comments, see: http://www.centerforfoodsafety.org/pubs/Bayer%20GlyTol%20Cotton%20Comments%20-%20CFS%20FINAL%208-18-08.pdf.

application rate of glyphosate on their GHB614 product.[111] However, Cheminova, Inc., a manufacturer of glyphosate and other pesticides based in Denmark, has applied for and obtained from EPA a tolerance increase for residues of glyphosate on cotton gin byproducts (from 175 to 210 ppm) that was specifically linked to introduction of GlyTol cotton.

> "Cheminova, Inc. has requested a Section 3 registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for application glyphosate to glyphosate-tolerant cotton including Bayer GHB614 cotton (GlyTol cotton), a genetically modified cotton being commercialized by Bayer Crop Science. As a result, the petitioner has requested that the current tolerance for cotton, gin byproducts be increased to 210 ppm."[112]

In this same FR notice, EPA also refers to an Agency review entitled "Glyphosate Label Amendment to Permit Application of Glyphosate to Bayer's Glyphosate-Tolerant Cotton GHB614."[113] Thus, it appears that introduction of Bayer's GlyTol cotton requires both a tolerance increase and a glyphosate label amendment, suggesting that higher rates of glyphosate will be applied to this glyphosate-tolerant cotton; otherwise, there would seem to be little reason to seek and obtain a tolerance increase. The preexisting glyphosate tolerance for cotton gin byproducts was 175 ppm, which itself represented an increase from the corresponding tolerance prevailing in 2000 of 100 pm.

Multiple herbicide-resistant crops

Agrichemical-biotech firms are also devoting substantial research and development efforts to herbicide-resistant crops that withstand two or more herbicides rather than just one.

DuPont-Pioneer has developed Optimum GAT soybeans[114] and corn, both of which combine enhanced GAT resistance to glyphosate with resistance to ALS-inhibitor herbicides. Optimum GAT soybeans were granted commercial approval last year; as noted above, Optimum GAT corn is pending approval by USDA. Optimum GAT crops combine resistance to the two classes of herbicides (glycines [of which glyphosate is the only member] and ALS inhibitors) to which weeds have developed the most extensive resistance (by acreage) in the United States (see Figure 4 above). BASF is also developing ALS inhibitor-resistant soybeans, which are currently pending deregulation by USDA as transformation event BPS-CV127-9.[115] These soybeans may well be stacked with resistance to glyphosate in the context of the Monsanto-BASF joint-licensing agreement (discussed below).

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[111] APHIS (2009). "Determination of Non-regulated Status for Glyphosate-Tolerant (GlyTol) Cotton, Gossypoium hirsutum, event GHB614: Final Environmental Assessment, April 15, 2009, Response to Comments section, p. 24.

[112] EPA (2009). "Glyphosate; Pesticide Tolerances," FR Vol. 24, No. 120, June 24, 2009, pp. 29963-29996.

[113] Id., p. 29964.

[114] See USDA website listed above, petition 06-271-01p. For CFS comments, see: http://www.centerforfoodsafety.org/pubs/Dupont%20GAT%20Comments%20FINAL%2012-4-07.pdf.

[115] See USDA website noted above, petition #09-015-01p. Though USDA does not identify the class of herbicides to which these soybeans are resistant, a search on the transformation event turned up a field trial application notice in Japan, where BPS-CV127-9 soybeans are identified as resistant to imidazolinone, one class of ALS inhibitor herbicides; see http://www.bch.biodic.go.jp/english/lmo_2008.html.

In collaboration with the University of Nebraska, Monsanto has developed soybeans that are tolerant to the chlorophenoxy herbicide dicamba.[116] These dicamba-tolerant soybeans are to be stacked with resistance to glyphosate in the context of a joint-licensing agreement with BASF, the largest producer of dicamba.[117] Dicamba-resistant corn and cotton are also projected, ***with potential triple-stacking of herbicide tolerance to dicamba, glyphosate and glufosinate.***[118]

Dow Agrosciences is developing corn and soybeans that are tolerant to the chlorophenoxy herbicide 2,4-D, one component of the Vietnam War defoliant Agent Orange and one of the first widely used herbicides, stacked with tolerance to aryloxyphenoxypropionate grass herbicides of the ACCase inhibitor class. Dow projects introduction of dual 2,4-D/ACCase-tolerant corn in 2012 and 2,4-D/ACCase-tolerant soybeans in 2013 or 2014.[119] The farm press reports that a similar dual-tolerant cotton variety may also be introduced.[120]

Finally, Monsanto and Dow are collaborating to produce "SmartStax" corn, which combines resistance to glyphosate and glufosinate, together with six Bt insecticidal toxins.[121]

There are several indications of the longer-term plans of biotechnology companies with respect to herbicide-tolerant crops. The table below, reproduced from a scientific paper by DuPont-Pioneer scientists, reveals that 12 transgenes conferring resistance to most major classes of herbicides have been developed, and represent likely candidates for a host of new (multiple) herbicide tolerant crops.

Non-glyphosate resistant transgenes that are not currently commercial
(adapted from Reference 48)

Herbicide/herbicide class	Characteristics	Reference
2,4-D	Microbial degradation enzyme	49
Aryloxyphenoxyoxypropionate ACCase inhibitor	Microbial aryloxyalkanoate dioxygenase	50
Asulam	Microbial dihydropteroate synthase	51
Dalapon	Microbial degradation enzyme	52
Dicamba	*Pseudomonas maltophilia,* O-demethylase	45
Hydroxyphenylpyruvate dioxidase (HPPD) inhibitors	Overexpression, alternate pathway, and increasing flux of pathway	53
Phenylurea	*Helianthus tuberosus*, P450	54
Paraquat	Chloroplast superoxide dismutase	55
Phenmedipham	Microbial degradation enzyme	56
Phenoxy acid (auxin)	Microbial, aryloxyalkanoate dioxygenase	50
Phytoene desaturase (PDS) inhibitors	Resistant microbial and Hydrilla PDS	57
Protoporphyrinogen oxidase (PPO) inhibitors	Resistant microbial and *Arabidopsis thaliana* PPO	58

[116] Behrens, M.R. et al (2008). "Dicamba resistance: enlarging and preserving biotechnology-based weed management strategies," *Science* 316: 1185-1188; Service, R.F. (2008). "A growing threat down on the farm," *Science* 316: 1114-1117.
[117] Monsanto (2009). "BASF and Monsanto formalize agreement to develop dicamba-based formulation technologies," Press Release, Jan. 20, 2009, http://monsanto.mediaroom.com/index.php?s=43&item=683
[118] Robinson, E. (2008). "Weed control growing much more complex, new tools coming," Delta Farm Press, March 27, 2008. http://deltafarmpress.com/cotton/weed-control-0327/index.html.
[119] Dow (2007). "Dow AgroSciences reveals progress on new herbicide tolerance trait," August 28, 2007. http://www.dowagro.com/newsroom/corporatenews/2007/20070828a.htm.
[120] Robinson, E. (2008), op. cit.
[121] http://www.monsanto.com/pdf/investors/2007/09-14-07.pdf.

Source: Excerpted from Green et al (2007). "New multiple-herbicide crop resistance and formulation technology to augment the utility of glyphosate," *Pest Management Science* 64(4):332-9.

Likewise, a recent patent assigned to DuPont-Pioneer envisions development of individual herbicide-tolerant crops that tolerate application of seven or more different herbicides.

> "In some embodiments, a composition of the invention (e.g. a plant) may comprise two, three, four, five, six, seven, or more traits which confer tolerance to at least one herbicide, so that a plant of the invention may be tolerant to at least two, three, four, five, six, or seven or more different types of herbicides."[122]

Ongoing field tests involving HT crops:
The table above lists herbicide-resistance transgenes available for developing GE crops with new HT traits, but does not tell us whether these new HT traits are being field-tested in GE crops. CFS undertook an analysis of USDA's GE crop field trial database in an attempt to determine which HT traits/crops are currently undergoing field tests.[123] As of April 7, 2009, there were 812 active permits issued by USDA for GE crop field trials; 283 or 35% involved herbicide-tolerant crops (some of these permits authorized field-testing of other traits in addition to herbicide tolerance). Since some field trial permits authorized field testing of various single-trait HT plants each resistant to different herbicides (e.g. some glyphosate-resistant, others dicamba-resistant), the total number of HT phenotypes was 327. Still other permits involved combinations of 2 or 3 HT traits in the same plant (23 and 4 permits, respectively); when these HT traits are counted separately, the total number of HT traits comes to 358.[124] Of these 358 HT traits, 164 (46%) were glyphosate-resistance, 47 (13%) were dicamba-resistance, 24 (7%) were glufosinate-resistance,[125] and 18 (5%) ALS inhibitor-resistance.[126] Interestingly, a significant proportion of HT traits (105 or 29%) were labeled as "confidential business information" (CBI) or otherwise not specified (e.g. the phenotype entry was merely "herbicide tolerance" or "agrichemical tolerance").

Active HT crop field trial permits involve 12 crops, though the great majority of permits (91%) are for HT soybeans (118), HT corn (99), HT cotton (23) and HT alfalfa (19). Of the 283 permits, 242 (85.5%) were granted to one of the big 6 biotechnology/ agrichemical firms:

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[122] "Novel Glyphosate-N-Acetyltransferase (GAT) Genes," U.S. Patent Application Publication, Pub. No. US 2009/0011938 A1, January 8, 2009, paragraph 33.

[123] Two searches conducted at http://www.isb.vt.edu/cfdocs/fieldtests1.cfm. All active permits for GE crop field trials determined on 4/7/09 by checking the "phenotype category" on first page, then selecting all phenotype categories and "field test permits currently in effect" and "short record" on the next page. For active HT crop field trials, search conducted on 4/5/09 by checking "phenotype category" on first page and "herbicide-tolerance," "field test permits currently in effect" and "full record" on the next webpage. Permits with "status" of "withdrawn" or "denied" were excluded from the analysis of both total active field trials and active HT crop field trials.

[124] It is important to note that the relatively few field trials involving plants with multiple (2 or 3) HT traits does ***not*** indicate correspondingly little interest in developing multiple HT crops. USDA "deregulation" of a single-trait HT crop event covers any progeny of that event, including conventional crosses with any other already deregulated HT crop. Thus, multiple HT crops can come to market without undergoing a separate deregulation process.

[125] Includes entries for phosphinothricin tolerance and one for "bar gene." Phosphinothricin is an alternate name for glufosinate, and the bar gene confers resistance to phosphinothricin.

[126] Includes entries for imidazolinone- and sulfonylurea-tolerance, since these are types of ALS inhibitor herbicides.

Monsanto (112), Dow (46), DuPont-Pioneer (42), Syngenta (18), Bayer (18), and BASF (6). The remainder were granted to smaller private firms (33) or universities (8).

The fact that over one-third (35%) of active GM crop field trial permits involve HT crops indicates continuing strong interest in this trait category among GE crop developers, underscoring the need for APHIS to deal comprehensively with HT crops in its revised rules. It is interesting to note the preponderance of glyphosate-tolerance in active HT field trial permits. This – and the entry into the glyphosate-resistance market of DuPont-Pioneer and Bayer noted above – indicates strong interest in deploying new crops with glyphosate-resistance, despite the growing problem of glyphosate-resistant weeds. We can infer from this that selection pressure for GR weeds will at the very least maintain its current high levels, and probably increase in the near- to medium-term future. Although only 4 HT traits are listed in USDA's database, the large number of "confidential" or otherwise unspecified HT traits (105 or 29%) indicates that GE crops with resistance to other herbicides (perhaps some of those listed in the table above) are being field-tested. Interestingly, the HT trait in all of Dow's 46 active field trial permits for HR crops (involving corn, soybeans, cotton and tobacco) was labeled CBI. Based on the information presented above, many of these HT crops are likely to be 2,4-D-resistant. Other companies also hid the identity of HT traits they are field-testing, including Bayer (19 permits), Syngenta (17) and Monsanto (15).

<u>5) Consequences of enhanced glyphosate and multiple herbicide tolerant crop systems</u>

Enhanced glyphosate tolerance in crops will likely accelerate the expansion of and level of resistance in glyphosate-resistant weeds, undermining the efficacy of this herbicide

Roundup Ready cropping systems have fostered overreliance on glyphosate for weed control. This overreliance has given rise to sharply expanding acreage infested with glyphosate-resistant weeds. Growers were encouraged to rely exclusively on glyphosate by Monsanto,[127] whose scientists discounted the possibility of glyphosate-resistant weed evolution.[128] Surprisingly, APHIS continues to repeat this abundantly disproven myth that weeds are not likely to develop resistance to glyphosate, or to do so only slowly, in the draft PEIS.[129] Despite repeated exhortations from weed scientists (and, belatedly, by Monsanto and other biotech companies) to use multiple herbicides to slow evolution of resistance to glyphosate, many growers have been reluctant to do so. Surveys still show fairly high levels of exclusive reliance on glyphosate for weed control in soybeans (40-50%) and lesser but still substantial dependence on glyphosate alone in cotton (about 20% of farmers).[130]

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[127] Shaner, D.L. (2000). "The impact of glyphosate-tolerant crops on the use of other herbicides and on resistance management," Pest Management Science 56: 320-26.
[128] Bradshaw LD, Padgette SR, Kimball SL and Wells BH, Perspectives on glyphosate resistance. *Weed Technol* **11**:189–198 (1997).
[129] USDA APHIS (2007). Introduction of Genetically Engineered Organisms, Draft Programmatic Environmental Impact Statement, July 2007. See pp. 119-121 for the thoroughly inadequate discussion of herbicide-tolerant crops, which fails to even name a single glyphosate-resistant weed population in the US.
[130] Foresman, C, Glasgow, L. (2008). "US grower perceptions and experiences with glyphosate-resistant weeds," Pest Management Science.

The enhanced tolerance to glyphosate discussed above enables farmers to apply higher rates of glyphosate, which in turn will encourage a delay in glyphosate application until weeds become larger.[131] (Higher doses allow larger weeds to be killed.) In the case of Roundup Ready Flex cotton, the ability to apply glyphosate throughout the crop's lifespan further facilitates this practice. Delaying application in turn increases the likelihood that weeds, including any resistant individuals that are present in the population, will mature to produce pollen and set seed. Pollen and seed carrying the resistance trait will spread it spatially (through cross-pollination with susceptible weeds) and temporally (seeds with resistance trait entering the seed bank). This helps explain why weed experts continually exhort farmers to control weeds when they are small, and NOT to delay application until they are larger.

The short-term fix of enhanced glyphosate tolerance will thus faciliate continued postponement of the diversification of weed management practices (including non-chemical options[132]) that all agree is essential to save glyphosate as a viable weed control tool. Enhanced glyphosate resistance will thus likely have the effect of accelerating the rate of increase of glyphosate-resistance in weeds, and the demise of glyphosate as an effective weed control agent.

Some argue that combining glyphosate tolerance with tolerance to one or more additional herbicides provides the opportunity for better control of weeds resistant to any one of the HT crop-associated herbicides, in particular GR weeds.[133] However, there are several problems with this line of thinking. First, it is very unclear whether growers will make much use of any non-glyphosate herbicides to which the crop is tolerant, at least in the near-term, especially if enhanced glyphosate tolerance gives the grower the option of applying higher rates of glyphosate. The predilection for sticking with glyphosate will be especially strong in those crops that combine tolerance to glyphosate and ALS inhibitors. ALS inhibitor use on corn and especially soybeans has dropped off sharply in recent years, [134] in part due to massive evolution of ALS inhibitor-resistant weeds (see Figure 4). In fact, it is well established that the widespread inefficacy of many ALS inhibitors was one factor driving adoption of Roundup Ready crops.[135] In addition, because the ALS inhibitor resistance trait has little or no fitness costs in many weed species,[136] many of the resistant weeds reported in the late 1980s and early 1990s likely retain their resistance, further discouraging use of ALS inhibitors. Some reports even suggest that ALS

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[131] Green et al (2007). "New multiple-herbicide crop resistance and formulation technology to augment the utility of glyphosate," *Pest Management Science* 64(4):332-9. Green et al suggest a money- and time-saving motive for this practice: "Many growers waited until the weeds were large in the hope that all the weeds had emerged and only one application would be needed."

[132] Owen, MDK (2008), op. cit. Owen discusses crop rotation as one non-chemical method to mitigate weed resistance.

[133] Green et al (2007), op. cit.

[134] See discussions in CFS comments on DuPont-Pioneer's Optimum GAT soybeans and corn, cited above, which reference USDA NASS data on percent of overall acres of each crop treated with ALS inhibitor herbicides. The decline in acres treated with ALS inhibitors is particularly sharp with soybeans, but is also occurring with corn.

[135] Owen & Zelaya (2005). "Herbicide-resistant crops and weed resistance to herbicides," *Pest Management Science* 61: 301-311.

[136] Powles & Preston (2006), "Evolved glyphosate resistance in plants: biochemical and genetic basis of resistance," *Weed Technology* 20: 282-289, see p. 285.

inhibitor-resistant weeds can have ***enhanced*** fitness in the absence of selection pressure from ALS inhibitor use.[137]

Multiple herbicide-resistant weeds
The likely tendency of growers to make preferential use of glyphosate on dual glyphosate/ALS inhibitor-tolerant crops will continue to exert selection pressure for development of dual-HR weeds. This is particularly true of common waterhemp, which has massive populations resistant to ALS inhibitor herbicides throughout the Midwest (up to 5.1 million acres, according to WSSC-HRAC, but possibly much more). Thus, such dual-tolerant crops will likely do little if anything to stem the steep rise in glyphosate use with dramatically increasing adoption of RR corn. WSSC-HRAC currently list three biotypes of weeds that already possess dual glyhosate/ALS inhibitor-resistance: a population of resistant horseweed in Ohio that infest up to 500 acres; a population of dual-resistant common waterhemp in Illinois; and a population of triple-resistant common waterhemp infesting up to 10,000 acres in Missouri (also resistant to PPO inhibitors). The resistance to the PPO inhibitors developed, predictably, from use of PPO inhibitors to kill waterhemp that had become resistant to ALS-inhibitors.[138] Both Missouri and especially Illinois have million acre infestations of ALS-inhibitor-resistant common waterhemp. The problem could become much worse. One Midwestern weed expert has heard anecdotal reports from farmers of inconsistent control of common waterhemp with glyphosate. He confirmed substantial inherent variability in the susceptibility to glyphosate (18-fold) in an Iowa population of common waterhemp, was able to select for populations with decreased sensitivity to glyphosate, and concluded that: "the potential for the evolution of glyphosate resistance is significant." He further noted that the potential for glyphosate resistance "is relevant as most *A tuberculatus* [waterhemp] populations in the Midwest are suspected to be resistant to ALS-inhibiting herbicides and ***further selection pressure by glyphosate may select for multiple-resistant populations."***[139]

Multiple herbicide resistance in this weed is of great concern because waterhemp is considered the number one weed problem for Illinois corn and soybean growers, in part because of its ability to grow 2-3 meters tall, emerge over an extended period of time late into the growing season, and substantially decrease corn yields even at relatively low levels of infestation.[140]

We have noted the emergence of several new populations of multiple-herbicide resistance weeds above, and cited weed experts as projecting many more arising in the near future, in connection with HT crop systems.

Burnout of glyphosate, followed by weeds resistant to other HT-crop associated herbicides
In the longer term, the burnout of glyphosate as an effective weed control tool will likely drive adoption of crops genetically engineered for tolerance to dicamba, 2,4-D and other herbicides, in

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[137] Tranel & Wright (2002). "Resistance of weeds to ALS-inhibiting herbicides: what have we learned?" *Weed Science* 50: 700-712, see p. 706.
[138] Owen & Zelaya (2005), op. cit.
[139] Zelaya & Owen (2005). "Differential response of *Amaranthus tuberculatus* (Moq ex DC) JD Sauer to glyphosate," *Pest Manag Sci* 61: 936-950.
[140] Steckel & Sprague (2004). "Common waterhemp (*Amaranthus rudis*) interference in corn," *Weed Science* 52: 359-64.

turn spawning new waves of weeds resistant to those herbicides. In short, the "pesticide treadmill" will be likely be accelerated by the "transgenic treadmill."[141]

6) Health consequences of herbicide-tolerant crop systems

In prior comments on this rulemaking and elsewhere, CFS has pointed to the adverse health and environmental impacts of increasing herbicide use, including glyphosate. If crops tolerant to dicamba, 2,4-D and other herbicides become prevalent, we can expect substantial increases in their use, as glyphosate use has exploded with proliferation of Roundup Ready crops. This in turn will lead to exacerbation of negative health impacts on farmers/farmworkers who apply these pesticides. Two near-term HT crop systems described above involve tolerance to dicamba and 2,4-D, which are members of the class of chlorophenoxy herbicides and are well-known to have carcinogenic and/or endocrine disrupting activity.

> "Dicamba is an old, relatively high-risk herbicide. It is genotoxic (damages the DNA in cells) and has been linked to elevated rates of cancer among farm populations. It is mobile in soils and prone to leaching to groundwater. Dicamba is moderately persistent and will no doubt trigger a host of environmental problems if its use jumps 10-fold or more, as is likely if dicamba resistant soybeans are widely adopted."[142]

According to anecdotal reports from several farmers, dicamba, once applied, is very prone to being lifted and carried by the wind, in some cases for a mile or more, to damage other plants and crops. Human exposure to revolatized, drifting dicamba is of course also likely. Increased use of dicamba from adoption of dicamba-resistant soybeans could thus have both negative health impacts as well as serious agronomic and economic impacts on neighboring growers, including crop damage and associated economic losses. It might also lead to costly "defensive" adoption of dicamba-resistant crops not from desire to make use of the trait, but rather for protection against damage that would otherwise be caused by dicamba drift. Glyphosate spray drift has had serious negative impacts on neighboring non-Roundup Ready growers, and some farmers reportedly purchase Roundup Ready crops for precisely such "defensive" reasons.[143] Arkansas state officials were or are considering regulations to minimize glyphosate spray drift damage to non-RR crops.[144] Needless to say, many other herbicides likely pose similar drift threats to neighboring growers.

2,4-D is another chlorophenoxy herbicide that has been associated with a number of adverse health impacts on agricultural workers who apply it: increased risk of cancer, particularly non-

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[141] Binimelis, R., et al. ''Transgenic treadmill": Responses to the emergence and spread of glyphosate-resistant johnsongrass in Argentina. Geoforum (2009), doi:10.1016/j.geoforum.2009.03.009.

[142] Excerpted from: Organic Center (2007). "Dicamba-resistant soybeans to the rescue?" The Organic Center, June 2007, http://www.organic-center.org/science.hot.php?action=view&report_id=96. For an account of dicamba's adverse health impacts , see Cox, C. (1994). "Dicamba Fact Sheet," Journal of Pesticide Reform 14(1), Spring 1994, at: http://www.pesticide.org/dicamba.pdf.

[143] Arax, M. and J. Brokaw (1997). "No Way Around Roundup," *Mother Jones*, January/February 1997. http://www.motherjones.com/news/feature/1997/01/brokaw.html.

[144] Bennett, D. (2007). "A difference of opinion: glyphosate drift and formulations," *Delta Farm Press*, January 29, 2007. http://deltafarmpress.com/news/070129-glyphosate-drift/index.html

Hodgkin's lymphoma, and increased rate of birth defects in children of men who apply the herbicide. 2,4-D is also a suspected endocrine disruptor.[145]

The State of California has recently placed the entire class of chlorophenoxy herbicides on its "toxics" list as probable human carcinogens.[146]

HR crops mean greater exposure to HR crop-associated herbicides:
A little-discussed consequence of "over-the-top" herbicide application to HR crops (for the most part impossible with herbicides used with conventional crops) is increased livestock exposure to the HR crop-associated herbicide in feed, and perhaps, at least in some cases, increased human exposure to residues of the herbicide in foods. Biotech companies have obtained new or increased herbicide "tolerances" (maximum allowable residues) from EPA to facilitate introduction of certain HR crops. For instance, at the request of Aventis CropScience (now Bayer CropScience), EPA established new tolerances for residues of glufosinate on food and feed products derived from transgenic versions of canola, cotton, corn, rice, soybean and sugar beet.[147] These tolerances were obtained specifically for Bayer's glufosinate-tolerant, LibertyLink versions of these crops. Monsanto has obtained from the EPA numerous tolerance increases for glyphosate residues associated with its Roundup Ready crops, including: from 6 ppm to 20 ppm for soybeans (raw agricultural commodity) several years before the commercial introduction of Roundup Ready soybeans;[148] from 0.2 ppm for sugar beets (as a whole) to 10, 10 and 25 ppm for sugar beet roots, tops and dried pulp, respectively, a few months after deregulation of the first Roundup Ready sugar beets;[149] and from 75 ppm to 175 ppm for alfalfa forage and 200 ppm to 400 ppm for alfalfa hay several years prior to Monsanto's first attempt to gain nonregulated status for Roundup Ready alfalfa in 2003.[150] In December 2008, EPA granted DuPont's request to amend existing glyphosate tolerances to include the N-acetyl-glyphosate metabolite produced by the GAT enzyme incorporated into its GAT soybeans and corn, and to substantially increase the (thus amended) glyphosate tolerance for aspirated grain fractions (fragments or dust of grain, often fed to beef livestock) from 200 to 310 ppm. This same rule also appears to increase glyphosate tolerances for a variety of meat byproducts.[151] As noted

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[145] For more, see "2,4-D: chemicalWATCH Fact Sheet," Beyond Pesticides, at: http://www.beyondpesticides.org/pesticides/factsheets/2,4-D.pdf. For restrictions on residential use of 2,4-D in various countries, see: http://en.wikipedia.org/wiki/2,4-D.

[146] Daily Green (2009). "30 'new' toxic chemicals to avoid," Daily Green, June 17, 2009. http://www.thedailygreen.com/environmental-news/latest/toxic-chemicals-47061601

[147] EPA (2003). Glufosinate-Ammonium; Pesticide Tolerance. *Federal Register*, Vol. 68, No. 188, Sept. 29, 2003: 55833-55849. It is interesting to note that EPA's tolerances apply only to ***transgenic*** versions of these crops.

[148] EPA RULE (1992). "Pesticide Tolerances and Food and Feed Additive Regulations for Glyphosate," Final Rule, *Federal Register,* Sept. 16, 1992, Vol. 57: 42700.

[149] EPA (1999). "Glyphosate; Pesticide Tolerance," Final Rule, Federal Register, April 14, 1999, Vol. 64, No. 71: 18360-18367.

[150] For old and new tolerances, respectively, see table at end of following rules: EPA (2000a). "Glyphosate; Pesticide Tolerance," Final Rule, Federal Register, Aug. 30, 2000, Vol. 65, No. 169: 52660-52667, http://www.epa.gov/EPA-PEST/2000/August/Day-30/p22168.htm; EPA (2000b). "Glyphosate; Pesticide Tolerance," Final Rule, Federal Register, Sept. 27, 2000, Vol. 65, No. 188: 57957-57966, http://www.epa.gov/EPA-PEST/2000/September/Day-27/p24318.htm.

[151] EPA (2008). "Glyphosate; Pesticide Tolerances," Final Rule, *Federal Register,* Dec. 3, 2008, Vol. 73, No. 233: 73586-73592; for old glyphosate tolerance for aspirated grain fractions and for various meat products, see EPA (2000b), op. cit. One problem in tracking glyphosate tolerances for specific items over time is the EPA's frequent reshuffling of tolerance categories.

above, the introduction of Roundup Ready Flex cotton was associated with a label change recommending 50% higher glyphosate application rates, while GlyTol cotton was associated with a glyphosate tolerance increase on cotton gin byproducts.

Based on this history, one can expect biotech companies to seek new and/or increased tolerances for the herbicides associated with new (multiple) HR crops as they come closer to commercial introduction. We note that multiple HR crops could easily have increased residues of two or more different herbicides, raising additional food and feed safety concerns (e.g. potential adverse synergistic effects of multiple herbicide residues).[152]

Multiple herbicide-resistant crops represent largely unchartered territory that requires careful assessment and regulation

Many weed scientists predicted little or no development of glyphosate-resistant weeds in the early and mid 1990s, prior to the introduction of Roundup Ready soybeans.[153] These optimistic predictions have been proven decisively wrong by events in the field, and should serve as a cautionary tale in assessments of the potential of enhanced glyphosate-tolerant and multiple herbicide-resistant crop systems to foster expanding populations of (multiple) herbicide-resistant weeds, and further increases in herbicide use, with negative environmental, human health and agronomic consequences.

7) Recommendations for APHIS regulation of HT crop systems

APHIS regulates GE crops under the Plant Protection Act (PPA). The PPA endows APHIS with the statutory authority to regulate practices that lead to the introduction and propagation of noxious weeds, for instance, importation or interstate movement of materials that may harbor seeds or other viable parts of weeds deemed noxious.

In these supplementary comments and prior comments on this rulemaking, CFS has demonstrated the clear propensity of HT crop systems (cultivation of an HT crop and associated herbicide application practices) to foster the rapid evolution and propagation of herbicide-resistant weeds that can be extremely aggressive, injurious to the interests of agriculture, and much more difficult to control or manage than the non-herbicide-resistant version of the same weed species. CFS has also presented case studies of several herbicide-resistant weeds ***that would not exist absent the introduction and unregulated use of the associated herbicide-tolerant crop systems, and which pose serious threats to the interests of agriculture.*** The case study of glyphosate-resistant Palmer amaranth, in particular, demonstrates the noxious character of an herbicide-resistant weed that owes its existence and massive propagation directly to the unregulated use of glyphosate-tolerant crop systems, and which is regarded by agronomic

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[152] For a brief discussion, see: Center for Food Safety's comments on USDA's Programmatic Environmental Impact Statement on GM crops, pp. 59-61, at http://www.centerforfoodsafety.org/pubs/USDA%20PEIS%20Comment%20Master%20FINAL%20-%209%2011%2007.pdf

[153] Waters, S. (1991). "Glyphosate tolerant crops for the future: development, risks, and benefits," Proceedings of the Brighton Crop Protection Conference: Weeds 165-170; Jasieniuk M, Constraints on the evolution of glyphosate resistance in weeds. *Resistant Pest Manag Newslett* **7**:31–32 (1995); Bradshaw LD, Padgette SR, Kimball SL and Wells BH, Perspectives on glyphosate resistance. *Weed Technol* **11**:189–198 (1997); Watkinson et al (2000). "Glyphosate-resistant crops: history, status and future," Pest Manag. Sci. 61: 219-224.

experts as presenting a serious threat to the viability of continued cotton production in the United States.

CFS encourages APHIS to exercize its noxious weed authority to assess, and regulate as needed, herbicide-tolerant crops and associated herbicide application practices (i.e. HT crop systems). Such regulation could take several forms, including:

1) Reject petitions for deregulation in those cases where the unregulated use of HT crop systems pose threats to the interests of agriculture, the environment, and/or human health, including the health of pesticide applicators. This regulatory option should be chosen when a cumulative assessment of the HT crop proposed for deregulation against the backdrop of existing HT crops demonstrates a significantly increased risks for increased herbicide use, accelerated development of noxious resistant weeds, increased weed control costs, etc.

2) Allow commercial cultivation of HT crop systems, but with appropriate restrictions and continuing regulatory authority, to mitigate potential risks. For instance, APHIS could:
   a) Impose "stacking" restrictions disallowing the combination of the GE crop event at issue with other GE crop events when such stacking would lead to unacceptable outcomes – e.g. enhanced glyphosate tolerance from combination of multiple modes of action of glyphosate tolerance, contributing to the "burnout" of glyphosate as an effective weed control tool;
   b) Geographic restrictions to disallow cultivation of the HT crop in areas where it would exacerbate existing problems re: excessive pesticide use and resistant weed evolution; and
   c) Mandatory monitoring for evolution of resistant weeds by university or other independent agronomic experts, with continuing regulatory authority to mitigate risks if and as they arise. A recommendation similar to this was recently recommended by the Government Accountability Office.[154]

3) Designate herbicide-resistant biotypes of weed species as federally-listed noxious weeds, in those cases where herbicide resistance confers upon the otherwise less problematic weed characteristics that raise it to the status of noxious. Designation of herbicide-resistant biotypes as noxious weeds should be accompanied by regulatory controls and restrictions, as needed, on the HT crop systems that accelerate the evolution of such weeds.

4) Mandatory herbicide-resistant weed management plans, to forestall or slow the development of weed resistance to HT crop-associated herbicide(s). The EPA's resistance management program for GE insect-resistant crops offers a valuable model for APHIS in this regard. To this end, APHIS should revive its moribund collaboration with EPA on developing herbicide-resistant weed management plans for each and every HT crop that is considered for commercial cultivation.

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[154] GAO (2008). "Genetically engineered crops: Agencies are proposing changes to improve oversight, but could take additional steps to enhance coordination and monitoring," Report to the Committee on Agriculture, Nutrition, and Forestry, U.S. Senate, U.S. Government Accountability Office, GAO 09-060, Nov. 2008, pp. 30-31.

5) APHIS should also confer with sister USDA agencies, such as the Agricultural Research Service, to better coordinate its regulatory practices with ongoing research activities. For instance, ARS's Action Plan: 2008-2013 (cited above) has significant components related to the mitigation and management of pesticide resistance, including herbicide-resistant weeds. These research initiatives include development of non-chemical weed control techniques, as are also being explored by academic scientists.[155] It makes no sense for APHIS to make decisions that lead to exacerbation of threats like herbicide-resistant weeds to which its sister agencies are seeking solutions.

6) APHIS should also seek input from independent agronomic experts to better inform its rule-making with respect to biotech crops, as recommended by a National Academy of Sciences committee in 2002, and as promised by former APHIS Administrator Bobby Accord.

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[155] As one example, for use of cover crops to mitigate GR Palmer amaranth, see: Culpepper, S. and J. Kichler (2009), op. cit.; and Robinson, E. (2008c). "Weed control growing much more complex, new tools coming," Delta Farm Press, March 27, 2008.