Environmental Protection Agency
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Comments to EPA on EPA's Proposed Registration of Enlist Duo™ Herbicide Containing 2,4-D and Glyphosate for New Uses on Enlist Corn and Enlist Soybeans in Ten Additional States

On October 15, 2014, the EPA registered Enlist Duo – an herbicide formulation containing the dimethylammonium salt of glyphosate and the choline salt of 2,4-dichlorophenoxyacetic acid (2,4-D) – for use on Enlist corn and soybeans, which have been genetically engineered for resistance to glyphosate and 2,4-D, in six states: Illinois, Indiana, Iowa, Ohio, South Dakota and Wisconsin. These comments are in response to EPA's proposal to register Enlist Duo for use in in ten additional states: Arkansas, Kansas, Louisiana, Minnesota, Missouri, Mississippi, Nebraska, Oklahoma, Tennessee and North Dakota.

Center for Food Safety (CFS) has engaged the EPA throughout the regulatory process for new uses of 2,4-D and Enlist Duo herbicide on Enlist corn and soybeans. CFS has also commented on the preliminary phase of EPA's registration review of 2,4-D. CFS's prior comments to EPA, together with supporting materials, are being submitted. In these comments, we make reference to past comments as follows:

CFS Enlist Duo 2012: Comments to EPA on Notice of Applications to Register New Uses of 2,4-D on Enlist Corn and Soybean, Docket No. EPA-HQ-OPP-2012-0330, submitted on June 22, 2012

CFS Registration Review 2013: Comments on Registration Review of the Herbicide 2,4-D, Docket No. EPA-HQ-OPP-2012-0330, submitted February 12, 2013

CFS Enlist Duo 2014: Appendix A: Comments to EPA on EPA's Proposed Registration of Enlist Duo™ Herbicide Containing 2,4-D and Glyphosate for New Uses on Herbicide-Tolerant Corn and Soybean, Appendix A, Docket Noj. EPA-HQ-OPP-2014-0195, submitted on June 30, 2014.

We here summarize key points from our past comments, and introduce new issues, together with supporting materials not previously submitted. The References section at the end of these comments list only new supporting materials.

American agriculture stands at a crossroads. Approval of Enlist Duo for use in ten additional states (16 altogether) will set American agriculture on an entirely unsustainable path of more intensive use of old and toxic pesticides, increased rates of cancer and other diseases, environmental harms, increasing crop damage from herbicide drift, increasingly intractable weeds, continuing consolidation of farmland in ever fewer hands, and sharply rising farmer production costs. This is the path American agriculture will take with EPA approval of the proposed registration of Enlist Duo. A more sustainable path is possible, but it will become ever less possible to take with the broader introduction of the Enlist crop system enabled by the proposed registration for ten additional states.

Agricultural biotechnology firms have long promised less dependence on toxic pesticides. Instead, hundreds of millions of dollars are being invested to engineer crops for resistance to multiple herbicides (Kilman 2010). Herbicides represent two-thirds of overall pesticide use in American agriculture (EPA 2011), and biotech agriculture's present and future is dominated by herbicide-resistant crops (Table 1). Dow officer John Jachetta welcomes these new crops as inaugurating "a new era" and "a very significant opportunity" for chemical companies to increase herbicide use and sales (as quoted in Kilman 2010). As pesticide regulator, EPA determines whether, and if so how, herbicides can be applied to these "next-generation" GE herbicide-resistant crops, including the application of Enlist Duo to Dow's Enlist corn and soybeans, the subject of these comments.

From bioremediation to herbicide-resistant crops

Dow's development of Enlist crops relied heavily on extensive public sector research into "bioremediation." An early goal of biotechnology research was to genetically engineer microbes to break down and hence detoxify pesticides and other harmful industrial chemicals contaminating our soils and water. European scientists discovered bacterial strains in soils that survived contact with 2,4-D and related chlorophenoxy herbicides (e.g. Horvath et al 1990, Kohler 1999). They isolated the strains and the genes that made the bacteria resistant to 2,4-D, and elucidated the mechanisms by which they degraded and detoxified these herbicides. Their ultimate aim was to clean up (bioremediate) 2,4-D-contaminated soils and waters (e.g. Kohler 1999). The EPA funded similar efforts to bioremediate 2,4-D contamination (Short et al 1991). Dow appropriated this research, splicing the 2,4-D resistance-conferring genes into corn and soybean varieties to create Enlist corn and soybeans (Wright et al 2010).[1] Dow and USDA project that Enlist crops will

[1] The 2,4-D-degrading enzyme from *Sphingobium herbicidovorans* (RdpA) was engineered into corn to generate Enlist corn, and renamed AAD-1 by Dow. The 2,4-D-degrading enzyme from *Delftia acidovorans* (SdpA) was engineered into soybeans to generate Enlist soybeans, and renamed AAD-12 by Dow (Wright et al 2010).

lead to an enormous three- to seven-fold increase in 2,4-D use, depending upon how widely they are planted (CFS Enlist Duo 2014: Appendix A, pp. 7 ff.).

Dow is not alone. Monsanto's glyphosate-resistant, Roundup Ready crops comprise 85% of world GE crop acreage. The original glyphosate resistance gene was derived from a soil bacterium that evolved resistance to glyphosate at Monsanto's Louisiana glyphosate production plant (Adler 2011). Monsanto's dicamba-resistant crops were similarly developed with use of a dicamba-degrading enzyme derived from bacteria first isolated from storm water retention ponds surrounding a dicamba manufacturing plant in Texas, and was also originally intended to bioremediate rather than increase pollution of the environment with this herbicide (Krueger et al 1989, Chakraborty et al 2005, Behrens et al 2007). Table 1 shows that all six major pesticide firms have developed similar herbicide-resistant crops, which dominate the industry's GE crop pipeline. Table 2 lists still other herbicide-degrading enzymes (likewise derived from soil bacteria) that are awaiting introduction into crops to make them resistant to most major classes of herbicides in use today. Dow has obtained patents on Enlist corn and soybeans that envision "stacking in" resistance to as many as eight additional families of herbicide (Cui et al 2013, Cui et al 2011).

Table 1: "Next Generation" GE Herbicide-Resistant Crops

Petition No.	Company	Crop	Herbicides	Status
13-262-01p	Dow	Cotton	2,4-D, glufosinate, ***glyphosate***	Pending approval
12-215-01p	Bayer/ Syngenta	Soybeans	HPPD inhibitors, glufosinate, ***glyphosate***	Approved 2014
12-185-01p	Monsanto	Cotton	Dicamba, glufosinate, ***glyphosate***	Preliminary approval
11-234-01p	Dow	Soybean	2,4-D, glufosinate, glyphosate	Approved 2014
10-188-01p	Monsanto	Soybean	Dicamba, ***glyphosate***	Preliminary approval
09-349-01p	Dow	Soybean	2,4-D, glufosinate, ***glyphosate***	Approved 2014
09-328-01p	Bayer	Soybean	Isoxaflutole, glyphosate	Approved 2013
09-233-01p	Dow	Corn	2,4-D, ACCase inhibitors, ***glyphosate***	Approved 2014
09-015-01p	BASF	Soybean	Imidazolinones	Approved 2014
07-152-01p	DuPont-Pioneer	Corn	Imidazolinones, glyphosate	Approved 2009

Partial list of genetically engineered, herbicide-resistant crops recently approved or pending approval by USDA. See: http://www.aphis.usda.gov/biotechnology/petitions_table_pending.shtml, last visited 12/15/14. Where glyphosate is bolded and italicized, the company has announced plans to breed a glyphosate resistance trait into commercial cultivars to be sold to farmers.

Thus, government and university-funded research originally undertaken to ameliorate pesticide pollution has been "repurposed" by industry to greatly increase it. The pesticide industry – led by Monsanto and Dow – is guiding American agriculture into an era of much increased use of and dependence on weed-killing pesticides, contrary to widespread misconceptions on this point.

Table 2: Non-glyphosate resistant transgenes that are not currently commercial

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

Source: Green et al (2007), Table 1.

Herbicide-resistant crops increase herbicide use

There is no doubt that herbicide-resistant (HR) crops have sharply increased the overall use of weed-killers in American agriculture. Benbrook (2012) found that HR corn, soybeans and cotton have led to application of 527 million more lbs. of herbicide than would have otherwise been used over the 16 years from 1996-2011. USDA's National Agricultural Statistics Service, source of gold-standard data on pesticide use in U.S. agriculture, recently reported that herbicide use on soybeans more than doubled from 61 million lbs. to 133 million lbs./year over the biotech era, from 1996 to 2012 (USDA NASS 2014).[2] As noted above, Dow projects that 2,4-D-resistant corn and soybeans will increase 2,4-D use in agriculture by three- to seven-fold, from 25.6 million lbs./year today to 77.8-176 million lbs./year by 2020, depending upon how widely they are grown. CFS has projected a more than ten-fold increase in dicamba use with introduction of dicamba-resistant soybeans and cotton (CFS Dicamba Comments 2014). Pennsylvania State University weed ecologists likewise project a large rise in use of 2,4-D and dicamba with introduction of soybeans resistant to these herbicides (Mortensen et al 2014). Because the huge increase in 2,4-D use projected with registration of Enlist Duo for Enlist crops will not reduce applications of glyphosate, overall herbicide use will rise sharply as well (CFS Enlist Duo 2014: Appendix A, pp. 7 ff.).

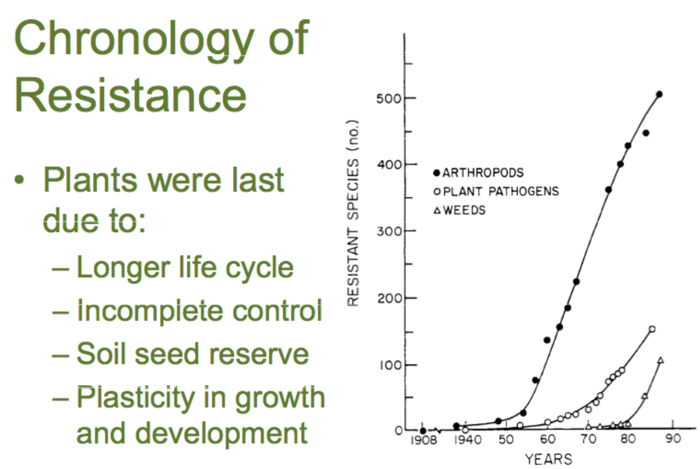
Why reduce reliance on pesticides?

Prior to the era of pesticide-promoting biotechnology, there was a widespread scientific and societal consensus on the need to reduce use of and reliance on pesticides, which was well summarized by USDA economists in a year 2000 publication (USDA ERS AREI 2000, p. 5). Many pesticides (including herbicides) are known or suspected to cause cancer, Parkinson's disease, and a host of other

[2] A small part of this increase is attributable to increased soybean plantings, from 64.2 million acres in 1996 to 77.2 million acres in 2012. Most is due to increased per acre use.

diseases, with farmers and infants/young children being particularly vulnerable: farmers because they are more highly exposed, young children because their developing systems are more vulnerable to pesticides' harmful effects. There is also ample evidence of environmental harm from excessive use of herbicides. Human health harms from exposure to 2,4-D are discussed below. Environmental harms are discussed in companion comments (CFS Enlist Duo Comments to EPA Science II – 12-15-14). These latter include threats to the habitat of the monarch butterfly, which is already in steep decline due to near elimination of its sole food source, milkweed plants, from corn and soybean fields, due to excessive glyphosate use on first generation herbicide-resistant crops.

Excessive reliance on pesticides (including herbicides) is also economically counterproductive for farmers, in that it triggers rapid evolution of pesticide resistance in target pests, just as overused antibiotics foster resistant bacteria. The figure below shows the extremely rapid rise of pesticide resistance in arthropods (e.g. insects), plant pathogens and most recently weeds. Resistance leads to additional pesticide use, which increases production costs. USDA estimates that up to 25% of pesticide expenditures are spent to achieve control of resistant pests (see discussion at CFS Enlist Duo 2012, pp. 21 ff.). Herbicide-resistant weeds have recently driven six-fold increases in weed control costs in areas where they are prevalent (Service 2013). Resistant weeds in connection with Enlist Duo and Enlist crops are discussed further below.



Source: Holt (2012).

2,4-D and human disease

CFS has addressed the human health harms of 2,4-D in prior comments to EPA (CFS Enlist Duo 2012, CFS Registration Review 2013, CFS Enlist Duo 2014: Appendix A). We will not repeat that discussion here, but rather summarize key points and present additional evidence.

<u>Bureaucratic blinders: 2,4-D registration review findings ignored</u>

CFS has repeatedly urged EPA to postpone any decision on registration of Enlist Duo until completion of the registration review of 2,4-D, begun in 2012 (CFS Enlist Duo

2012, CFS Registration Review 2013, CFS Enlist Duo 2014: Appendix A). EPA conducts comprehensive reviews of registered pesticides every 15 years to determine whether the pesticide's registrations should be cancelled or amended based on new scientific information regarding hazards, and changes in use patterns (e.g. increased use) since the last review. In the preliminary phase of its 2,4-D registration review, EPA briefly discussed a number of recent studies and data that strongly suggest previously unrecognized health harms from 2,4-D exposure (discussed in CFS Registration Review 2013). However, EPA has entirely ignored these studies and data in its human health review of Enlist Duo, apparently for no better reason than that different EPA divisions are conducting the two reviews, a classic case of bureaucratic blinders.

Enlist Duo registration is projected to lead to a massive, three- to seven-fold increase in the use of 2,4-D. This would mean that many-fold more rural people (farmers, farmworkers, their families, and other rural residents) would be exposed to 2,4-D, and exposed more frequently and at higher levels, than ever before. Much more 2,4-D would be released into the environment, exposing the general public to greater amounts of this herbicide in air, rainfall, water and as residues in food. CFS knows of no precedent in which a single new-use registration of a pesticide would enable such an enormous increase in use and exposure as the one at issue here. To approve such a huge increase in 2,4-D use without first thoroughly assessing credible evidence of previously unrecognized health harms is entire unacceptable.

<u>Medical vs. regulatory science: EPA's dismissal of human data</u>

The most certain means of determining whether a pesticide is harmful to human health would be to conduct human experimentation. Large numbers of people would be intentionally dosed with the pesticide over years, and their incidence of various diseases compared to that of a control population not exposed to the pesticide. Because human experimentation of this sort is clearly unethical, more indirect means must be employed.

EPA regulators assess pesticides in a very different manner than medical scientists. EPA relies almost entirely on animal experiments conducted by the registrant (e.g. Dow), together with dubious estimates of human exposure. Medical scientists also consider the results of animal experiments, but they prioritize concrete evidence of human health harms at the population level (epidemiological studies) and the individual level (poisoning episodes). This profound divergence in approach is well-expressed by Canadian physicians reviewing the toxicity of 2,4-D:

> "... two separate bodies of evidence are considered by the regulators (animal toxicity, exposure estimates) and the medical community (epidemiology). It may not be a surprise that they reach divergent conclusions regarding the advisability of using 2,4-D on lawns where children play" (Sears et al 2006).

In prior comments, CFS discussed the relative strengths and weaknesses of each approach, and how EPA unjustifiably rejects epidemiology studies linking exposure to 2,4-D to various adverse human health impacts, with particular reference to the strong epidemiological evidence linking 2,4-D exposure to the immune system cancer non-Hodgkin's lymphoma (CFS Enlist Duo 2012, pp. 56-63; CFS Enlist Duo 2014: Appendix A, pp. 9-11).

CFS urges EPA once again to carefully consider and integrate ***all*** available evidence for particular health endpoints to arrive at the best possible "weight of the evidence" determination of 2,4-D's health effects.

<u>2,4-D and non-Hodgkin's lymphoma</u>
The potential role of pesticides in triggering NHL has been the subject of intensive research by epidemiologists for several decades because the incidence of this immune system cancer has doubled in the U.S. population since the 1970s, and it is one of a handful of cancers that is found to be more prevalent in farmers than in the general population, despite the fact that farmers have a lower incidence of cancer overall (Zahm and Blair 1995). CFS discusses the strong evidence linking 2,4-D exposure to NHL in prior comments (see references above), and will not repeat those discussions here, except to note the results of one recent, authoritative study. Scientists with the International Agency for Research on Cancer conducted a comprehensive meta-analysis of the last 30 years of epidemiology studies exploring possible associations between exposure to pesticides and non-Hodgkin's lymphoma (NHL) (Schinasi and Leon 2014). They concluded that 2,4-D exposure is associated with a 40% higher likelihood of contracting NHL (Ibid, Table 5, odds ratio 1.4).

Additional studies demonstrating that 2,4-D exposure increases the risk of non-Hodgkin's lymphoma not submitted previously to EPA are being submitted with these comments: Hoar et al (1986), Hoar Zahm et al (1990), Cantor et al (1992), Mills et al (2005) and Pahwa et al (2012).

<u>2,4-D and neurotoxicity</u>
A good example of EPA's assessment failure is the limitation of its analysis of 2,4-D's neurotoxicity to the results of rat and rabbit experiments conducted by Dow. In contrast, CFS discussed five lines of mutually supporting evidence relating to various aspects of 2,4-D's neurotoxicity: increased risk of Parkinson's disease, neurological symptoms reported in 2,4-D poisoning episodes, epidemiology showing increased risk of fatal injuries in 2,4-D-exposed farmers, animal experiments, and mechanistic studies exploring the cellular and biochemical mechanisms by which 2,4-D exerts neurotoxic effects (CFS Enlist Duo 2014: Appendix A, pp. 11-14).

Additional evidence of 2,4-D's neurotoxicity not covered in prior comments is presented here. In experiments conducted on excised rabbit choroid plexus, tissue that plays a critical role in regulating the transport of substances across the blood-brain barrier (Kim et al 1988), Pritchard (1980) demonstrated that 2,4-D is actively transported across the barrier by an anionic organic acid transport system; and that it competitively inhibits elimination of the serotonin metabolite 5-hydroxy-indoleacetic acid (HIAA) from the brain. Kim et al (1983) conducted experiments on both excised choroid plexus tissue and intact rabbits, and showed that 2,4-D competitively inhibits elimination of salicylate (aspirin) from the brain. The upshot of these experiments is that 2,4-D could directly cause neurotoxicity, or indirectly lead to neurotoxicity by inhibiting the normal elimination of HIAA, salicylates and similar anionic organic acids from the brain – substances that are neurotoxic at elevated levels (Kim et al 1988).

2,4-D and Parkinson's disease

Parkinson's disease (PD) is an incurable, debilitating, degenerative nervous system disorder that afflicts an estimated 1 million Americans. There is a huge literature on PD and pesticides. In a limited search, CFS identified five high-quality studies that have found associations between Parkinson's disease and exposure to 2,4-D in particular (1) and chlorophenoxy herbicides as a class (4). Because 2,4-D is by far the most heavily used herbicide of this class,[3] adverse effects associated with chlorophenoxys are likely attributable in whole or in large part to 2,4-D.

1) Tanner et al. (2009) performed a case–control study involving 519 subjects with Parkinson's disease recruited from eight large movement disorder clinics in North America. Subjects whose occupation included frequent pesticide use were nearly twice as likely to have Parkinson's disease (PD), with an odds ratio (OR) of 1.90.[4] Those exposed to 2,4-D in particular were still more likely to have contracted PD (OR = 2.59, or roughly 2 ½-fold higher risk).

2) Brighina et al. (2008) performed a large study of 844 case–control pairs, and found that exposure to chlorophenoxy acids or esters was associated with a increased risk of PD in younger subjects (OR = 1.52); 2,4-D was the most commonly reported of the chlorophenoxys, which in turn was the only subclass linked to PD: "In total, our subjects reported exposure to 44 different chemical subclasses of pesticides, but no other chemical subclass of pesticides was significantly associated with PD."

3) Semchuk et al (1992) conducted a study of 130 Canadian residents with Parkinson's disease, and the strongest risk factor was found to be previous occupational exposure to herbicides, with chlorophenoxy herbicides implicated in particular.

4) Hancock et al (2008) assessed 319 subjects with PD, and found PD incidence to be associated with exposure to both insecticides and herbicides: "…our findings add support to the limited data implicating specific classes of pesticides, notably organochlorines, organophosphorous compounds, chlorophenoxy acids/esters, and botanicals, as potential risk factors for PD."

[3] EPA estimates that 25-29 million lbs. of 2,4-D were applied in American agriculture in 2007, versus just 2-4 million lbs. of MCPA, the second most heavily used chlorophenoxy (EPA 2011, Table 3.6).
[4] The odds ratio (OR) expresses the ratio of the odds of disease occurring in an exposed population to the odds of it occurring in an unexposed group. OR's > 1.0 indicate a greater likelihood of disease in the exposed population; OR = 2.0 signifies double the risk, etc.. See http://practice.sph.umich.edu/micphp/epicentral/odds_ratio.php.

5) Elbaz et al (2009) investigated 224 subjects with PD from an agricultural area in France. Farming as an occupation as well as professional pesticide use were significantly associated with an increased risk of PD. Exposure to chlorophenoxy herbicides was associated with a trend toward higher risk of PD, which became statistically significant when age of onset was restricted to greater than 65 years.

Many other studies that did not break down exposure by particular subclass have also found that exposure to pesticides, especially herbicides, is associated with increased risk of PD. Gorell et al. (1998) found a very strong association between PD and herbicide exposure, which increased after controlling for other confounding factors (OR = 4.10). The risk of PD was still higher in subjects who reported 10 years or more of occupational herbicide exposure (OR = 5.8).

Priyadarshi et al (2000) conducted a meta-analysis[5] of 19 studies published between 1989 and 1999, and found that the majority of the studies reported a "consistent elevation in the risk of PD with exposure to pesticides" and that "the risk of PD increased with increased duration of exposure." Based on a comprehensive review, Brown et al (2006) concluded that: "From the epidemiological literature, there does appear to be a relatively consistent relationship between pesticide exposure and PD. This relationship appears strongest for exposure to herbicides and insecticides, and after long durations of exposure." A more recent assessment came to similar conclusions: "This review affirms the evidence that exposure to herbicides and insecticides increase the risk of PD" (van den Mark 2012).

The projected increase in 2,4-D use with Enlist Duo registration would make it the second most heavily used pesticide in all of U.S. agriculture, second only to glyphosate, and dramatically increase overall herbicide use and exposure. The evidence described above leaves little doubt that this would result in substantially more cases of Parkinson's disease in the American population.

<u>Heart attacks and diabetes</u>

Multiple lines of evidence suggest that exposure to 2,4-D and other chlorophenoxy herbicides increases the risk of heart disease and diabetes. A study of over 26,000 workers from 12 countries involved in the manufacture or spraying of chlorophenoxy herbicides and/or chlorophenols for various periods between 1939 to 1992 found that they suffered from higher rates of all circulatory disease, ischemic heart disease and potentially diabetes (Vena et al 1998). These effects were attributed to dioxin contaminants in the chlorophenoxy herbicides and chlorophenols. CFS discusses the evidence for dioxin contamination of 2,4-D in prior comments, which included detection of significant levels of dioxins in 2,4-D in tests conducted by USDA scientists and Australian researchers (CFS Enlist Duo 2012, pp. 63-65; CFS Registration Review 2013: Appendix B, pp. 53-56). EPA did

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[5] A meta-analysis is a study of studies that seeks to identify statistically significant patterns across similar studies. Meta-analyses have greater statistical power to detect associations than individual studies.

not respond to CFS's assessment of this issue, or to our recommendations that EPA conduct its own testing of off-the-shelf formulations of 2,4-D for dioxin content rather than rely on industry tests (CFS Enlist Duo 2014: Appendix A, pp. 17-18).

EPA scientist Dina Schreinemachers conducted an ecologic study to determine if similar associations might be observed in residents of wheat-growing states where chlorophenoxy herbicides (chiefly 2,4-D) are heavily used in agriculture: Minnesota, Montana, North and South Dakota (Schreinemachers 2006). USDA data show that at least 85% of spring wheat acres were treated with chlorophenoxys in these states during the 1980s and 1990s, thus making wheat acreage a good surrogate of exposure (Schreinemachers 2010). Mortality data for the relevant counties was collected for two periods: 1979-1988 and 1989-1998. Schreinemachers found that the incidence of mortality from heart attacks (acute myocardial infarctions, or AMI) and diabetes was significantly higher in residents of counties where wheat was heavily grown versus those counties where wheat-growing was less common. Schreinemachers concluded:

"The fact that mortality from AMI increases with wheat percentage for both sexes, both younger and older subjects, and both 1979-1988 and 1989-1998 mortality cohorts suggests the effects are associated with wheat agriculture."

In a follow-up study, Schreinemachers explored possible associations between 2,4-D exposure and biomarkers linked to increased risk of acute myocardial infarction and type-2 diabetes. Schreinemachers used data from the Centers for Disease Control's National Health and Nutrition Examination Survey III, 1989-1994 (NHANES III) to conduct this study. In NHANES III, the blood and/or urine of volunteers are tested for a wide range of naturally occurring compounds associated with nutritional status (e.g. lipids, vitamins) as well as pesticides and other xenobiotic compounds. Those subjects who had been exposed to 2,4-D (i.e. had detectable levels in urine) exhibited, on average, lower levels of high-density lipoproteins (HDL) in blood tests; those with lower HDL levels also had higher triglyceride levels. Low HDL and high triglyceride levels are both recognized risk factors for acute myocardial infarctions and diabetes (Schreinemachers 2010).

Three different studies using different subject groups and widely different study designs and methodologies all point to chlorophenoxy and hence 2,4-D exposure as a risk factor for heart attacks and diabetes.

<u>2,4-D and other health impacts: flaws in EPA's Enlist Duo assessment</u>
The Environmental Working Group and Natural Resources Defense Council discussed a number of serious flaws in EPA's assessment of animal studies conducted by Dow on 2,4-D (EWG 2014, NRDC 2014a. 2014b). These flaws included incorrectly setting the No Observed Adverse Effects Level (NOAEL) at a level where signs of toxicity were observed in the extended one-generation oral feeding study on rats; disregarding endocrine toxicity and immunotoxicity findings from animal studies; failure to apply the ten-fold safety factor provided for by the Food Quality Protection Act to protect children from pesticide toxicity, in cases where animal

tests show the young are more susceptible than adults; and omitting consideration of the inhalation exposure pathway from the aggregate exposure estimate, particularly problematic given 2,4-D's propensity to drift and expose those in the vicinity of sprayed fields.

EWG points to a number of potential human health hazards resulting from EPA's setting of the point of departure for 2,4-D exposure higher than is demanded by the results of animal studies. These include reproductive toxicity (based on increased uterus weight in young female rats and reduced reproductive organ weight in adult male rates); thyroid toxicity (based on reduced levels of T4 and T3 thyroid hormone, and increased levels of thyroid stimulating hormone); immune system toxicity (based on reduced thymus weights in male rats); and kidney toxicity (based on increased kidney weight in young female rats and degenerative lesions in male and female rats). Each of these effects was found in the course of the extended one-generation reproductive toxicity study at a level (300 ppm) that EPA incorrectly deemed to be a No Observed Adverse Effects Level. Some toxicity effects were observed at even a lower dose, 100 ppm. These included increase thyroid weight (female rats) and reduced weights of body, kidney, liver, spleen and testes in male rats. Thus, EPA should set 100 ppm as the Lowest Observed Adverse Effect Level (LOAEL).

If EPA were to make these corrections – and properly apply the FQPA 10-fold safety factor to protect children's health – EPA's estimate of chronic exposure to 2,4-D from food and drinking water would exceed the safety threshold for children 1 to 5 years of age.

The discussion above makes clear that approval of the proposed registration of Enlist Duo would put the health of Americans – especially farmers, residents of rural communities, and young children – at risk, and should for that reason be rejected. The economic, environmental and social costs of Enlist Duo, discussed below, make its registration still less acceptable.

Economic, environmental and social costs of the proposed registration

Under FIFRA, EPA can register Enlist Duo for the proposed uses only if they do not cause "unreasonable adverse impacts on the environment," defined in part as "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide…"

EPA's sole attempt to assess the economic and social costs and benefits of the Enlist Duo registration is contained in a 10-page memorandum entitled "Discussion of the benefits for Enlist Duo use on herbicide resistant soybeans and corn (DP# 405852), April 3, 2014." The title of this memo illustrates a fundamental flaw: EPA assumes only benefits, and makes no attempt to assess the economic, environmental and social ***costs*** of registration, in direct violation of FIFRA's mandate. A second fatal flaw is that the memo is based entirely on a submission by Dow. Dow is not an uninterested party in this matter, and as one might expect its submission is highly biased in favor of finding "benefits" and no costs of its Enlist Duo herbicide. It is entirely unclear why EPA did not consult other independent sources. EPA's assessment is also incompetent, revealing basic misunderstandings about herbicide-resistant crops and weeds in general, and Enlist crops and Enlist Duo in particular. CFS discusses the serious flaws in EPA's "benefits" assessment in prior comments (CFS Enlist Duo 2014: Appendix A, pp. 18-31).

This documented discussion also addresses two major costs of the registration – crop injury from 2,4-D drift, and rapid evolution of 2,4-D resistance in weeds – and why EPA's proposed mitigation measures for these adverse will prove to be unworkable and ineffective. We here provide summaries of these issues.

<u>Crop injury from herbicide drift</u>
Herbicide drift is a serious and underreported problem. Herbicide-resistant crops lead to increased drift and associated crop damage by promoting intensive herbicide use later in the season when crops are more susceptible to drift damage. For this reason, glyphosate as used with Roundup Ready crops has become a leading culprit in drift-related crop damage. The chief predictor of drift and associated crop damage is intensity and timing of use, though drift is exacerbated when volatile herbicides are used. 2,4-D is volatile, drift-prone and can damage a wide range of crops. Even with modest use and extensive regulation, 2,4-D drift is a leading cause of crop injury. Glyphosate and 2,4-D are ubiquitous in air, water and rain. EPA's assessment of 2,4-D choline drift is vitiated by excessive reliance on models and failure to evaluate real-world data. EPA's proposed mitigation measures are unrealistic and unworkable, and it has a poor record of regulating drift, which further undermines confidence in them. By leading to a vastly more 2,4-D applied later in the season, approval of Enlist Duo would result in sharply increased crop damage and thus impose huge costs on growers of sensitive crops.

<u>Environmental and economic costs of herbicide-resistant weeds</u>
Use of Enlist Duo on Enlist crops (the Enlist system) would foster rapid emergence of weeds resistant to 2,4-D, as acknowledged by USDA and weed scientists. Because the Enlist system would be used primarily by farmers whose fields are infested with weeds resistant to glyphosate and often other herbicides, the result would be extremely intractable weeds immune to both herbicides. EPA ignores the many costs of 2,4-D and multiple herbicide-resistant weeds that would be generated by the Enlist system. These include greater use of toxic herbicides and associated human health and environmental harms; higher weed control costs for farmers; increased soil erosion from greater use of tillage; and reduced use of sustainable weed control practices that involve lesser reliance on herbicides. In anticipation of 2,4-D/glyphosate-resistant weeds, Dow has already added additional herbicide resistance traits to Enlist crops to permit high-level, post-emergence use of glufosinate and other weed-killers to control them. As weeds acquire resistance to these chemicals as well, Dow envisions adding multiple combinations of resistance to as many as nine classes of herbicide. This chemical arms resistance race between crops and weeds would ensure rapidly increasing use of additional toxic herbicides long into the future, generating substantial "benefits" for Dow and other pesticide

firms, sharply rising weed control costs for farmers, and rising adverse impacts on human health and the environment.

EPA ignores these costs, and evaluates only putative benefits of the Enlist system. But even this limited assessment is invalidated by fundamental flaws. EPA lacked requisite cost data on the cost of Enlist Duo, Enlist seed, and alternative weed management programs, misunderstands how farmers would use the Enlist system, and relies entirely on a faulty and biased assessment by the registrant. A proper accounting shows that whatever fleeting economic benefits the Enlist system provide are swamped by the subsequent costs just a few years down the line. Dow's stewardship plan is no different than Monsanto's for Roundup Ready crops, and would be equally ineffective. EPA's proposed mitigation for 2,4-D resistant weeds – a monitoring program that entirely lacks any prevention component – would be also ineffective and unworkable. EPA should reject the proposed registration because the economic and environmental costs that would ensue are far greater than any short-term benefits.

<u>Environmental costs: increased soil erosion</u>
Soil erosion rates have remained completely flat over the period of Roundup Ready crop adoption (1997-2010), disproving the myth that herbicide-resistant crops save soil. In fact, herbicide-resistant weeds fostered by herbicide-resistant crop systems lead to greater use of tillage, which increases soil erosion (see CFS Enlist Duo: Appendix A, p. 28, and references cited therein).

<u>Social costs: increased consolidation of cropland</u>
The one confirmed, if dubious, benefit of herbicide-resistant crop systems like the Enlist crop system is a reduction in labor needs for managing weeds. Weed control has traditionally been one of the more labor-intensive tasks in farming. Roundup Ready (RR) soybeans have been estimated to reduce labor needs for weed control by 15% (USDA's draft EIS on Enlist corn and soybeans, p. 75). USDA economists agree that: "HT [herbicide-tolerant] seeds reduce labor requirements per acre" (MacDonald et al 2013, p. 28). One use to which this "saved labor" can be put is to farm more acres, bidding up the price of land (including leases). Larger growers are generally in a better position to absorb these added costs, and so outcompete small and medium-size growers, who are thereby put at a competitive disadvantage and potentially out of business. This explains why USDA economists conclude that herbicide-resistant seeds (among other factors) have fostered increased consolidation among field crop farmers since 1995 (MacDonald et al 1995, p. 27).

MacDonald et al (2013) assess this consolidation in the U.S., finding that: "The midpoint acreage for harvested cropland rose by 114 percent, from 500 acres in 1982 to 1,071 acres in 2007." This tremendously rapid consolidation of farmland has – driven in part by herbicide-resistant crops – has helped drive smaller producers out of business. The registration of Enlist Duo for use on Enlist crops will have the same negative socioeconomic impacts on small and medium-size farmers as Roundup Ready crops have had. EPA has completely failed to assess this impact.

As farms become larger, driven in part by herbicide-resistant crops, growers face increasing resource and time constraints, and more sustainable methods of managing weeds, which generally require more labor, become less and less feasible. Sustainable weed management techniques such as the planting of cover crops, more complex crop rotations, and judicious use of tillage, are less likely to be used. Instead, growers will increasingly rely on herbicide-resistant crop systems, resulting in a toxic spiral of increasing weed resistance and still more herbicide use in response.

Conclusion

In these comments and prior ones, CFS has presented reasonable and science-based arguments demonstrating that EPA should reject the proposed registration of Enlist Duo for use on Enlist corn and soybeans, to protect human health, the environment, and the true and sustainable economic interests of American farmers and U.S. agriculture. At the very least, any decision should be postponed until EPA can conduct the needed comprehensive and critical review in the context of the 2,4-D registration review process. CFS is confident that an objective, science-based review would necessitate denial of the requested registration.

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