THE CENTER FOR FOOD SAFETY

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Comments on Registration Review of the Herbicide 2,4-D
Docket No. EPA-HQ-OPP-2012-0330
Federal Register, Vol. 77, No. 24, December 14, 2012, pp. 74479 – 81

I. BACKGROUND

The Center for Food Safety (CFS) appreciates the opportunity to comment on EPA's preliminary work plan and associated documents for initiation of its registration review of 2,4-dichlorophenoxyacetic acid (2,4-D). CFS has found six (6) documents in EPA docket EPA-HQ-OPP-2012-0330 opened for the review, and will refer to them in the comments below as follows:

Work Plan:	2,4-D Preliminary Work Plan – Registration Review: Initial Docket Case Number 73, December 2012
BEAD:	BEAD Chemical Profile for Registration Review: 2,4-D Chemical Case, Biological and Economic Analysis Division, Product Review Panel date: May 8, 2012
SLUA:	2,4-D: Screening Level Usage Analysis (SLUA), March 23, 2012
Human Incidents:	2,4-D: Review of Human Incidents, Health Effects Division, September 4, 2012
Human Health:	2,4-D: Human Health Assessment Scoping Document in Support of Registration Review, Office of Pesticide Programs, December 2, 2012
EFED:	EFED Registration Review Problem Formulation for 2,4-D, Environmental Fate and Effects Division, November 15, 2012.

EPA is undertaking a registration review of 2,4-D. Mandated by The Food Quality Protection Act of 1996, the purpose of the registration review program is to provide EPA with an opportunity to periodically (every 15 years) assess the risks that a pesticide may 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 pesticide was last registered.[1]

These four grounds for registration review are both interdependent and to some extent independent of one another. That is, changes in any one area may alter the risk profile of the pesticide and necessitate changes in the pesticide's registration (e.g. revocation of some registered uses, or changes to specific conditions for certain registered uses) to protect human health, or to protect the health of pesticide applicators and/or the environment from unreasonable adverse effects. These may be elaborated as follows:

1) New scientific information revealing that the pesticide is more or less toxic for one or more endpoints or organisms, including endangered species, than previously thought;
2) New risk detection methods that reveal pre-existing threats that had hitherto gone unobserved;
3) Altered use patterns that, for instance, increase the pesticide's use, increase the exposure of applicators and/or the general public to the pesticide, expand use of the pesticide to new geographic regions, generate new or exacerbate existing threats, etc.
4) Changes in policy such that risks previously not accounted for, or discounted, become unacceptable, whether or not the underlying factual situation (science, detection methods, pesticide use practices) has changed.

Since the EPA concluded its last registration review of 2,4-D in 2005, three new uses of 2,4-D have been proposed. Dow AgroSciences has applied to EPA to:

1) Register the choline salt of 2,4-D for use on DAS-402780-9 corn (Enlist AAD-1 Corn), genetically engineered for resistance to 2,4-D and other aryloxyphenoxypropionate herbicides;
2) Register a premix of 2,4-D choline salt and glyphosate for use on DAS-402780-9 corn; and
3) Register the choline salt of 2,4-D for use on DAS-68416-4 soybeans (Enlist AAD-12 soybeans), genetically engineered for resistance to 2,4-D.[2]

The Center for Food Safety (CFS) submitted detailed legal and scientific comments on these proposed new uses, which are excerpted in Appendix A and incorporated as part of these comments. CFS also submitted comments to USDA's Animal and Plant Health Inspection Service (APHIS) regarding APHIS's draft environmental assessment and draft plant pest risk assessment for Dow's petition for determination of nonregulated status for DAS-68416-4 soybeans, which are excerpted in Appendix B, and also incorporated as part of these comments. To avoid repetition in the body of these comments, we will make reference below to our previously submitted comments to EPA and USDA APHIS in the following form: Appendix A, pp. 3-4. CFS has submitted these Appendices to the docket under the filenames "CFS Appendix A" and "CFS Appendix B," respectively. CFS has also submitted to the docket the documents referenced in these comments, including Appendices, under filenames that correspond to the

[1] See description of registration review program at http://www.epa.gov/oppsrrd1/registration_review/
[2] Federal Register, Vol. 77, No. 100, May 23, 2012, pp. 30524-30526, items 12, 13 & 14.

citations, e.g. Bernards et al 2012.

In our new use registration comments, CFS requested that EPA defer any action on these pending registration decisions until completion of the 2,4-D registration review process (Appendix A, p. 61). The grounds for this request have to do with the serious and in part novel issues that arise from the use of 2,4-D in the context of 2,4-D-resistant crop systems, which include:

1) Many-fold increase in agricultural use of 2,4-D, and attendant human health and environmental impacts;
2) Increased exposure to dioxins from greater 2,4-D production and use, in particular as it relates to EPA's ongoing review of dioxin toxicity and recent establishment of stricter (lower) dioxin exposure standards for non-cancer risks;
3) Unprecedented shift in use of 2,4-D to much later in the season (post-emergence use), leading to a dramatic rise in drift-related crop injury as well as occupational dermal/inhalational and non-occupational inhalational exposure;
4) Likelihood of rapid evolution of weeds resistant to 2,4-D and related herbicides, as enhanced by the shift in usage patterns to predominantly post-emergence use;
5) Potential human health and environmental harms from 2,4-DCP metabolites generated in 2,4-D-resistant crops (but not or only in minute quantities in other crops) when sprayed with 2,4-D;
6) Elevated risks to threatened and endangered species from vast increases in 2,4-D use.

A registration review that fails to give careful consideration of these issues cannot possibly accomplish its intended purpose. Yet a perusal of EPA's preliminary registration review documents gives no indication that EPA plans to incorporate an assessment of the new uses with Enlist corn and soybeans. EPA not only fails to discuss, but ***does not even mention***, these pending registration actions, a completely unacceptable omission. The Biological and Economic Analysis Division (BEAD) notes that: "Use patterns may change in response to future conditions and market opportunities" (BEAD, p. 2), an oblique reference to Enlist corn and soybeans. In fact, 2,4-D-resistant crops will certainly impact "future conditions" and create "market opportunities" for new, significantly increasing use of 2,4-D.

EPA cannot consider new uses of 2,4-D with 2,4-D-resistant crops in one context, then pretend that such proposed uses do not exist in the context of registration review. Under EPA regulations for registration review at 40 CFR 155.50 (a), the EPA is to establish a docket for each registration review case, and "place in this docket information that will assist the public" in commenting on the Agency's review. The information to be placed in the docket includes: "A list of current registrations and registrants, any FEDERAL REGISTER notices regarding ***pending registration actions,*** and current or pending tolerances…." (emphasis added).

EPA did not place the Federal Register notice cited above requesting new uses of 2,4-D on Enlist corn and soybeans in the registration review docket, despite the fact that they are undeniably three "pending registration actions."[3] Thus, members of the public who have not already been

[3] The new use applications were made on March 23, 2012, nearly a year ago. EPA opened an initial comment period for these applications that ended on June 22, 2012, nearly eight months ago.

independently informed of these pending actions have been denied knowledge of their existence, and hence the opportunity to comment on them. EPA must include the proposed new uses in the registration review docket to permit meaningful public input.

Equally important, if such pending registration actions are relevant to the public, as EPA's regulations insist they are, it is of still greater importance that EPA consider them in its review, for quite obvious reasons. A pesticide that has no unreasonable adverse effects on the environment when used at one level may very well have unreasonable adverse effects when its usage increases dramatically. To conduct a registration review based on past usage patterns in the full knowledge that "pending registration actions" may well dramatically increase use, alter use patterns, and cause greater adverse impacts than at present would make a mockery of the registration review program.

It would also represent a tremendous waste of resources. Registration reviews often require five years or more to complete. If 2,4-D use patterns change dramatically during the course of the registration review,[4] yet that review is based on past usage practices, any conclusions EPA reaches may well be rendered invalid and legally suspect by the time the review is concluded.

CFS urges EPA to fully account for changes in 2,4-D use and alterations in its patterns of use that would occur during the course of the registration review if the pending registration requests for use of 2,4-D on 2,4-D-resistant corn and soybeans are granted. Alternately, EPA could conduct dual-track analyses. The first, based on denial of the new use registrations, would be reasonably based on 2,4-D use patterns over the past decade or so, as now covered in BEAD (pp. 3-8). A second analysis would then be based on 2,4-D usage practices to be expected should the new use registrations be granted.

II. EPA'S ANALYSIS OF 2,4-D USAGE

EPA provides an extremely brief and inadequate analysis of 2,4-D use in "BEAD: Chemical Profile for Registration Review: 2,4-D Chemical Case," hereinafter referred to as "BEAD." As noted above, BEAD made no attempt to assess the changes in 2,4-D use that would be enabled by the proposed registrations for Enlist corn and soybeans. BEAD also fails to provide any agronomic explanation for past changes in 2,4-D use that it does record. For instance, BEAD data (Table 2, p. 5) show substantial increases in 2,4-D use (both pounds applied and total acres treated) on soybeans, cotton and to a lesser extent corn from the 2001-2005 period to the 2006-2010 period. Since 2,4-D is frequently recommended to control glyphosate-resistant (GR) weeds, and GR weeds have expanded dramatically over this time period in precisely those three crops, these increases are very likely attributable to farmers making increasing use of 2,4-D to control GR weeds. Agronomically informed assessments of 2,4-D use patterns are critical for estimating future use, for instance if the requested new use applications are granted.

CFS provides such informed analyses of 2,4-D use patterns in Appendix B (pages 5-10) for soybeans and Appendix A (pages 6-13) for corn and soybeans. Four critical aspects of these analyses deserve emphasis. First, Enlist corn and soybeans eliminate, for all practical purposes,

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[4] We note that Dow AgroSciences anticipates introduction of 2,4-D-resistant corn in 2014, suggesting that it expects EPA to register 2,4-D choline salt for use on it before that time (Gillam 2013).

the biological constraint of crop injury that has hitherto been a major factor limiting the extent, the frequency, and the intensity (lbs./acre) of 2,4-D use in American agriculture since its introduction in the 1940s. Second, Enlist crops would facilitate a strong shift in 2,4-D use patterns, from predominantly early season use (pre-emergence) at present to mid-season, post-emergence use, particularly on soybeans. The shift to post-emergence herbicide use patterns is associated with increased drift-related crop injury episodes and more rapid evolution of herbicide-resistant (HR) weeds. HR weeds in turn trigger greater herbicide use as well as more tillage operations and associated soil erosion. Third, use of Enlist corn and soybean systems will foster rapid evolution of 2,4-D resistance in weeds already resistant to glyphosate and often other herbicides. Multiple HR weeds are already a huge and growing problem in U.S. agriculture, and will be greatly exacerbated by Enlist crops. Finally, only a renewed commitment to much greater use of non-chemical weed control tactics in the context of truly Integrated Weed Management can slow the epidemic emergence of herbicide resistance in weeds.

Based on reasonable adoption scenarios and usage rates, CFS estimates that Enlist corn and soybeans would each lead to roughly a 60-70 million lb./year increase in overall 2,4-D use in American agriculture, compared to a total of 7 million lbs. used on both corn and soybeans at present. BEAD estimates that an average of 28 million lbs. of 2,4-D was applied each year in all of U.S. agriculture from 2006-2010 (BEAD, p. 5-6), though this might be a slight underestimate since a few lower-use states are excluded. 21 million lbs. are applied to crops other than corn or soybeans, and usage on these crops may be expected to continue at roughly similar levels. Once they are widely adopted, Enlist corn and soybeans would lead to an estimated 120-140 million lbs. of additional 2,4-D use, for 140 to 160 million lbs. total agricultural use of this herbicide. This would represent a five-fold increase in overall agricultural use of 2,4-D. Dow's expected introduction of 2,4-D-resistant cotton would move increase usage still more.

It should not be thought that this is an unrealistic scenario for herbicide use driven by an HR crop system and the resistant weeds it fosters. EPA estimated glyphosate usage, driven by Roundup Ready crops and glyphosate-resistant weeds, at 180-185 million lbs. in 2007, and current usage easily exceeds 200 million lbs. While glyphosate use with Roundup Ready crops significantly displaced use of other herbicides, a similar phenomenon is not expected with 2,4-D used with Enlist crop systems. This is because 2,4-D is a broadleaf herbicide that will be used primarily to kill glyphosate-resistant weeds, while broader-spectrum glyphosate will continue to be used in conjunction with it to kill grass-family weeds and others it controls more effectively. Additional analysis is presented in the usage analysis and resistant weed sections of Appendices A and B.

III. UPDATE ON RESISTANT WEEDS

CFS provides a documented discussion of the problem of glyphosate- and multiple herbicide-resistant weeds in Appendix A (pp. 16-34) and Appendix B (16-40). Three developments since those comments were submitted deserve mention. First, a three-year survey of glyphosate-resistant weeds in 31 states by the agri-marketing firm Stratus asserts that 49% of farmers surveyed in 2012 had glyphosate-resistant weeds on their farm in 2012, up from 34% of farmers in 2011; that 61.2 million acres of cropland are now infested by GR weeds; that GR weeds are rapidly expanding in the Midwest; and that ever more farmers report two or more resistant species on their farms (Stratus 2013).

Second, a detailed survey of glyphosate-resistant weeds in North Dakota and Minnesota reveal an astonishing rate of GR weed emergence in these northern Midwestern and Northern Plains states from just 2006 to present (Stachler 2012), underscoring the point that glyphosate- and multiple herbicide-resistant weeds are rapidly emerging in areas outside of the South.

Still more troubling are data recently posted to the International Survey of Herbicide-Resistant Weeds (ISHRW). CFS has periodically compiled ISHRW data on GR weeds, as discussed in the Appendices (see also CFS GR Weed List 2012 in supporting materials). ISHRW recently updated its list of GR weeds to show vastly more GR weed biotypes with additional resistance to other herbicide modes of action (see GR Weeds ISHRW 2-12-13[5]). To take one example, ISHRW now shows that all 13 GR common waterhemp biotypes in the U.S. have additional resistance to one (10) or two (3) other modes of action; that is, all 13 biotypes have dual- or triple herbicide-resistance. Just one year ago, only three of the 11 GR biotypes were recorded as having multiple resistance (see CFS GR Weed List 2012). ISHRW also now lists GR biotypes of many other weed species (e.g. Palmer amaranth) as having multiple herbicide-resistance rather than just glyphosate resistance.

These data underscore an extremely important point. HR crops systems are no "solution" to weed resistance. Rather, they will provide at best very short-term relief, at the cost of still more intractable, multiple herbicide-resistant weeds just a few years down the line. The biotechnology industry understands this quite well, and has already packed its near-term product pipeline with crops resistant to one to three herbicides each. In fact, fully 12 of 16 GE crops awaiting deregulation by USDA are herbicide-resistant.[6] But this is only the beginning. Biotechnology firms are looking even further into a future of spiraling weed resistance, as indicated by the following passage from a patent awarded to DuPont:

> "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***."
> (DuPont-Pioneer Patent 2009, par. 33, emphasis added)

The current trend of sharply increasing herbicide use, due largely to epidemic emergence of glyphosate-resistant weeds, will continue its upward spiral in concert with the introduction of HR crops resistant to ever more herbicides and the emergence of weeds resistant to them, with mounting costs in terms of harm to human health and the environment.

IV. EPA's HUMAN HEALTH ASSESSMENT OF 2,4-D

CFS provided a detailed discussion of 2,4-D's demonstrated and probable adverse impacts on human health in comments on the new use registration applications, which include a discussion of dioxins in 2,4-D (see Appendix A, pp. 49-61). Neither of the two health-related documents in

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[5] Also available at: http://www.weedscience.org/Summary/MOA.aspx?MOAID=12.
[6] See top two tables at http://www.aphis.usda.gov/biotechnology/petitions_table_pending.shtml, last visited Feb. 12, 2013.

the registration docket (Human Health, Human Incidents) adequately address a number of important concerns raised in those comments, although we recognize these documents were not meant to constitute a full evaluation of 2,4-D's impacts on human health, and that reference is made to such fuller evaluations. However, CFS questions the adequacy of those evaluations, such as those contained in the 2005 reregistration eligibility decision. Under EPA's regulations for registration review, 40 CFR 155.50 (c)(4) states that: "Submitters may request the Agency to reconsider data or information that the Agency rejected in a previous review" and that "…submitters must explain why they believe the Agency should reconsider the data or information in the pesticide's registration review."

We request that EPA carefully consider (or reconsider) all of the 2,4-D-related health concerns raised by CFS in the discussion in Appendix A, which provides valid grounds for such reconsideration. We request that EPA give particularly close attention to the following issues.

First, EPA should reassess the strong evidence linking exposure to chlorophenoxy herbicides such as 2,4-D to non-Hodgkin's lymphoma in farmers and other pesticide applicators.

Second, EPA should assess recent epidemiological evidence linking 2,4-D exposure to increased likelihood of contracting Parkinson's Disease.

Third, we request that EPA consider the strong medical evidence demonstrating that oral exposure to 2,4-D can have toxic effects on the liver.

Fourth, EPA should reconsider the endocrine-disrupting effects of 2,4-D, for instance the evidence for lower sperm counts in occupationally-exposed pesticide applicators.

Fifth, EPA should undertake a comprehensive review of 2,4-D-related dioxins, along the lines suggested in the Appendix A discussion (pp. 59-61). To briefly summarize, CFS found that EPA is relying heavily on pesticide industry assurances of reduced levels of dioxin contaminants in 2,4-D; that independent scientific testing casts great doubt on such assurances, suggesting that dioxin levels in 2,4-D have not declined as claimed by industry; that EPA should itself conduct, or commission independent scientists to conduct, a comprehensive testing program for dioxins in a broad array of 2,4-D formulations; that EPA should consider dioxins generated during the manufacture of 2,4-D, and dioxins emitted during incineration of unwashed 2,4-D jugs, in its overall assessment of dioxins related to 2,4-D.

As further discussed in Appendix A, such an assessment is particularly needed for two reasons. First, in the course of EPA's ongoing review of dioxin toxicity, the Agency recently established a low chronic oral reference dose for non-cancer risks from dioxin exposure, and is presently working to establish a similar standard for cancer risks. Second, the vast increase in 2,4-D use that would accompany the anticipated wide-spread introduction of Enlist corn and soybeans assuming the new use registrations are granted would greatly increase exposure to dioxins as contaminants in 2,4-D, as well as dioxins generated during manufacture of the herbicide and incineration of unwashed containers containing residues of it.

EPA should also give full consideration to 2,4-D-related dioxins in assessing the probable health impacts of the herbicide, as detailed above.

We note that the single paragraph discussion of dioxin and furan contaminants in 2,4-D (Human Health, p. 3) merely reiterates past Agency assessment of the issue, and fails to answer any of the serious issues raised above with respect to 2,4-D-related dioxins. In particular, that passage points to the 2005 RED conclusion that dietary exposure to dioxin/furan contaminants in 2,4-D presents no toxicological concern. This conclusion must be reassessed in light of the chronic oral reference dose for non-cancer risks established by EPA in 2012. EPA must also assess not only dietary, but occupational, exposure to 2,4-D-related dioxins.

EPA notes that 2,4-D is one of a number of phenoxy herbicides, a class that includes MCPA, 2,4-DB and 2,4-DP, and that "[a]lthough the various phenoxy herbicides have similar structural components, HED [Health Effects Division] has no data indicating that they have a common mode of toxic action. Therefore, a cumulative risk assessment has not been performed for these compounds" (Human Health, p. 13). In contrast to EPA, epidemiologists often treat chlorophenoxy herbicides as a group in studies, presumably because dioxin contaminants are generated in a number of herbicides of this class, and dioxins are generally understood to be the (most) toxic component of chlorophenoxy herbicides. For instance, epidemiologists at the National Cancer Institute found that:

"In epidemiological investigations focusing on pesticides, the strongest association has been between non-Hodgkin's lymphoma and phenoxyacetic acid herbicides." (Blair & Zahm 1995).

Thus, EPA should consider grouping together pesticides that share the common feature of dioxin contamination as byproducts of the production process for cumulative risk assessment.

CFS pointed to basic flaws in EPA's approach to using epidemiological studies (Appendix A, pp. 56-59). We request that EPA consult closely with experts in epidemiology at the National Cancer Institute of the National Institutes of Heath, especially but not exclusively in regard to the oft-cited epidemiological connection between exposure to phenoxy herbicides such as 2,4-D and non-Hodgkin's lymphoma in pesticide applicators. Such consultations should be informed by EPA's assessment of 2,4-D-related dioxins, as described above.

<u>2,4-DCP metabolites</u>

A unique attribute of 2,4-D-resistant crops treated with 2,4-D is that the degradative enzyme that confers resistance to 2,4-D (AAD-1 in Enlist corn, AAD-12 in Enlist soybeans) converts 2,4-D to non-phytotoxic 2,4-dichlorophenol (2,4-DCP). Metabolism of 2,4-D in crops that do not contain one of these enzymes proceeds quite differently, with little or no generation of 2,4-DCP or its conjugates in plant tissues.

A recent study (Jerschow et al 2012) explored the relationship between exposure to dichlorophenols and allergies in a nationally representative sample of 2,211 persons enrolled in the U.S. National Health and Nutrition Examination Survey 2005-2006. Detection of dichlorophenol metabolites in urine (2,4-dichlorophenol and/or 2,5-dichlorophenol) served as a marker of exposure. Having a high level of one or more dichlorophenol metabolites in urine

(75^{th} percentile or above) was significantly associated with sensitization to food and environmental allergens. After adjustment of the data to account for potential confounding variables, having high levels of the two dichlorophenol metabolites in urine remained significantly associated with sensitization to food allergens (OR 1.8, 95% CI 1.2-2.5, p = 0.003). Jerschow et al (2012) propose two possible explanations for these findings. First, the antibiotic effect of dichlorophenols, which are prevalent in the environment. could reduce microbial exposure, and numerous epidemiological studies have strongly linked increased hygiene to atopy. Second, dichlorophenols may have a direct effect on the immune system that promotes sensitization to food allergens.

The major source of 2,4-DCP in the environment is degradation of 2,4-D in contaminated soil and water. 2,4-DCP has been detected in soils and waste streams near industrial sites, and it may volatilize into the air. Exposure to 2,4-DCP occurs by inhaling contaminated air, ingesting contaminated water, or from dermal contact. A lipid-soluble molecule, 2,4-DCP is readily absorbed from the skin, intestine or lungs. Interestingly, 2,4-DCP is a minor metabolite of 2,4-D in humans and animals (CDC 2012), as in plants. 2,4-D-resistant crops represent a potential significant new source of exposure to 2,4-DCP in foods, and may increase sensitization to food allergens in exposed individuals. Further discussion of 2,4-DCP metabolites as they relate to both potential human toxicity in food and environmental toxicity is provided below.

2,4-D exposure and fatal injuries

Waggoner et al (2013) assessed pesticide use and fatal injury among farmers in the Agricultural Heath Study. Of the 49 pesticides investigated, the authors found that just seven herbicides were positively associated with risk of fatal injury. Of these seven, only "2,4-D and cyanazine were associated with fatal injury in exposure-response analysis." As EPA notes, "[r]esearchers observed a 20-50% increased risk of fatal injury among those exposed to 2,4-D, and significant exposure response relation (p for trend 0.01);" "the observation of associations with several herbicides somewhat undermines the role of chance explanation;" and "Given the seriousness of the outcome and frequency of use of 2,4-D and herbicides in general, more research is warranted" (Human Incidents, p. 4). The authors of the study note that: "While we recognize the complexity in assessing multiple simultaneous exposures, our pesticide results did not appear to be confounded by frequency of other farm activities" (Waggoner et al 2013).

The authors found their results to be "unexpected," because "[t]ypically, insecticides rather than herbicides are associated with neurotoxicity…and neurotoxicity might predispose to higher rates of fatal injury." However, examination of the common side effects of chlorophenoxy herbicide exposure may help to explain their results. As discussed by Cox (2006), Bradberry et al (2004) found that 2,000 chlorophenoxy herbicide incidents are reported to poison control centers in the U.S. each year. 2,4-D is by far the most heavily used chlorophenoxy herbicide in American agriculture. According to the abstract of Bradberry et al (2004),[7] chlorophenoxy herbicides have a multitude of acute effects. Some could be implicated in the increased rates of fatal injury observed by Waggoner et al (2013).

According to Bradberry et al (2004), adverse effects following ingestion include hypotension,

[7] CFS did not have access to the full study, abstract is in supporting materials.

ataxia (loss of the ability to coordinate muscular movement), nystagmus (rapid, involuntary, oscillatory motion of the eyeball), hallucinations, convulsions, paralysis; myopathic symptoms including limb muscle weakness, loss of tendon reflexes, myotonia (tonic spasm or temporary rigidity of one or more muscles); and hyperventilation. Substantial dermal exposure to 2,4-D in particular has led to progressive mixed sensorimotor peripheral neuropathy. Peripheral neuromuscular symptoms have occurred after occupational inhalation exposure. As reported in Cox (2006), EPA has previously reported 2,4-D poisoning incidents as involving effects such as dizziness, headaches, and eye irritation.

The plethora of neuromuscular effects following exposure to chlorophenoxy herbicides is particularly striking. Neuromuscular deficits and loss of muscular coordination from exposure to 2,4-D and related phenoxy herbicides could well be responsible for injuries in the dangerous business of farming.

2,4-D-related human health incident reports

EPA reports 2,202 human health incidents involving 2,4-D in the 5.5 years from 2007 to mid-2012 recorded in its Aggregate Incident Data System (IDS) (Health Incidents, p. 3). Though most are said to be of low severity, "the high absolute number of incidents (relative to other pesticides in IDS) reported involving 2,4-D may suggest the need for a more in depth Tier II analysis during the Preliminary Risk Assessment of Registration Review." Unfortunately, EPA provides absolutely no description of these reports. It would be interesting to know how many involve neuromuscular symptoms, such as those described above, or other symptoms that might help explain Waggoner et al (2013)'s results. EPA is urged to draft a much fuller account of these 2,4-D exposure incidents and make it available in the registration review docket; EPA should also provide public access to the IDS database, if it does not already do so.

EPA registered 459 2,4-D-related incidents in its Main IDS module, which is reserved for "higher severity outcomes," over the same 5.5-year period. Here, too, next to no information is provided on the nature of these more serious health impacts. EPA should make descriptions of these incidents available to the public, and provide a much fuller summary of them in the registration review docket. Six incidents issued in death. In the one incident described by EPA, "a 41 year old male sprayed diluted product earlier in the day. Later that day he experienced confusion, dizziness, conductive disturbance, and hypoglycemic shock. He was taken to the ER" (Human Incidents, Table 1, p. 7). Confusion or dizziness is consistent with some of the chlorophenoxy herbicide effects noted above, and could be related to increased incidence of serious accidents, for instance in operation of farm machinery.

EPA notes that the great majority of these more serious incidents involve exposures to 2,4-D as well as other chemicals, and suggests that these much more numerous incidents will be discounted and perhaps ignored in the course of the registration review (Human Incidents, p. 3). This would be a grave mistake. The ultimate goal of EPA's analysis should be to safeguard the health of farmers and the public from the toxic effects of 2,4-D in whatever form it is used, not to mechanically complete a product database. 2,4-D is increasingly used in conjunction with other herbicides; one new use application pending before the Agency is for use of a 2,4-D-glyphosate premix formulation. The trend to increasing use of multiple herbicides in premix formulations must not be used an excuse to ignore health effects from exposure to them. While adverse effects from exposure to product mixtures may occasionally be neatly "disentangled" as attributable to only component A or component B, there is growing recognition that disease and acute health effects are often multifactorial, attributable to more than one cause or agent. EPA is urged to fully assess all serious health incidents related to 2,4-D, whether the exposure is to 2,4-D alone, or to 2,4-D in combination with additional products. Given the results of Waggoner et al (2013), particular attention should be paid to patterns of adverse effects that could contribute to increased rates of accidents and fatal injuries.

2,4-D and respiratory immune responses

Slager et al (2009) reviewed data from the Agricultural Health Study to investigate associations between exposure of commercial pesticide applicators to 34 pesticides and rhinitis. Significant positive associations were found for just five of the 34 pesticides. Exposure to both 2,4-D and glyphosate ***over the past year*** was associated with significantly increased incidence of rhinitis (odds ratio 1.42, 95% confidence interval 1.14 to 1.77, as reported in the abstract). EPA incorrectly reported this study as showing that increased rhinitis was observed in applicators using both glyphosate and 2,4-D ***"over the lifetime,"*** and also erred in reporting an odds ratio of 1.34[8] (Human Incidents, p. 4). As EPA notes, rhinitis is a marker for upper respiratory immune reaction to pesticides, and further research is called for to understand the full import of the study. EPA should not discount the significance of this study because the association was found to applicators exposed to both 2,4-D and glyphosate. On the contrary, this herbicide combination is increasingly used by farmers to battle glyphosate-resistant weeds. One of the three new use applications for 2,4-D requested by Dow involves a premix formulation of 2,4-D and glyphosate. Simultaneous exposure to the two herbicides will increase dramatically, in tandem with 2,4-D-resistant corn adoption, if EPA grants the requested new use application. This could mean a sharp rise in rhinitis, and potentially more serious immune-related conditions of the respiratory tract in its train.

All of these demonstrated, probable and suspected human health impacts associated with 2,4-D take on added significance with the potential for a massive increase in use of this herbicide in association with 2,4-D-resistant crop systems.

V. EPA's ENVIRONMENTAL EFFECTS ASSESSMENT OF 2,4-D

Data Needs for Environmental Risk Assessment: 2,4-D Residues and Metabolites

In EPA's EFED Registration Review Problem Formulation for 2,4-D, the Analysis Plan identifies "stressors of ecological concern for terrestrial and aquatic organisms as the 10 forms of 2,4-D" (EFED, p. 23). The only metabolite or degradate that will be considered as a stressor of concern in ecological risk assessments is 2,4-DCP (DCP), based on studies showing it to be more toxic than 2,4-D for some aquatic organisms. EPA notes that registrants did not submit any studies on the environmental fate and effects of DCP, but that there are some studies in the

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[8] EPA mistakenly cited the odds ratio for exposure to 2,4-D alone (see Table 2: OR 1.34, 95% CI 1.09 to 1.64). In view of this odds ratio and confidence interval, it is unclear to us why Slager et al did not also regard exposure to 2,4-D alone as being associated with increased risk of rhinitis.

ECOTOX database on DCP in aquatic habitats (EFED, p. 30).

If 2,4-D is approved for use on Enlist corn, soybeans and cotton, there will be a new route of exposure to DCP for both terrestrial and aquatic organisms via DCP conjugates that accumulate in the tissues of these plants. Basically, the genetically engineered enzyme that confers resistance to 2,4-D does so by metabolizing 2,4-D to 2,4-DCP, which is then converted almost entirely to glycoside conjugates of DCP, as we describe in detail in previous comments (Appendix A, pp. 35 – 39; Appendix B, pp. 79 - 83). The levels of conjugated DCP can be quite high. Free DCP is likely to be liberated from these conjugates during digestion in animals that eat the tissues, and by microbes as the tissues are broken down during decay processes.

The toxicity of conjugates of DCP when delivered to animals via ingestion of plant tissues has not been studied. It is possible that the conjugates themselves are toxic, or that they are toxic only to the extent that DCP is released during digestion (Appendix A, pp. 36 – 38; Appendix B, pp. 87). This needs to be ascertained.

There are studies showing that insects may be more sensitive to DCP than 2,4-D, potentially putting pollinators at risk (Appendix A, pp. 39 – 43; Appendix B, pp. 88 - 89). Since 2,4-D is translocated throughout the plant from the site of application to growing tissues, and the engineered enzyme is likely to be expressed throughout the plant as well, we expect that DCP conjugates will accumulate in pollen, nectar, and guttation liquid, where honeybees and other pollinators will be exposed. In cotton plants, extra-floral nectaries, including those on leaves, are also likely to be sources of DCP conjugates for honeybees and other insects (CFS 2013, p. 70 – 73, Borem et al. 2003, Röse et al. 2006, Underhill 2010).

Herbivores and detritivores will also be exposed to these new metabolites, as well, via 2,4-D resistant plant tissues (Appendix B, p. 87).

Therefore, in order to do an ecological risk assessment, EPA not only needs to know the fate and toxicity of 2,4-D, but EPA also needs to know the fate and toxicity of the novel metabolites and degradates of 2,4-D in plant tissues engineered to be resistant to 2,4-D.

These data gaps need to be filled. EPA should include the levels and toxicity of DCP conjugates in the "Anticipated Data Needs" (Work Plan, p. 4). Levels of DCP conjugates in vegetative tissues at various times after 2,4-D applications need to be reported, along with fate of the DCP conjugates during tissue decomposition when leaves, stems and roots decay in soil or water. Levels of DCP conjugates in pollen, nectar, extrafloral nectaries and guttation liquid need to be determined in order to assess risk to pollinators, comparing results to 2,4-D and metabolites in the same tissues of 2,4-D treated, non-engineered plants. Data needs also include toxicity of DCP conjugates to various taxa, with particular attention to toxicity to honeybees and other pollinators.

Data Needs for Human Health Risk Assessment: 2,4-D Tolerances

Data on levels and toxicity of DCP conjugates collected for the Environmental Risk Assessment, above, should then inform a reevaluation of the tolerance criteria for 2,4-D. In the 2,4-D Human

Health Assessment Scoping Document in Support of Registration Review (Human Health), EPA states that "the residue of concern for tolerance regulation and risk assessment in 2,4-D *per se*…" including both free and conjugated 2,4-D (Human Health, pp. 6, 16). We have argued that the residue of concern should now be expanded to include DCP and conjugates of DCP in light of the activity of the engineered enzyme in 2,4-D resistant crops (Appendix A, pp. 38 – 39; Appendix B, p. 87) in order to take into account the major new metabolites. In particular, tolerances for animal feed are likely to need to be raised in light of these data (Appendix B, pp. 84 - 87).

Environmental Risk Assessment: Mechanism of Action

Although 2,4-D was the first synthetic herbicide to be widely used, entering the market in 1946 (BEAD, p. 2), aspects of its mechanism of action are still being elucidated, with implications for assessments of 2,4-D's impacts in the environment.

The EFED provides a summary of the mechanism of action of 2,4-D in killing weeds (EFED, p. 9). Previous research has shown that 2,4-D enters plants and then is transported via the vascular system to growing regions where it disrupts growth processes normally controlled by the plant hormone auxin.

For example, a recent study from Purdue University has identified a root-localized auxin transporter protein, called ABCB4, that also binds 2,4-D, contributing to its herbicidal activity (Kubeš et al. 2012):

> … ABCB4 appears to be a direct herbicidal target of 2,4-D. Binding of 2,4-D to ABCB4 results in increased accumulation of both 2,4-D and other auxins in root epidermal cells and is likely to amplify the herbicidal effects of the compound including swelling, separation of epidermal and cortical cell layers of the root, and decreased root surface area due to loss of root hairs… (Kubeš et al. 2012, p. 651)

Apparently, ABCB4 normally fine-tunes the amount of auxin inside root cells by transporting it inside when concentrations are low, and outside when they are high. However, when 2,4-D binds this protein – even before entering inside the root cells – the transporter gets switched to the "import only" mode, moving natural auxin and 2,4-D in but not out. This results in herbicide and natural auxin levels that are too high, inhibiting root hair elongation, and perhaps disrupting other root cell functions.

Some plants are naturally more resistant to 2,4-D than others. For example, most grasses can tolerate higher levels of 2,4-D without serious injury than dicots can. One reason is that grasses can inactive 2,4-D once it is inside the plant. Since ABCB4 is located on the outside of plant cells, though, 2,4-D can switch it into the intake-only mode before 2,4-D has a chance to be inactivated in these grass roots. The result may be shorter root hairs, even in these relatively 2,4-D resistant plants, and thus a decrease in drought tolerance and nutrient uptake if grasses – including corn – are exposed to 2,4-D via water or soil contamination.

This new mechanism of action for 2,4-D should be taken into account when considering the impacts of different patterns of use on water and soil contamination levels, and whether more plants may be at risk from these exposures than previously thought.

Also, the authors of the study suggest that 2,4-D resistant crops may be at risk of impaired root function if their roots are exposed to 2,4-D:

> "This suggests that ABCB4 is an unexpected target of 2,4-D action," Murphy said. "It's something that we have to be aware of with the commercial introduction of 2,4-D resistant soybeans and other dicot crops."…
>
> Murphy said the findings suggest that application techniques that limit 2,4-D entry into soils are important to ensure that production with engineered 2,4-D resistant crop plants does not require additional fertilizer and/or water inputs. (Purdue Newsroom 2011)

Environmental impacts of the increased use and new pattern of 2,4-D applications if new use on Enlist crops is approved should be assessed in light of this new mechanism of action of 2,4-D binding to the outside of roots, in addition to the previous mechanisms of action with 2,4-D inside of the plant.

<u>Environmental Risk Assessment: Increased off-site movement of 2,4-D</u>

EPA needs to assess how changes in patterns of use of 2,4-D will affect off-site movement of the herbicide and its metabolites if it is used with 2,4-D resistant crops, as we discuss in detail in previous comments (Appendix A, pp. 13 – 16; Appendix B, pp. 71 - 77). Not only will more 2,4-D be used per acre, the increase in post-emergence applications will be more likely to coincide with life-stages of crops and wild plants that are more sensitive to injury. In addition, drift-related injury will be exacerbated if the drop nozzle requirement for post-emergence application in the existing 2,4-D label for corn removed. Also, 2,4-D is likely to be used more widely in the landscape, creating more sources for 2,4-D drift and water pollution in a given area.

Volatility of 2,4-D formulations adds to risk of injury from drift, and severe injury to crops from such volatilization has been reported, yet EPA does not model volatility in their risk assessments (see, for example, US-EPA 2009, as cited in Appendix A). This is presumably because off-site movement due to volatilization is too difficult to predict in real-world situations. However, EPA does consider data from laboratory and field studies of volatility of different forms of 2,4-D, along with incident data (EFED, p. 25), when assessing risks.

Volatility data and incident reports are limited in their ability to predict the true risk of injury from off-site movement of 2,4-D. For example, Dow makes much of their plans to promote use of only 2,4-D choline on Enlist crops. Although Dow claims that its 2,4-D choline is less volatile than other 2,4-D salts, it is unclear to what extent this would mitigate crop injury under field conditions. Spray drift (versus vapor drift) has more to do with weather conditions, application equipment, and the applicators' practices than with the properties of the herbicide formulation. Even if 2,4-D choline is less drift-prone, any improvement in mitigating drift that it might present will be swamped by vastly increased use. In any case, neither EPA nor Dow will be able to prevent the use of cheaper, highly-drift prone formulations.

Official incident reports do encompass injury from all types of off-site movement, including injury from spray drift, volatilization and water contamination, but it is likely that they greatly underrepresent injury to crops and wild plants from 2,4-D use (Appendix A, pp. 15 – 16). EPA needs to develop methods to estimate the degree of underrepresentation in the incident report databases, and also to more accurately determine the amount of injury to non-target organisms from 2,4-D applications. For example, off-site 2,4-D movement that causes injury to wild organisms, including those that are threatened and endangered, is much less likely to be reported than injury to crops, and yet may have serious consequences for the environment (Appendix A, p. 16).

Biodiversity in and around fields of 2,4-D resistant crops is likely to decrease in response to changes in 2,4-D use, as we discuss (Appendix A, pp. 44 – 46; Appendix B, pp. 74 - 77), with habitats both adjacent to and distant from treated fields at risk. These herbicide-induced changes in plant populations can then indirectly impact "microbial communities, occurrence of plant pathogens, or diminished insect populations. Both direct and indirect effects could lead to numerous negative impacts on ecosystem services including wildlife habitat, nutrient cycling, control of soil erosion, recreation, timber or pulp production, livestock grazing, control of noxious plant species and aesthetics…." (Olszyk et al. 2004, as cited in Appendix A, pp. 45 - 46).

Herbicides such as 2,4-D that selectively kill dicots may be particularly injurious to butterflies, often considered an indicator of ecosystem health. If these herbicides are applied frequently and over a broad area – as will happen with 2,4-D use on Enlist crops– negative impacts on butterflies are particularly strong. A study of pesticide effects on butterflies in agricultural areas of England makes this point:

> The frequency and number of pesticide applications, the spatial scale of treatment and the degree of field boundary contamination during each spray occasion will determine the extent of damage to butterfly habitats and populations, and the rate at which populations will return to their original densities. (Longley and Sotherton 1997).

Researchers implemented experimental mitigation measures to determine whether changes in pesticide use would result in more butterflies in the landscape. One of these measure involved limiting the use of "persistent broadleaf herbicides" near field edges, and instead using herbicides that were more specifically targeted against grasses:

> The outer section of a tractor-mounted spray boom (approximately 6 m) is switched off when spraying the outer edge of a crop, avoiding the use of certain chemicals (persistent broadleaf herbicides and all insecticides other than those used for controlling the spread of Barley Yellow Dwarf Virus). Whilst the rest of the field is sprayed with the usual compliment of pesticides, more selective chemicals (e.g. graminicides rather than broad-spectrum herbicides) are sprayed on the edges (Boatman and Sotherton, 1988). (Longley and Sotherton 1997, p. 8).

They found that there were indeed more butterflies after taking these measures, and also that there were more dicots, the main source of nectar, as well as more biodiversity in general:

> In addition, as a result of selective herbicide use, Conservation Headlands are rich in broadleaved plants, thereby increasing the availability of nectar resources for butterfly species. (Longley and Sotherton 1997, p. 8)
>
> The unsprayed headlands have also been shown to benefit the survival of rare weeds (Schumacher, 1987; Wilson, 1994), small mammals (Tew, 1988), beneficial invertebrates (Chiverton and Sotherton, 1991; Cowgill et al., 1993) and gamebird chicks (Rands, 1985; Rands, 1986). However, to be of long-term value for butterfly conservation, unsprayed headlands need to be maintained over consecutive years to allow the survival of those species which are univoltine and have poor powers of dispersal. (Longley and Sotherton 1997, p. 9)

In conclusion, these researchers emphasize the need for research on impacts of pesticide use over time:

> In addition to short-term studies, covering single cropping seasons, information is also needed on the effects of different spray and cropping regimes over several seasons on butterfly communities in exposed areas. Only then will it be possible to make reliable predictions and recommendations for butterfly conservation on arable farmland. (Longley and Sotherton 1997, p. 12)

Implications of this butterfly study in England are clear for use of 2,4-D with Enlist crops: 2,4-D is an herbicide that selectively kills broadleaved plants (dicots), the main nectar source for adult butterflies, even those species whose larvae feed on grasses. 2,4-D is also likely to be used more often during a season, more extensively in an area, and from year to year with Enlist crops than it is currently used in agriculture. This is exactly the opposite use pattern than that recommended for mitigation of pesticide impacts on butterflies, that were also shown to be protective of biodiversity in general.

EPA should take his study, and others that look at impacts of herbicides on biodiversity, into account in their environmental assessment for the 2,4-D registration review, including possible changes in use on 2,4-D resistant crops.

<u>Endangered Species</u>

All of the harms from increased use of 2,4-D on Enlist crops to plants, animals, and other organisms, and to their habitats, discussed above and in our previous comments, apply to species that are at risk of extinction (Appendix A, pp. 47 – 49; Appendix B, pp. 77 – 79). Endangered species near fields planted to Enlist crops will be at increased risk from exposure to 2,4-D via drift of particles and vapor, runoff, accidental over-spraying, and recently sprayed plant parts and soil. Their habitats will be at higher risk of being altered from changes in plant populations with attendant impacts.

In addition to impacts from 2,4-D drift and run-off, we ask that EPA take into account the potential toxicity of Enlist crops, after applications of 2,4-D choline, to listed species that might eat corn, soybean and cotton leaves, roots, stems, or flower parts. Migrating birds, for example, eat parts of the corn plant. Bees consume corn, soybean and cotton pollen, and soybean and cotton nectar, and presumably other insects also utilize pollen, leaves, roots, and other plant parts. Corn detritus washes into wetlands where it is consumed by aquatic organisms, and is also broken down in soil by detritivores. These crops are planted widely, thus many species are potentially impacted. Thus the levels and toxicity of 2,4-D and its metabolites and degradates within plant tissues need to be considered in the complete endangered species assessment that is part of this registration review.

As noted by EPA, when 2,4-D use was assessed for risks to the California red-legged frog (CRLF) and Alameda whipsnake (AW), the determination was that it "may affect and [is] likely to adversely affect" these listed species for all uses except on citrus and potatoes (EFED, p. 4). Since many threatened and endangered animals share the basic food and habitat requirement of CRLF and AW, including other amphibians and reptiles, but also mammals and birds, we expect that the EPA will find that use of 2,4-D on Enlist crops will similarly be "likely to adversely affect" prey and habitats of threatened and endangered animals found near these fields.

We are aware of only one EPA consultation over 2,4-D impacts on threatened and endangered species that has proceeded to the "biological opinion" stage, for Pacific salmonid fishes (NMFS 2011, as cited in Appendix A, p. 48; but not cited in EFED). These are fish species that spawn in the floodplains of the Pacific coast, and then go to sea for a few years before returning up rivers and creeks to their original spawning ground to begin again. Here the NMFS concluded that agricultural uses of 2,4-D were "likely to adversely modify" critical habitat because of injury to plants. They expressed concern about toxicity to plants from agricultural applications near riparian zones in the floodplains, for example (NMFS 2011, p, 540 – 543). Riparian vegetation "provides shade, bank stabilization, sediment, chemical and nutrient filtering, and provides a niche for the terrestrial invertebrates that are also salmon prey items…We believe the a.i. [2,4-D] will have a detrimental effect on riparian vegetation…" (NMFS 2011, p. 627 – 628).

Again, many threatened and endangered aquatic species will have similar habitat requirements for water quality and prey, including some that are in habitats near corn, soybean and cotton cultivation and thus could be impacted by the increased use of 2,4-D on Enlist crops.

According to the NMFS opinion of June 30, 2011, EPA was to implement "reasonable and prudent alternatives" (RPA) in order to mitigate harm to Pacific salmonids from use of 2,4-D:

> The RPA is comprised of seven required elements that must be implemented in its entirety within one year of the EPA's receipt of this Opinion to ensure the registration of these pesticides is not likely to jeopardize endangered or threatened Pacific salmonids under the jurisdiction of NMFS or destroy or adversely modify critical habitat designated for these species. For each active ingredient, the elements of the RPA apply only to those ESUs/DPSs where NMFS has determined that registration of that a.i. is likely to jeopardize listed species and/or destroy or adversely modify designated critical habitat (Table 148 and Table 149). These elements rely upon recognized practices for reducing the loading of pesticide products into aquatic habitats. (NMFS 2011, p. 776, as cited in

Appendix A, p. 48)

We were not able to find a record of EPA complying with this implementation timetable, nor did we see mention made of this biological opinion in the docket materials. Certainly the 2,4-D registration review should incorporate the results of this opinion in the complete endangered species assessment.

Again, this registration review will include the first complete endangered species assessment for 2,4-D. Based on results of the few species that have been assessed, above, EPA should take into account the changes in use of 2,4-D associated with use on Enlist crops before granting a new use registration for such use. EPA's consultation duties under the ESA and the agency's compliance with the ESA on the direct and indirect impacts of its approval action in no way vitiates the ESA duties of any other agencies (such as USDA/APHIS) for the impacts of their own approval action.

VI. CONCLUSION

We request that EPA give serious consideration to the many serious concerns raised in these comments and appendices regarding 2,4-D in the course of the registation review. We emphasize once again that it is imperative that EPA incorporate realistic estimates for significantly increased use and altered use patterns of 2,4-D that would accompany introduction of 2,4-D-resistant crops under the proposed new use registrations. We would be happy to answer any questions or discuss these matters at your convenience.

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