THE CENTER FOR FOOD SAFETY

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Comments to EPA on Notice of Receipt of Applications to Register New Uses of 2,4-D on Enlist AAD-1 Corn and Soybean

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Docket Nos. EPA-HQ-OPP-2011-0835; EPA-HQ-OPP-2012-0306

Dow AgroSciences LLC (Dow) has filed applications (2,4-D New Use Registration Applications) to the U.S. Environmental Protection Agency (EPA) to register new uses for pesticide products containing 2,4-D, a registered active ingredient, under Section 3(c) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).[1] Specifically, Dow has filed the three following new use registration applications:

1. Docket No. EPA-HQ-OPP-2011-0835. Active Ingredient: 2,4-D choline salt. Proposed Classification/Use: Enlist AAD-1 Corn (DAS-402780-9 Corn)
2. Docket No. EPA-HQ-OPP-2011-0835. Active Ingredient: 2,4-D choline salt and glyphosate. Proposed Classification/Use: Enlist AAD-1 Corn (DAS-402780-9 Corn)
3. Docket No. EPA-HQ-OPP-2012-0306. Active Ingredient: 2,4-D choline salt. Proposed Classification/Use: Enlist AAD-12 Soybeans ((DAS-68416-4 Soybean)

Dow's 2,4-D New Use Registration Applications propose new uses of 2,4-D choline salt on Dow's 2,4-D resistant DAS-402780-9 corn and DAS-68416-4 soybeans (henceforth also referred to as Enlist corn and Enlist soybeans), which have been genetically engineered (GE) to

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[1] 7 U.S.C. §§ 136 *et seq.*

resist the herbicide 2,4-D. Dow's new use registration application also proposes the new use of 2,4-D choline salt and glyphosate on 2,4-D resistant DAS-402780-9 corn. Dow has also petitioned the Animal Plant Health and Inspection Service (APHIS) of the U.S. Department of Agriculture to deregulate DAS-402780-9 corn and DAS-68416-4 soybeans.[2]

Pursuant to FIFRA Section 3(c)(4), on May 23, 2012, EPA published a notice of receipt of Dow's applications for new uses of 2,4-D on Dow's 2,4-D resistant DAS-402780-9 Corn and DAS-68416-4 Soybeans in the Federal Register.[3] The Center for Food Safety (CFS) submits the following comments concerning issues that EPA should consider in its review of Dow's new use registration applications under FIFRA, the Federal Food, Drug, and Cosmetic Act (FFDCA)[4], and the Endangered Species Act (ESA)[5].

CFS is a non-profit, membership organization that works to protect human health and the environment by curbing the proliferation of harmful food production technologies and by promoting organic and other forms of sustainable agriculture.[6] CFS represents more than 200,000 members throughout the country that support sustainable forms of food production such as organic agriculture and regularly purchase organic products. Concurrently, CFS is also submitting 19,063 comments from CFS True Food Network members urging EPA to carefully consider the "unreasonable adverse effects"[7] of 2,4-D new use on Dow's 2,4-D resistant DAS-402780-9 corn and DAS-68416-4 soybeans.

SUMMARY OF ARGUMENTS

First, in preparing its risk assessment of Dow's New Use Registration Applications under FIFRA, EPA must assess whether they cause changes to existing use patterns of 2,4-D, and any direct and indirect impacts of the proposed new use of 2,4-D on 2,4-D resistant corn and soybeans. EPA cannot register the proposed new use of 2,4-D if the agency determines that these shifts in use pattern and their related impacts result in unreasonable adverse effects on the environment. The proposed new use of 2,4-D choline salt on Dow's 2,4-D resistant DAS-40278-9 Corn and DAS-68416-4 Soybean will not only result in an overall increase in the volume of 2,4-D used in U.S. agriculture, but will also enable more frequent applications of 2,4-D at higher rates directly over the top of the crops as they are growing. The proposed new use of 2,4-D choline salt on transgenic corn and soybeans designed to withstand the pesticide will also result in more 2,4-D applications later in the production cycle. Moreover, the proposed new use will dramatically alter existing use of 2,4-D on soybeans (which is currently limited to applications before planting), by allowing 2,4-D to be applied on Dow's 2,4-D resistant DAS-68416-4 Soybean after plants have emerged. Thus, Dow's proposed new uses of 2,4-D choline as part of

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[2] *See* APHIS, Petition for Nonregulated Status Granted or Pending, http://www.aphis.usda.gov/biotechnology/not_reg.html (last visited June 17, 2012).
[3] 77 Fed. Reg. 30,524-26 (May 23, 2012).
[4] 21 U.S.C. §§ 301 *et seq*.
[5] 16 U.S.C. §§ 1531-1544.
[6] *See generally* www.centerforfoodsafety.org.
[7] 7 U.S.C. § 136a(c)(5).

the company's 2,4-D resistant crop system will enable in a many-fold increase in the acreage of U.S. farmlands being treated with 2,4-D.[8]

Second, under the FFDCA, EPA has a duty to analyze the proposed new use of 2,4-D and set tolerance levels that ensure the residue of 2,4-D under the proposed new use is safe. EPA's determination of safety requires that EPA takes into account the aggregate human exposure to 2,4-D residue, not just from dietary pathways but also exposure through water and residential uses. As detailed below, the proposed new use pattern of 2,4-D, which will result in more frequent applications of 2,4-D as well as prolonged use of 2,4-D, may alter the residue levels of 2,4-D in or on food.

Third, EPA should consider Dow's New Use Registration Applications under FIFRA's unconditional registration criteria. Dow's New Use Registration Applications propose unprecedented use of 2,4-D on GE crops designed to withstand the herbicide application, thus introducing a new herbicide-resistant crop system in U.S. agriculture (hereafter the 2,4-D resistant crop system). This new paradigm demands that EPA make its risk assessment and registration determination based on a critical review of all relevant data. EPA must ensure that its risk assessment is truly a functional equivalent of NEPA by taking a "hard look" at all reasonably foreseeable consequences of registering 2,4-D use on 2,4-D resistant corn and soybeans.

Finally, given the unprecedented nature of Dow's new use proposal, EPA must ensure meaningful public participation by (1) publishing all relevant information as well as the agency's draft risk assessment; and (2) providing a second opportunity for public comment.

RELEVANT LEGAL STANDARDS

The Federal Insecticide, Fungicide, and Rodenticide Act

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) authorizes EPA to regulate the registration, use, sale, and distribution of pesticides in the United States. FIFRA defines pesticides broadly to include herbicides—"any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccants."[9] Under FIFRA, EPA is "charged to consider the effects of pesticides on the environment." [10]

Pursuant to FIFIRA, EPA oversees both initial registration of an active ingredient as well as any new uses of the registered active ingredient. EPA's FIFRA implementing regulations define "new use" as:

> New use, when used with respect to a product containing a particular active ingredient, means: (1) Any proposed use pattern that would require the establishment of, the increase in, or the exemption from the requirement of, a

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[8] *See* Nat'l Agricultural Statistics Serv., USDA, Crop Acreage (June 30, 2011), aavailable at http://usda01.library.cornell.edu/usda/current/Acre/Acre-06-30-2011.pdf

[9] 7 U.S.C. § 136(u)(2).

[10] *Fairhurst v. Hagener*, No. CV-03-67-BU-SHE, 2004 U.S. Dist. LEXIS 30161, at *49 (D. Mont. Mar. 24, 2004).

> tolerance or food additive regulation under section 408 or 409 of the Federal Food, Drug and Cosmetic Act; (2) Any aquatic, terrestrial, outdoor, or forestry use pattern, if no product containing the active ingredient is currently registered for that use pattern; or (3) Any additional use pattern that would result in a significant increase in the level of exposure, or a change in the route of exposure, to the active ingredient of man or other organisms.[11]

Section 3(c) of FIFRA states that a manufacturer must submit an application to register any new uses of a registered active ingredient.[12] EPA's evaluation of the proposed pesticide use must take into account its "impacts on human health, occupational risks, and environmental risks."[13] EPA cannot register the pesticide unless EPA concludes that the proposed new use "will not generally cause unreasonable adverse effects on the environment" when "perform[ing] its intended function" and "when used in accordance with widespread and commonly recognized practice."[14] "Unreasonable adverse effects on the environment" includes "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."[15]

The Federal Food, Drug, and Cosmetic Act

The Federal Food, Drug, and Cosmetic Act (FFDCA)[16] prohibits the introduction of "adulterated" food into interstate commerce.[17] The Act requires that where use of a pesticide will result in any pesticide residue being left on food, the EPA must either set a "tolerance" level for the amount of allowable pesticide residue that can be left on the food, or set an exemption of the tolerance requirement.[18] The tolerance or exemption requirements apply to raw agricultural commodities such as DAS-402780-9 corn and DAS-68416-4 soybeans.[19]

The FFDCA mandates EPA to "establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the EPA Administrator determines that the tolerance is safe".[20] For a tolerance level to be "safe," the statute requires EPA determine "that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."[21] "Aggregate exposure" includes not only dietary exposure through food consumption, but also includes "exposures through water and residential uses."[22]

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[11] 40 C.F.R. § 152.3(p).

[12] 7 U.S.C. § 136a(c)(1); 40 C.F.R. § 152.42.

[13] EPA, Overview of Risk Assessment in the Pesticide Program (May 9, 2012), at http://www.epa.gov/pesticides/about/overview_risk_assess.htm.

[14] 7 U.S.C. § 136a(c)(5).

[15] 7 U.S.C. §136(bb).

[16] 21 U.S.C. § 301 *et seq.*

[17] 21 US.C. § 331.

[18] 21 U.S.C. § 346a(1).

[19] 21 U.S.C. § 321(r) defines "raw agricultural commodities" as "any food in its raw or natural state, including all fruits that are washed, colored or otherwise treated in their unpeeled natural form prior to marketing."

[20] 21 U.S.C. § 342(a)(2)(A) (emphasis added); *see also* 40 C.F.R. § 180.1(f).

[21] 21 U.S.C. § 346(a)(2)(A)(ii).

[22] *Natural Res. Def. Council v. Whitman*, No. C 99-03701-WHA, 2001 WL 1221774 (N.D. Cal. Nov. 7, 2001).

Endangered Species Act

As recognized by the Supreme Court, the ESA is "the most comprehensive legislation for the preservation of endangered species ever enacted by any nation."[23] The ESA's statutory scheme "reveals a conscious decision by Congress to give endangered species priority over the 'primary missions' of federal agencies."[24] Federal agencies are obliged "to afford first priority to the declared national policy of saving endangered species."[25]

Section 7(a)(2) of the ESA requires every federal agency to consult the appropriate federal fish and wildlife agency—Fish and Wildlife Service (FWS), in the case of land and freshwater species and the National Marine Fisheries Service (NMFS) in the case of marine species—to "insure" that the agency's actions are not likely "to jeopardize the continued existence" of any listed species or "result in the destruction or adverse modification" of critical habitat.[26] The ESA's implementing regulations broadly define agency action to include "all activities or programs of any kind authorized, funded or carried out … by federal agencies," including the granting of permits and "actions directly <u>or indirectly</u> causing modifications to the land, water or air."[27] A species' "critical habitat" includes those areas identified as "essential to the conservation of the species" and "which may require special management considerations or protection."[28]

To facilitate compliance with section 7(a)(2)'s prohibitions on jeopardy and adverse modification, the ESA requires each federal agency that plans to undertake an action to request information from the expert agency "whether any species which is listed or proposed to be listed [as an endangered species or a threatened species] may be present in the area of such proposed action."[29] If FWS/NMFS advises the agency that listed species or species proposed to be listed <u>may</u> be present, the agency <u>must</u> then prepare a biological assessment for the purpose of identifying any such species that are likely to be affected by the proposed agency action.[30]

If, based on a biological assessment, an agency determines that its proposed action may affect any listed species and/or their critical habitat, the agency generally must engage in formal consultation with FWS/NMFS.[31] At the end of the formal consultation, FWS/NMFS must provide the agency with a "biological opinion" detailing how the proposed action will affect the threatened and endangered species and/or critical habitats.[32] If FWS/NMFS concludes that the proposed action will jeopardize the continued existence of a listed species or result in the destruction or adverse modification of critical habitat, the biological opinion must outline

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[23] *Tenn. Valley Authority v. Hill*, 437 U.S. 153, 180 (1978).
[24] *Id.* at 185.
[25] *Id.*
[26] 16 U.S.C. § 1536(a)(2); *see also* 50 C.F.R. § 402.01(b).
[27] 50 C.F.R. § 402.02 (emphasis added).
[28] 16 U.S.C. § 1532(5)(A).
[29] 16 U.S.C. § 1536(c)(1); *see also* 50 C.F.R. § 402.12(c).
[30] *Id.*
[31] 50 C.F.R. § 402.14.
[32] 16 U.S.C. § 1536(b); 50 C.F.R. § 402.14.

"reasonable and prudent alternatives" to the proposed action that would avoid violating ESA section 7(a)(2).[33]

Pending the completion of formal consultation with the expert agency, an agency is prohibited from making any "irreversible or irretrievable commitment of resources with respect to the agency action which has the effect of foreclosing the formulation or implementation of any reasonable and prudent alternative measures."[34]

National Environmental Policy Act

NEPA requires federal agencies to prepare a detailed environmental impact statement (EIS) for all "major Federal actions significantly affecting the quality of the human environment."[35] NEPA "ensures that the agency ... will have available, and will carefully consider, detailed information concerning significant environmental impacts; it also guarantees that the relevant information will be made available to the larger [public] audience."[36]

As a preliminary step, an agency may prepare an environmental assessment (EA) to decide whether the environmental impact of a proposed action is significant enough to warrant preparation of an EIS.[37] If an agency decides not to prepare an EIS, it must supply a "convincing statement of reasons" to explain why a project's impacts are insignificant.[38] "The statement of reasons is crucial to determining whether the agency took a 'hard look' at the potential environmental impact[s] of a project."[39] An EA must "provide sufficient evidence and analysis for determining whether to prepare an EIS or a finding of no significant impact" [40] NEPA regulations require the analysis of direct, indirect, and cumulative effects in NEPA documents, including EAs.[41] The assessment must be "complete, reasoned, and adequately explained.,"[42] demonstrating that the action agency took a "hard look" at the potential environmental impacts of its action.[43]

Whether there may be a significant effect on the environment requires consideration of two broad factors: context and intensity. A number of factors should be considered in evaluating intensity, including, "[t]he degree to which the proposed action affects public health or safety," "[t]he degree to which the effects on the quality of the human environment are likely to be highly controversial," "[t]he degree to which the possible effects on the human environment are highly uncertain or involve unique or unknown risks," "[t]he degree to which the action may establish a precedent for future actions with significant effects or represents a decision in principle about a

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[33] 16 U.S.C. § 1536(b)(3)(A).
[34] 16 U.S.C. § 1536(d).
[35] 42 U.S.C. § 4332(2)(C).
[36] *Robertson v. Methow Valley Citizens Council,* 490 U.S. 332, 349(1989).
[37] 40 C.F.R. § 1508.9.
[38] *Save the Yaak v. Block,* 840 F.2d 714, 717 (9th Cir. 1988).
[39] *Id.*
[40] *Id.*
[41] *See* 40 C.F.R. §§ 1508.8, .9, .13, .18.
[42] *Northwest Coalition for Alternatives to Pesticides v. U.S. E.P.A.*, 544 F.3d 1043, 1052 n.7 (9th Cir. 2008).
[43] *Blue Mountains Biodiversity v. Blackwood*, 161 F.3d 1208, 1211 (9th Cir. 1998). *Nat'l Parks & Conservation Ass'n v, Babbit*, 241 F.3d 722, 731 (9th Cir. 2001) (quoting 40 C.F.R. § 1508.27).

future consideration," "[w]hether the action is related to other actions with individually insignificant but cumulatively significant impacts," and "[t]he degree to which the action may adversely affect an endangered or threatened species or its habitat."[44] An action may be "significant" if just one of these factors is met.[45]

The Council on Environmental Quality

NEPA also established the Council on Environmental Quality (CEQ) and charged CEQ with the duty of overseeing the implementation of NEPA.[46] The regulations subsequently promulgated by CEQ, 40 C.F.R. §§ 1500-08, implement the directives and purpose of NEPA, and "[t]he provisions of [NEPA] and [CEQ] regulations must be read together as a whole in order to comply with the spirit and letter of the law."[47] CEQ's regulations are applicable to and binding on all federal agencies.[48] Among other requirements, CEQ's regulations mandate that federal agencies address all "reasonably foreseeable" environmental impacts of their proposed programs, projects, and regulations.[49]

COMMENTS

I. Introduction

The proposed new use of 2,4-D choline salt on Dow's DAS-40278-9 corn and DAS-68416-4 soybeans, which have been specifically engineered to resist the application of Dow's 2,4-D, marks a significant departure from existing use patterns of 2,4-D on conventional corn and soybeans. The novelty of the proposed new use on the two most widely planted agricultural crops in the United States demands that EPA carefully consider the "economic, social, and environmental costs" associated with the proposed new uses in its risk assessment.[50]

The proposed registrations relate to the herbicidal component of Dow's 2,4-D resistant crop system (the Enlist Weed Control System) of 2,4-D resistant corn and soybeans. Dow's 2,4-D resistant crop system would facilitate weed control based primarily on post-emergence applications of 2,4-D and/or glyphosate on DAS-40278-9 corn and DAS-68416-4 soybeans (Blewett *et al.*. 2011). These crop systems are explicitly intended for farmers whose fields are infested with weeds resistant to glyphosate, which have spread across approximately 17 million acres of U.S. cropland, largely due to unregulated use of glyphosate in the context of the

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[44] 40 C.F.R. § 1508.27(b)(2), (4), (5), (6), (7), (9).
[45] *Ocean Advocates v. U.S. Army Corps of Eng'rs*, 361 F.3d 1108, 1125 (9th Cir.2004); *see also Nat'l Parks & Conservation Ass'n*, 241 F.3d at 731 (either degree of uncertainty or controversy "may be sufficient to require preparation of an EIS in appropriate circumstances.").
[46] *See* 42 U.S.C. §§ 4321, 4344.
[47] 40 C.F.R. § 1500.3.
[48] 40 C.F.R. §§ 1500.3, 1507.1; *see, e.g., Hodges v. Abraham*, 300 F.3d 432, 438 (4th Cir. 2002).
[49] *See* 40 C.F.R. §§ 1502.4, 1508.8, 1508.18, & 1508.25.
[50] 7 U.S.C. §136(bb); *see* Nat'l Agricultural Statistics Serv., USDA, Crop Acreage (June 30, 2011), *available at* http://usda01.library.cornell.edu/usda/current/Acre/Acre-06-30-2011.pdf (reporting that corn acreage planted in 2011 totaled 92.3 million acres, a 5 percent increase from 2010; and soybean acreage planted in 2011 totaled 75.2 million acres).

Roundup Ready (glyphosate-resistant) crop systems, though they may also be used by farmers with weeds resistant to other modes of action, such as ALS inhibitors and triazines.[51]

The proposed registrations of 2,4-D choline salt and/or glyphosate for use on Enlist field corn and of 2,4-D choline salt for use on soybeans raise a number of serious issues that EPA has never confronted in any past registration decision on 2,4-D. These issues arise from an inescapable biological fact: the enzymes engineered into Enlist corn and soybeans will facilitate greatly altered usage patterns of phenoxy auxin herbicides like 2,4-D vis-à-vis past usage on conventional corn and soybeans.

The aryloxyalkanoate dioxygenase-1 enzyme (AAD-1) expressed in DAS-40278-9 corn confers upon it the ability to survive, with little or no crop injury, many-fold higher rates of 2,4-D applied during a likely much broadened application window relative to any previous corn variety. The AAD-12 enzyme enables entirely new post-emergence use of high rates of 2,4-D on DAS-68416-4 soybeans through much of the growing season, in comparison to extremely limited pre-emergence use with any previous soybean variety.

AAD-1 also confers high-level resistance to dichlorprop and perhaps other phenoxy auxin herbicides, as well as enabling entirely new post-emergence use of aryloxyphenoxypropionate herbicides such as quizalofop and cyhalofop. AAD-12 confers novel, high-level resistance to additional phenoxy auxin herbicides such as MCPA as well as to pyridyloxyacetate herbicides such as triclopyr and fluroxypyr (Wright *et al.*. 2010).

Thus, AAD-1 and AAD-12 would biologically enable new or sharply increased use of at least seven herbicides from three distinct chemical classes (two modes of action) on varieties of America's two most widely planted crops. The advent of these traits that confer high-level resistance to multiple herbicides will greatly increase the potential for and magnitude of off-label herbicide uses.

II. EPA Should Not Conditionally Register Dow's New Use Registration Applications

Even though EPA usually reviews applications for new uses of registered active ingredients under its conditional registration criteria, the novelty of the proposed new uses of 2,4-D choline salt and the changes in existing 2,4-D use patterns as applied in the 2,4-D resistant crop system warrants EPA to commence a complete review of Dow's New Use Registration Applications for unconditional registration. EPA's FIFRA implementing regulations provide that EPA may initiate review using the unconditional registration criteria in FIFRA Section 3(c)(5)—as opposed to conditional registration criteria set forth in FIFRA Section 3(c)(7) "in special cases where [EPA] finds immediate review to be warranted."[52]

Under FIFRA's criteria for unconditional registration, EPA can register the proposed new use of 2,4-D choline salt on 2,4-D resistant corn and soybeans only if EPA concludes that the proposed new use will not have "unreasonable adverse effects on the environment" after

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[51] *Id.*

[52] 40 C.F.R. § 152.111 (giving EPA discretion to decide whether to use conditional registration or unconditional registration criteria).

reviewing all data in EPA's possession.[53] Unlike a conditional registration pursuant to FIFRA Section 3(c)(7), unconditional registration requires that EPA determine that "no additional data is necessary" for the agency to assess "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."[54] In contrast, EPA can conditionally register a new use application so long as the agency concludes that the proposed new use will "not significantly increase the risk of any unreasonable adverse effect on the environment" and that the "proposed use [is] identical or substantially similar to any currently registered pesticide and use thereof."[55]

As explained in the comments herein, existing scientific studies, academic papers—including Dow's own submissions to APHIS in its petition for deregulating Dow's 2,4-D resistant DAS-40278-9 Corn—demonstrate that the proposed new use patterns of 2,4-D choline on GE, 2,4-D resistant corn and soybeans may have significant adverse impacts on human health and the environment. The proposed new use would substantially alter the existing use of 2,4-D as applied to Dow's 2,4-D resistant corn and soybeans. Thus, EPA must assess Dow's New Use Registration Applications for the proposed use of 2,4-D choline salt on Dow's 2,4-D resistant DAS-40278-9 corn and DAS-68416-4 soybean strictly under FIFRA criteria for unconditional registration.

III. NEPA Demands that EPA Take a Hard Look at All Reasonable Foreseeable Environmental Impacts Stemming from Dow's Proposed Use of 2,4-D Choline Salt on 2,4-D Resistant Corn and Soybeans

It is also necessary for EPA's analysis to satisfy the agency's duties under NEPA. While it is true that some federal courts have excused EPA from "formal compliance with NEPA", that is only where its FIFRA analysis is the functional equivalent of an EIS, and FIFRA's conditional registration criteria falls short of the "hard look" that NEPA mandates on all federal agencies, including EPA.[56] As explained above, EPA should not conditionally register Dow's new uses. But if it does, it must comply with NEPA and prepare an EIS.

A conditional registration violates NEPA by allowing the EPA to register a pesticide or its use without consideration of "detailed information concerning significant environmental impacts," and excludes public scrutiny and participation on potential significant environmental effects stemming from the registered use.[57] For its FIFRA analysis to functionally satisfy NEPA's hard look requirement, EPA must demand that Dow submit a complete application, satisfy any data gaps, and conduct and produce peer-reviewed studies on any potential unreasonable adverse effects on the environment stemming from Dow's proposed new use of 2,4-D choline salt on Dow's 2,4-D resistant corn and soybeans.

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[53] 7 U.S.C. 136a(c)(5).

[54] 7 U.S.C. §136(bb).

[55] 7 U.S.C. § 136a(c)(7).

[56] *Cf. Merrell v. Thomas*, 807 F.2d 776 (9th Cir. Or. 1986).

[57] *See Robertson v. Methow Valley Citizens Council*, 490 U.S. 332, 349(1989).

IV. The Proposed Use of 2,4-D Choline Salt on Dow's 2,4-D Resistant Corn and Soybeans Would Significantly Alter Use Patterns of 2,4-D

The proposed registrations would sharply alter use patterns of 2,4-D vis-à-vis current usage on corn and soybeans in several major ways: 1) increased rates per application; 2) a strong shift from pre-emergence and early-season use to post-emergence use later in the season; and 3) an increase in acres treated. Together, these changes will lead both to a sharp increase in 2,4-D use, and to patterns of use that have adverse consequences for human health, agriculture, and the environment.

At present, 2,4-D is little used on corn or soybeans. The latest available figures from USDA's National Agricultural Statistics Service are from 2010 (corn) and 2006 (soybeans). In 2010, farmers applied 5 forms of 2,4-D to 10% of U.S. corn acreage. An average of 1.12 applications were made on treated acreage, at an average rate of 0.35 lb./acre/application. Overall, 3.3 million lbs. were applied.[58]

In 2006, three forms of 2,4-D were applied to 10% of soybean acreage. An average of 1.0 application was made to treated acreage, at an average application rate of 0.48 lbs/acre and 0.50 lbs/acre per year. Overall usage in the 19 Program States, representing 96% of soybean acreage, was 3.53 million lbs., for an estimated 3.67 million lbs. nationally.

2,4-D use on DAS-40278-9 corn and DAS-68416-4 soybeans would be the product of the rate applied per application, the number of applications per season, and the number of acres planted. The usage rate and number of applications per year are dependent on several factors, including the amount that can be applied without injuring the crop, the limits in the proposed registrations, and the weed challenges faced by farmers. Frames of reference for the number of acres that would be planted to Enlist corn and soybeans include overall corn and soybean acreage, herbicide-resistant corn and soybean acreage, and prevalence of herbicide-resistant weeds. Each of these factors is discussed in the comments.

V. EPA Should Consider All Economic, Social and Environmental Costs Stemming from Dow's Proposed New Use of 2,4-D Choline Salt on Novel 2,4-D Resistant Corn and Soybeans

Under FIFRA, EPA cannot register a pesticide for a specified use if such use will result in "unreasonable adverse effects on the environment."[59] EPA must determine whether Dow's proposed use of 2,4-D choline salt as part of a 2,4-D resistant crop system will lead to "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the [new] use of [2,4-D choline salt]" on Dow's 2,4-D resistant corn and soybeans. As explained in detail below, the proposed new use of 2,4-D choline salt formulation on GE DAS-40278-9 corn and DAS-68416-4 soybeans will have significant "economic, social and environmental costs" such that its use will "cause unreasonable adverse effects on the environment."[60] EPA should consider these costs in its risk assessment of

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[58] Benbrook (2012).

[59] *Id*.

[60] *See* 7 U.S.C. § 136a(c)(5).

Dow's New Use Registration Applications.

Moreover, under FIFRA, EPA has the authority to request additional information from the applicant.[61] The studies and data cited herein highlight potential risks and effects on U.S. agriculture, plants and species, mankind and the environment that EPA must evaluate critically in its risk assessment. At a minimum, EPA must request Dow to submit additional data and documentations where appropriate to ensure that the proposed new use of 2,4-D choline salt as part of Dow's 2,4-D resistant crop system would not have "unreasonable adverse effects on the environment."

a. The Proposed Use of 2,4-D Choline Salt on Corn and Soybeans Engineered to Withstand 2,4-D Differs Substantially From Current Uses of 2,4-D on Conventional Corn and Soybeans.

EPA should critically analyze how the proposed new use registrations will increase and alter existing uses of 2,4-D when applied to 2,4-D resistant corn and soybeans. Comparison of current 2,4-D labels for corn and soybeans and those proposed for Enlist corn and soybeans (see figures below) reveals major differences that will have substantial impacts on 2,4-D usage patterns in these crops.

Corn

Permitted use of 2,4-D on existing corn hybrids comprises up to 1.0 lb./acre pre-emergence, 0.5 lb./acre post-emergence over the top to corn less than 8" tall or with drop nozzles up to tassel stage, and 1.5 lbs./acre preharvest. The proposed registration for DAS-40278-9 retains the same pre-emergence limit of 1.0 lb./acre, but differs in four important ways with respect to post-emergence use:

1) Two rather than one POST application is permitted;
2) The maximum POST rate doubles from 0.5 to 1.0 lb/acre;
3) The permissible application window for applying 2,4-D directly over the top of the crop is lengthened from corn up to 8" tall to corn that has reached the V8 stage or 48" in height (whichever occurs first); and
4) The use of drop nozzles that is currently required for POST applications after corn is 8" tall would be removed for Enlist corn (DEA, p. 76).

Finally, the current label for 2,4-D (but not the proposed registration for DAS-40278-9) allows for a 1.5 lb./acre preharvest treatment.

Dow has made much of the fact its proposed registration would not increase the maximum annual amount of 2,4-D that could be applied per acre of corn, which would remain unchanged at 3 lbs./acre. However, it is clear that the proposed registration would lead to a substantial increase in and altered use pattern of 2,4-D use on every acre of Enlist corn that displaces an existing hybrid.

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[61] 7 U.S.C. § 136a(c)(3)(A).

At present, corn growers use on average just 0.38 to 0.50 lbs. of 2,4-D per acre per year (USDA-NASS AgChem 2010), only one-eighth to one-sixth of what could be legally applied. The large gap between actual and permitted use is explained by the fact that most growers do not apply 2,4-D pre-emergence or preharvest, which uses comprise 83% (2.5 of 3.0 lbs.) of the overall label, but rather use 2,4-D primarily as a post-emergence herbicide (Knake 1996, p.3).

The proposed registration quadruples the amount of 2,4-D that could be legally applied post-emergence, from 0.5 lb./acre to 2.0 lbs./acre. Expressed differently, the POST proportion increases from 17% to 67% of permitted annual use. Since most 2,4-D is applied to corn post-emergence, and the Enlist corn system is specifically designed to facilitate increased POST use, one can expect the proposed registration to substantially increase the pounds of 2,4-D applied to corn, despite the fact that maximum annual use remains unchanged at 3 lbs./acre/year.

Such use would also be shifted to later in the season. First, the label permits direct application to much larger plants (48" versus 8"). Second, the increase from one to two permitted applications will encourage those growers who do use two applications to space them out so as to obtain optimal, season-long weed control.

Soybeans

The proposed registration for Enlist soybeans would have a still bigger impact on the amount and pattern of 2,4-D use. At present, 2,4-D use on soybeans is limited to pre-plant/burndown use at a maximum of 1 lb./acre/year. Based on Dow's petition for deregulation of DAS-68416-4 soybeans to USDA, the company has proposed a tripling of the label to 3 lbs./acre per year (see figure below). The preplant/burndown use would remain unchanged at 1 lb/acre, while the proposed registration would add two applications of 0.5 to 1 lb./acre POST, for total permitted post-emergence use of 2 lbs/acre/season up through the R2, full-flowering stage of development.

The proposed registration for Enlist soybeans would lead to increases in both preplant and post-emergence use of 2,4-D. Preplant usage is currently constrained by 2,4-D's (limited) residual activity – the potential for emerging seedlings to be damaged by 2,4-D applied soon before crop emergence. According to Dow (DAS-68416-4 Petition, p. 123):

> "Currently, for soybeans without the *aad-12* gene, 2,4-D can be applied only as a burndown or pre-emergence application at up to 1.0 lb ae/A (1120 g ae/ha). 2,4-D currently cannot be applied at burndown or pre-emergence to conventional soybeans any later than 7-15 days (0.5 - 1.0 lbs ae/A, or 560 - 1120 g ae/ha of ester formulations) or 15-30 days (0.5 – 1.0 lbs ae/A, or 560 - 1120 g ae/ha of amine formulations) prior to planting, due to potential for crop injury."

Thus, Enlist soybeans would eliminate the risk of crop injury from application of 2,4-D at 0-15 days pre-plant (ester formulations) or 0-30 days pre-plant (amine formulations) that obtains for currently grown soybean varieties.[62] This expanded pre-plant application window would permit

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[62] CFS has no information on the residual activity of 2,4-D choline salt.

growers to more fully exploit the 1 lb./acre pre-plant portion of the label. As noted above, average pre-plant usage of 2,4-D is 0.5 lb./acre, just half that permitted.

However, the much bigger impact of the proposed registration would be to enable entirely new post-emergence use of 2,4-D. In 2011, fully 94% of U.S. soybean acreage was planted to Roundup Ready varieties. Roundup Ready soybeans have fostered a huge shift to weed control programs that rely exclusively or primarily on post-emergence use of glyphosate. Growers who are already accustomed to a POST weed control regime with Roundup Ready soybeans, and who then switch to adopt Enlist soybeans, would be likely to make substantial use of the post-emergence portion of the label.

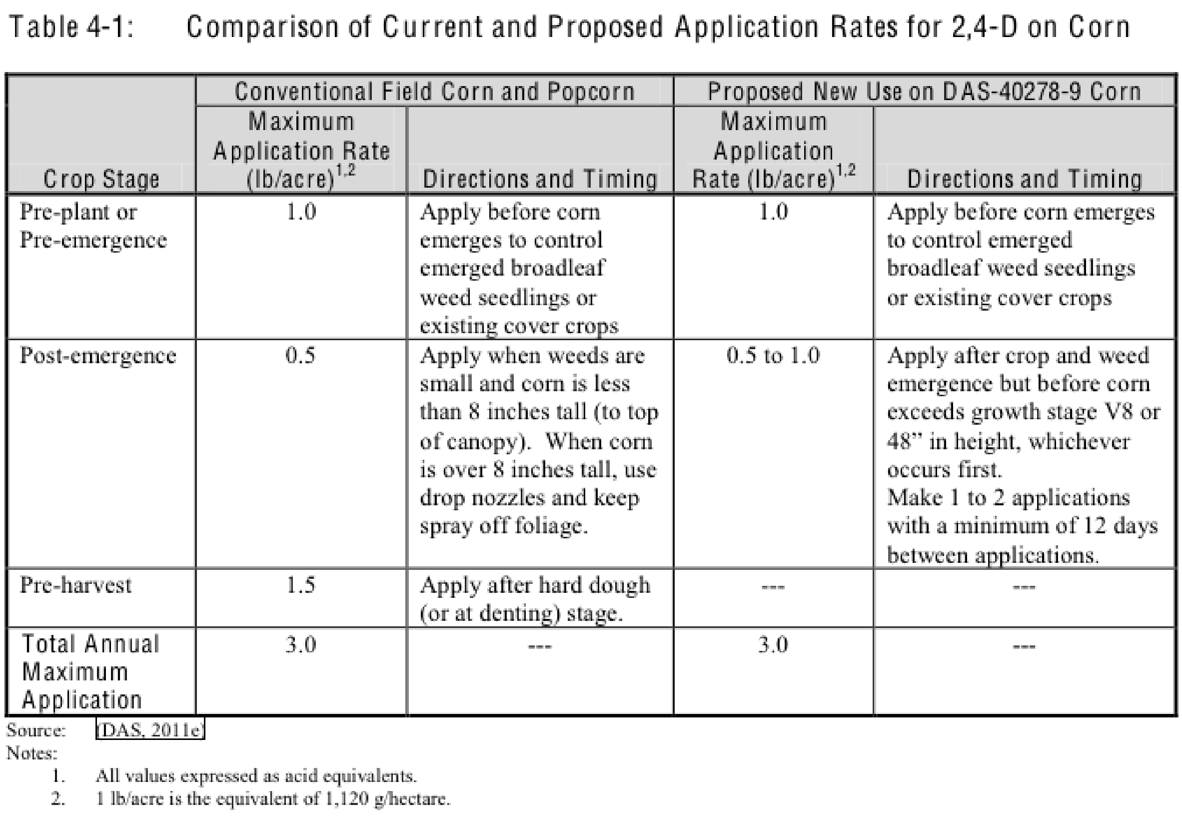

Table 4-1: Comparison of Current and Proposed Application Rates for 2,4-D on Corn

	Conventional Field Corn and Popcorn		Proposed New Use on DAS-40278-9 Corn	
Crop Stage	Maximum Application Rate (lb/acre)^{1,2}	Directions and Timing	Maximum Application Rate (lb/acre)^{1,2}	Directions and Timing
Pre-plant or Pre-emergence	1.0	Apply before corn emerges to control emerged broadleaf weed seedlings or existing cover crops	1.0	Apply before corn emerges to control emerged broadleaf weed seedlings or existing cover crops
Post-emergence	0.5	Apply when weeds are small and corn is less than 8 inches tall (to top of canopy). When corn is over 8 inches tall, use drop nozzles and keep spray off foliage.	0.5 to 1.0	Apply after crop and weed emergence but before corn exceeds growth stage V8 or 48" in height, whichever occurs first. Make 1 to 2 applications with a minimum of 12 days between applications.
Pre-harvest	1.5	Apply after hard dough (or at denting) stage.	---	---
Total Annual Maximum Application	3.0	---	3.0	---

Source: (DAS, 2011e)
Notes:
1. All values expressed as acid equivalents.
2. 1 lb/acre is the equivalent of 1,120 g/hectare.

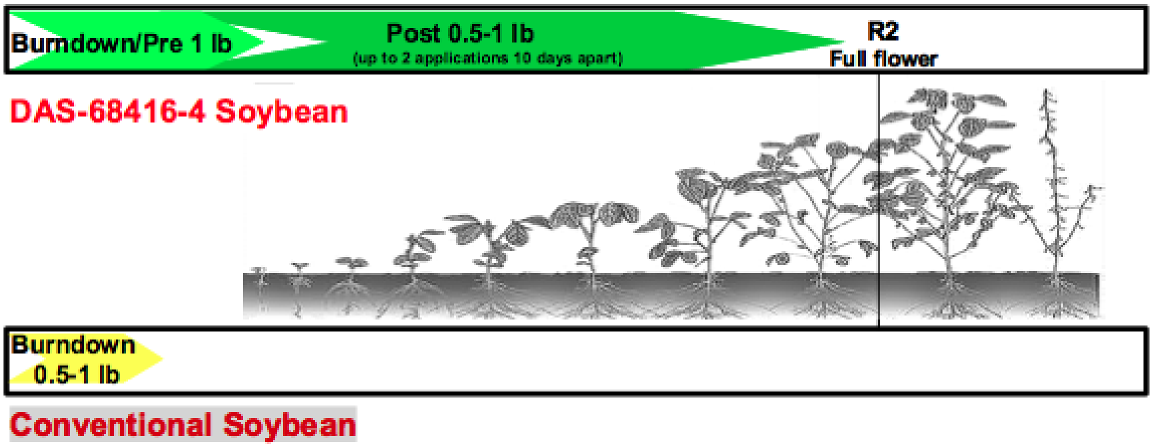

Figure 47. 2,4-D herbicide application timing and rates for conventional and DAS-68416-4 soybeans.

2,4-D Applications and Herbicide-Resistant Weeds

Enlist corn and soybeans are targeted for use especially by farmers with glyphosate-resistant weeds, but also those with weeds resistant to other classes of herbicide, such as ALS inhibitors and triazines (Blewett et al.. 2011, p. 4). Several of the most problematic herbicide-resistant weed species (e.g. common waterhemp and Palmer amaranth) emerge not just in one "flush," but rather through much of the season, leading to multiple applications. Many farmers who grow Enlist corn and soybeans to control such weeds would likely make two post-emergence applications of 2,4-D rather than just one. In addition, the likely evolution of "creeping resistance" to 2,4-D (e.g. in horseweed) with use of Enlist crop systems would put upward pressure on usage rates over time. The likely impacts of the proposed registrations on weed resistance are discussed further below.

Herbicide-Resistant Corn and Soybean Acreage

Current growers of herbicide-resistant corn and soybean varieties (nearly all glyphosate-resistant) might be more likely adopters of Enlist corn and soybeans, since these farmers are accustomed to POST weed control regimes, and are more likely to have glyphosate-resistant weeds. Aggregate acreage of herbicide-resistant corn and soybeans has tripled over just the past decade, from 45.7 million acres in 2000 to 137.1 million acres in 2011, reflecting a large increase in the proportion of soybeans that are herbicide-resistant (54% to 94%), and a still greater rise in corn (7% to 72%). While there is limited potential for increased herbicide-resistant (HR) soybean adoption, there is still considerable "room" for more HR corn. The sharp rise in glyphosate-resistant corn acreage has been the major factor driving evolution of glyphosate-resistant weeds in recent years in Midwestern states where Roundup Ready soybean/Roundup Ready corn rotations (and hence continual glyphosate selection pressure) are increasingly common. Since current HR corn and HR soybean growers are more likely adopters of Enlist corn and soybeans, this already large and growing "universe" of HR corn/soybeans suggests a large and growing potential market for Enlist corn and soybeans.

EPA should consider the adverse environmental effects stemming from the increased 2,4-D use should EPA register 2,4-D choline salt for the proposed new use on the 2,4-D resistant corn and soybeans. The use of accompanying herbicides on other herbicide-resistant crops have dramatically increased overall pesticide and herbicide use in the past thirteen years.[63] The registered new use of 2,4-D choline salt on DAS-40278-9 corn and DAS-68416-4 soybeans would lead to a massive increase in the amount of 2,4-D being applied in U.S. agriculture. This increase in 2,4-D use is certain because currently, 2,4-D is not applied at all on soybean after emergence, and existing use of 2,4-D on conventional corn is just over 1/10 of EPA's total maximum allowance. Indeed, according to estimates by one agricultural scientist, widespread planting of 2,4-D resistant corn alone could lead to as much as a 30-fold increase in 2,4-D use on corn by the end of the decade.[64] This would increase overall 2,4-D use in U.S. agriculture from the existing 27 million lbs per year to over 100 million lbs per year.[65]

Thus, EPA's review of Dow's proposed new use of 2,4-D on the 2,4-D resistant corn and soybeans must include a critical assessment of the increase in volume and frequency of 2,4-D use in U.S. agriculture, as well as any environmental impacts stemming from such an increase in volume and frequency. EPA should look beyond the existing total maximum annual application of 2,4-D allowed to the amount of 2,4-D that is currently being applied on corn and soy. EPA should require Dow to submit data and models to predict the amount of increase in 2,4-D use that is likely to occur, the geographic regions where the new 2,4-d choline salt formulation might be used, as well as any environmental effects associated with such a massive increase in 2,4-D use.

Organisms in field edges could receive higher and more frequent doses of 2,4-D during the growing season when it is used with DAS-40278-9 corn and DAS-68416-4 soybeans. For corn, this is because the proposed label for 2,4-D use on DAS-40278-9 corn allows for two applications to the growing corn plant rather than just one, and at double the application rate, than is currently allowed on conventional corn. This means that four-fold more 2,4-D can be applied to DAS-40278-9 corn during this critical "post-emergence" period (2 vs. 0.5 lbs/acre). In addition, an important drift-reducing measure required for application of 2,4-D to conventional corn (use of drop nozzles) has been eliminated from the proposed label for DAS-40278-9 corn. Drop nozzles direct the spray downwards below the crop foliage where it is less likely to drift. The combination of more frequent and higher doses, applied without the use of drift-reducing drop nozzles, means that the proposed new use with DAS-40278-9 corn presents a considerably higher risk of plant-damaging drift than 2,4-D used under the current label on conventional corn. Of course, 2,4-D is not used at all in conventional soybeans during the growing season, so all post-emergent applications will represent a new threat to sensitive plants in the vicinity. We ask the EPA to consider whether the purported reduction in drift with 2,4-D choline will compensate for these differences in amount, equipment, and timing of sprays.

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[63] Charles Benbrook, Organic Ctr., *Impacts of Genetically Engineered Crops on Pesticide Use: The First Thirteen Years* (Nov. 2009).

[64] *See* http://www.centerforfoodsafety.org/projected-increase-in-24-d-use-with-introduction-of-24-d-resistant-corn-through-2019-benbrook2012/.

[65] Based on EPA (2011), *Pesticide Industry Sales and Usage: 2006 and 2007 Market Estimates*, Table 3.6, which shows 25-29 million lbs. 2,4-D used agriculturally in 2007.

We also ask the EPA to consider how conventional corn growers actually use 2,4-D. As explained in detail above, at present, corn growers use on average just 0.38 to 0.50 lbs. of 2,4-D per acre per year (USDA-NASS AgChem 2010), only one-eighth to one-sixth of what could be legally applied. Moreover, on average, corn growers make 1.12 applications per year instead of the three allowed (Benbrook 2012, USDA-NASS AgChem 2010).

In fact, growers apply less 2,4-D than allowed because corn can be injured by labeled rates of 2,4-D (Nice et al.. 2004). Some growers are willing to risk injury to their corn by using 2,4-D presumably because it is inexpensive and effective on some of their problem weeds, but they mitigate that risk by using 2,4-D with caution; that is, sparingly.

EPA should consider how the proposed new use of 2,4-D choline salt on 2,4-D resistant corn and soybeans is free from existing biological constraints that limit current applications of 2,4-D on corn and soybeans. Using corn as an example, because DAS-40278-9 corn is engineered to express AAD-1 protein it is resistant to much higher levels of 2,4-D than conventional corn (DAS Petition 2011, p. 103), at least through the V8 stage a few weeks before pollen shed, and perhaps throughout its life (tolerance testing has only been reported by DAS through the V8 stage, (see pollen gene expression, these Comments). Without these biological constraints, growers will no longer have to balance weed control with risk of injuring their corn, and thus will be more likely to use the full rate allowed.

Instead, growers of 2,4-D resistant corn and soybean will be encouraged to use the full rate of Dow's proposed 2,4-D applications per application as part of Dow's stewardship program for supposedly delaying weed resistance to 2,4-D (Blewett 2011, p. 7). Also, Dow will encourage growers to buy a premix of 2,4-D and glyphosate to apply to DAS-40278-9 corn that has been stacked with the Roundup Ready trait (US-EPA 2011), a likely combination from the start. With the premix, if a grower wants to apply the full rate of glyphosate per hectare to control certain weeds, they will simultaneously be obliged to apply the full rate of 2,4-D as well.

A reasonable prediction, then, for how much 2,4-D a grower is likely to use on DAS-40278-9 corn is at least one application at 1 lb a.e./acre. This is already about 2.5X to 3X times higher than the rate conventional growers use now per application. And if there are no biological constraints in terms of injury to their corn, it is likely that growers will use more than one application per season if weed pressure warrants it. Cost of applying more herbicide is likely to be the main constraint instead of yield loss from injury.

We expect that the rate per application of 2,4-D on DAS-68416-4 soybeans will also exceed current levels. In 2006, soybean growers applied less than 0.5 lb of 2,4-D per application as a burndown treatment compared to the allowed rate of 1.0 lb per application (USDA NASS AgChem 2006). Post-emergent applications of 2,4-D to DAS-68416-4 soybeans are likely to be higher in concentration than the current average (Mortensen et al.. 2012).

Harm from Changes in Timing of 2,4-D Applications in the Growing Season

As explained above, not only will growers use a higher rate of 2,4-D, these applications are more likely to coincide with life-stages of plants that are the most sensitive to injury because the DAS-40278-9 corn itself is less sensitive to injury during spring and summer than is conventional corn. For <u>DAS-68416-4 soybeans, the use of 2,4-D after planting is completely new, so the difference in timing is even more pronounced and likely to cause harm.</u>

Total Use of 2,4-D on DAS-40278-9 Corn and DAS-68416-4 Soybeans at the Landscape Level

Another way that the DAS-40278-9 corn and DAS-68416-4 soybean cropping systems will increase 2,4-D use is by an increase in the total number of corn and soybean acres that are treated with 2,4-D, from about 10% of acres now to a likely 55% of corn acres in 2019 (Benbrook 2012). Similarly, only 10% of total soybean acres were treated with 2,4-D in the most recent survey (USDA NASS AgChem 2006), but a large increase in acres treated is projected if 2,4-D is registered for use on DAS-68416-4 soybeans (Mortensen et al.. 2012). At a landscape level this increase will result in a larger number of individuals of a wider array of species in proximity to DAS-40278-9 corn and DAS-68416-4 soybeans and thus 2,4-D.

Also, corn and soybean acreage is expanding. USDA-NASS data show that combined acreage planted to both corn and soybeans crops has increased by 23% over the past two decades, from 132.0 million acres (1990) to 167.5 million acres (2011). Further increases in corn acreage, driven primarily by continued demand for ethanol, are expected, from 92.3 million acres in 2011 to 94 to 96 million acres by the end of the decade (APHIS-DEA). Some of the expansion is at the expense of former Conservation Reserve Program land not recently in agricultural production (Brooke et al. 2009), and more wild native species are likely to impacted by 2,4-D, including threatened and endangered species (see below).

<u>b.</u> <u>EPA Should Consider Impacts of 2,4-D Drift Under the Proposed New Use of 2,4-D Choline on Dow's 2,4-D Resistant Corn and Soybean.</u>

Drift injury from 2,4-D to plants and other non-target organisms

In its risk assessment of Dow's Proposed New Use Registrations, EPA must consider the economic and environmental costs stemming from the injury to other commercial crops, as well as non-target organisms, from the drift of the proposed new use of 2,4-D on DAS-40278-9 corn and DAS-68416-4 soybeans. 2,4-D is a volatile herbicide that is prone to drift beyond the field of application to damage neighboring crops and wild plants. 2,4-D vapor injures most broadleaf (i.e. non-grass) plants at extremely low levels, as low as three-billionths of a gram per liter of air (Breeze & West 1987). Particularly sensitive crops include grapes (Walker 2011), tomatoes, cotton (Bennett 2006), soybeans, sunflower, and lettuce. Two surveys of state pesticide regulators establish that 2,4-D drift is already responsible for more episodes of crop injury than any other pesticide (AAPÇO 1999, 2005).

Crop injury is a significant biological restraint on the use of 2,4-D with currently grown commercial corn hybrids. Injury concerns constrain both the rate and time of application. In tests on a commercial corn hybrid (Hi II X 5XH751), Dow applied 2,4-D DMA at various rates at the 2-4 leaf stage, and recorded percent injury 14 days after treatment. Percent injury recorded was 10%, 14% and 29% at 2,4-D application rates of 560, 1120 and 2240 g ae/hectare, equivalent to 0.5, 1.0 and 2.0 lbs. per acre, respectively (DAS Patent 2009, Table 25, paragraph

0354). Application of 4480 g ae/ha (4 lbs./acre) to an unspecified conventional hybrid at the V4 stage caused 35% injury 14 days after treatment (DAS USDA Petition, p. 103). A significant level of crop injury at a POST application rate of just 0.5 lb./acre may help explain the lesser average 2,4-D rate of 0.35 lb./acre reported by USDA NASS (see above). In addition, post-emergence use at later growth stages can cause significant malformations in the corn plant (APHIS-DEA, p. 79).

In contrast, DAS-40278-9 is engineered to withstand extremely high rates of 2,4-D. Dow reports negligible plant injury of 5% or less (14 days after treatment at the V4 stage) from application of 4480 grams per hectare, equivalent to 4 lbs./acre, the highest rate tested (DAS USDA Petition, p. 103).

Because broadleaf crops are extremely sensitive to 2,4-D, crop injury bars any post-emergence use of 2,4-D on soybeans. Hence, current usage is limited to pre-plant/burndown applications, which as noted above average roughly 0.5 lbs./acre annually. Dow scientists report that 2,4-D-resistant soybeans withstand applications rates of 4 lbs./acre or more (4.48 kg ae/ha) (Wright et al. 2010).

While such high rates are not expected to be applied very often to Enlist corn and soybeans (they exceed the proposed label rate), it is important to understand that they could be. Under certain circumstances, farmers growing these crops might be tempted to exploit the crop's considerable resistance by applying high 2,4-D rates, for instance to deal with particularly intractable weeds (e.g. weeds that are large or have evolved low-level 2,4-D-resistance), an option not available to growers of other corn or soybean varieties. Enlist corn and soybeans thus dramatically loosen the biological constraint of crop injury that currently limits (as much or more than EPA's label) rates of 2,4-D that can be safely applied to currently grown corn and soybeans varieties.

Thus, use of 2,4-D under the proposed registrations with Enlist corn and soybeans would greatly increase drift injury to crops over already high levels by enabling higher rates, on much greater acreage, sprayed later in the season when neighboring crops and plants have leafed out and are thus more susceptible to drift injury (Mortensen et al. 2012). Drift-related injury would be exacerbated if the drop nozzle requirement for POST applications in the existing 2,4-D label were to be removed. As discussed above, the magnitude of the increase in 2,4-D use with Enlist corn and soybeans could be substantial, with an up to 30-fold increase in corn projected by Benbrook (2012), and a roughly equal increase possible in soybeans (Mortensen et al.. 2012). With the proposed label for 2,4-D permitting four times more 2,4-D from post-emergence applications in corn (2 vs. 0.5 lbs./acre/year), and an entirely new 2 lbs./acre from POST applications in soybeans, the impacts on growers of many broadleaf crops could be severe.

A recent episode in California may be a harbinger of things to come. In the San Joaquin Valley, 1,000 acres of pasture were recently sprayed with 2,4-D under hot and windy conditions (Cline 2012). At least 15,000 acres of cotton and a 50-acre pomegranate orchard were damaged, with effects noted at up to 100 miles from the application site.

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.

Vineyard operators are especially at-risk (Hebert 2004). Growers of vegetables, fruits and other smaller-acreage crops are already sparse in corn-soybean country. The introduction of Enlist corn and soybeans could thin their ranks still further, decreasing what little crop diversity remains in the heartland. Growers of conventional and glyphosate-resistant soybeans would also be threatened by drift. There is already substantial litigation over drift-related crop injury, pitting farmer against farmer, and it would escalate dramatically with use of 2,4-D on Enlist crops under the proposed registrations (Huff 2011).

Drift from 2,4-D applications under Dow's proposed new use could also be injurious to wild plants; an environmental cost that EPA should include in its risk assessment._EPA is well aware that 2,4-D is a particularly potent poison for many species of plants, especially dicotyledons (broadleaf plants) that are sensitive to very low levels. Hormone-mimic herbicides such as 2,4-D injure some plants at lower concentrations than other widely used herbicides.

If 2,4-D is moving off-site far enough to cause injury to crops, it is undoubtedly also causing injury to wild plants. Drift of 2,4-D is most likely to impact vegetation near the site where it is applied, so borders of fields and adjacent fencerows, wetlands, woodlands, riparian areas, and old-fields are vulnerable. These areas provide most of the biodiversity found in agricultural landscapes (e.g., Boutin and Jobin 1998). But with a volatile herbicide such as 2,4-D, injury has also occurred at locations distant from the application site, as described above with injury to grapes, putting organisms in a variety of natural areas at risk.

There have been few studies of 2,4-D drift effects on wild plants and their communities. The EPA reviewed their Ecological Incident Information System (EIIS) database for "ecological incidents involving 2,4-D acid, salts and esters" through 2008 (US-EPA 2009, p. 100, and Appendix H) Reports include injury from off-site herbicide movement after applications of 2,4-D on conventional cornfields (US-EPA 2009, p. 115). Plants listed as injured from drift or runoff from agricultural areas include oak and poplar trees, but primarily concern various crops (Appendix H). There are also reports of small mammals being killed after ingesting 2,4-D used on crops, and of "kills" of aquatic organisms – fish and water snakes - after 2,4-D runoff or drift from agricultural areas (US-EPA 2009, Appendix H).

It is likely that crop injury from pesticide drift is significantly under-reported:

> When crops are damaged by off-target movement of herbicides, the affected growers may settle their differences without the intervention of government enforcement agencies or courts. However, in the absence of a damage report to a state agency or court settlement, there are no records of their occurrence, due to

> lack of a centralized herbicide incident reporting system in the United States. For incidents that are more contentious or serious, a likely sequence of events arising from herbicide damage to non-target crops may include: 1) a complaint to a state agency over damage cause[d] by an herbicide, 2) an ensuing investigation that may uncover a violation (but which may not resolve the economic loss by the farmer whose crop is affected), and 3) lawsuits that use the investigation as evidence of harm…However, the majority of lawsuits are settled out of court with the stipulation that the plaintiffs not divulge the contents of the settlement to anyone including the government. (Olszyk et al.. 2004, p. 225)

Thus, when only wild plants are harmed, injury may not be noticed or reported at all. Therefore, most information about risks of herbicide exposure for wild plants and ecosystems comes from experimental studies and comparative surveys rather than from incident reports (discussed below). It is clear that non-target organisms do risk injury from 2,4-D used in agriculture, and that proposed new use of 2,4-D on DAS-40278-9 corn and DAS-68416-4 soybeans is likely to increase that risk to the extent that the crop system involves increased use of 2,4-D. EPA must consider this significant adverse impact in its risk assessment of Dow's new use registration application.

Simply, the amount of injury that non-target organisms will sustain is determined by how sensitive they are to the 2,4-D formulations and by the dose they receive. Therefore, it is important for the EPA to make a realistic prediction of the amount of 2,4-D that will be used on DAS-40278-9 corn and DAS-68416-4 soybeans compared to conventional varieties in order to evaluate the impacts of their alternatives.

c. EPA Should Consider How the Proposed Use of 2,4-D Choline Salt on Dow's DAS-40278-9 Corn and DAS-68416-4 Soybean Promotes Weed Resistance and the Economic Costs of Weed Management.

EPA should also consider how the registered new use of 2,4-D choline salt on 2,4-D resistant corn and soybean will promote the development of resistant weed, which in turn result in applications of more toxic herbicides to the detriment of human health, animal species, and the environment, as well as an increase in the costs of weed control for farmers.[66]

Non-Herbicide Weed Management Techniques

Weeds can compete with crop plants for nutrients, water and sunlight, and thereby inhibit crop growth and potentially reduce yield. While less dramatic than the ravages of insect pests or disease agents, weeds nevertheless present farmers with a more consistent challenge from year to year. However, properly managed weeds need not interfere with crop growth. For instance, organically managed soybean and corn have been shown to yield as well as conventionally grown varieties despite several-fold higher weed densities (Ryan et al. 2010). Long-term cropping trials at the Rodale Institute reveal that average yields of organically grown corn were

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[66] See *Love v. Thomas*, 858 F.2d 1347 (9th Cir.1988) (overturning EPA's decision to suspend a pesticide's registration where EPA failed to consider economic costs to farmers due to inability to continue use of the registered product).

equivalent to those of conventionally grown corn, despite six times greater weed biomass in the organic system (Ryan et al. 2009). Weeds can even benefit crops – by providing ground cover that inhibits soil erosion and attendant loss of soil nutrients, habitat for beneficial organisms such as ground beetles that consume weed seeds, and organic matter that when returned to the soil increases fertility and soil tilth (Liebman 1993). These complex interrelationships between crops and weeds would seem to call for an approach characterized by careful management rather than indiscriminate eradication of weeds.

Farmers have developed many non-chemical weed management techniques, techniques that often provide multiple benefits, and which might not be utilized specifically or primarily for weed control (see generally Liebman-Davis 2009). For instance, crop rotation has been shown to significantly reduce weed densities versus monoculture situations where the same crop is grown each year (Liebman 1993). Cover crops – plants other than the main cash crop that are usually seeded in the fall and killed off in the spring – provide weed suppression benefits through exudation of allelopathic compounds into the soil that inhibit weed germination, and when terminated in the spring provide a weed-suppressive mat for the follow-on main crop. Common cover crops include cereals (rye, oats, wheat, barley), grasses (ryegrass, sudangrass), and legumes (hairy vetch and various clovers. Intercropping – seeding an additional crop amidst the main crop – suppresses weeds by acting as a living mulch that competes with and crowds out weeds, and can provide additional income as well (Liebman 1993). One common example is intercropping oats with alfalfa. Higher planting densities can result in more rapid closure of the crop “canopy,” which shades out and so inhibits the growth of weeds. Fertilization practices that favor crop over weeds include injection of manure below the soil surface rather than broadcast application over the surface. Techniques that conserve weed seed predators, such as ground beetles, can reduce the “weed seed bank” and so lower weed pressure. In addition, judicious use of tillage in a manner that does not contribute to soil erosion is also a useful means to control weeds.

Unfortunately, with the exception of crop rotation and tillage, such techniques are little used in mainstream agriculture. This is in no way inevitable. Education and outreach by extension officers, financial incentives to adopt improved practices, and regulatory requirements are just a few of the mechanisms that could be utilized to encourage adoption of more integrated weed management systems (IWM) that prioritize non-chemical tactics (Mortensen et al. 2012). Meanwhile, the problems generated by the prevailing chemical-intensive approach to weed control are becoming ever more serious.

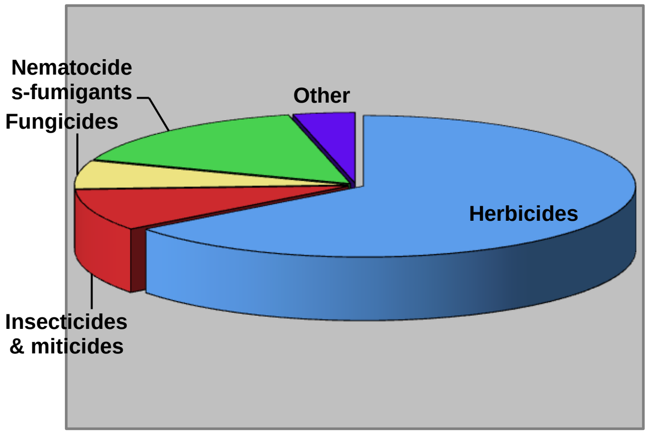
The high Costs of Herbicide-Only Weed Control

In 2007, U.S. farmers spent $4.2 billion dollars to apply 442 million lbs. of herbicide, and uncounted billions more on technology fees for herbicide-resistance traits in major crops. Overall, the U.S. accounts for one-quarter of world herbicide use (EPA Pesticide Use 2011, Tables 3.1, 5.2, 5.6). One might suppose that this intensive herbicidal onslaught would make American fields among the most weed-free in the world. But such is not the case. As farmers gradually came to rely more on more on herbicides as the preferred and then often the sole means to control weeds, herbicide-resistant weeds have become increasingly severe and costly.

The first major wave of herbicide-resistance came in the 1970s and 1980s as weeds evolved resistance to the heavily used triazines, such as atrazine (*see* Benbrook 2009a for this discussion). The next major wave of resistance comprised weeds resistant to ALS inhibiting herbicides in the 1980s and 1990s. Just five years intervened between introduction of the first ALS inhibitor herbicide in 1982 and the first resistance weed population (1987). One of the major factors persuading farmers to adopt Roundup Ready, glyphosate-resistant crops was the prevalence of weeds resistant to ALS inhibitors. Weeds have evolved resistance at least 21 "modes of action," or herbicide classes, in the world (ISHRW HR Weed Ranking 4/22/11).

According to the USDA's Agricultural Research Service, up to 25% of pest (including weed) control expenditures are spent to manage pesticide (including herbicide) resistance in the target pest (USDA ARS Action Plan 2008-13-App. II). With an estimated $7 billion spent each year on chemical-intensive weed control (USDA ARS IWMU-1), herbicide-resistant weeds thus cost U.S. growers roughly $1.7 billion (0.25 x $7 billion) annually. These expenditures to manage resistance equate to tens and perhaps over 100 million lbs. of the over 400 million lbs. of agricultural herbicide active ingredient applied to American crops each year (see figure below), as growers increase rates and make additional applications to kill expanding populations of resistant weeds.

Agricultural Pesticide Use in the U.S. by Type: 2007



Herbicides comprise by far the largest category of pesticides, defined as any chemical used to kill plant, insect or disease-causing pests. In 2007, the last year for which the Environmental Protection Agency has published comprehensive data, weedkillers (herbicides) accounted for 442 million lbs. of the 684 million lbs. of chemical pesticides used in U.S. agriculture, nearly seven-fold more than the insecticides that many associate with the term "pesticide." Source: "Pesticides Industry Sales and Usage: 2006 and 2007 Market Estimates," U.S. Environmental Protection Agency, 2011, Table 3.4 (EPA Pesticide Use 2011 in supporting materials).

Increasing the rate and number of applications, however, often rapidly leads to further resistance, followed by adding additional herbicides into the mix, beginning the resistance cycle all over again, just as overused antibiotics breed resistant bacteria. This process, dubbed the pesticide treadmill, has afflicted most major families of herbicides, and will only accelerate as

U.S. agriculture becomes increasingly dependent on crops engineered for resistance to one or more members of this by far largest class of pesticides (Kilman 2010).

Besides costing farmers economically via herbicide-resistant weeds, a chemical-intensive pest control regime also has serious public health and environmental consequences. Various pesticides are known or suspected to elevate one's risk for cancer, neurological disorders, or endocrine and immune system dysfunction. Epidemiological studies of cancer suggest that farmers in many countries, including the U.S., have higher rates of immune system and other cancers (USDA ERS AREI 2000). Little is known about the chronic, long-term effects of exposure to low doses of many pesticides, especially in combinations. Pesticides deemed relatively safe and widely used for decades have had to be banned in light of scientific studies demonstrating harm to human health or the environment. Pesticides also pollute surface and ground water, harming amphibians, fish and other wildlife.

Herbicide-resistant weeds thus lead directly to adverse impacts on farmers, the environment and public health. Adverse impacts include the increased costs incurred by growers for additional herbicides to control them, greater farmer exposure to herbicides and consumer exposure to herbicide residues in food and water, soil erosion and greater fuel use and emissions from increased use of mechanical tillage to control resistant weeds, environmental impacts from herbicide runoff, and in some cases substantial labor costs for manual weed control. Herbicide-resistant weeds are thus both the consequence of unsustainable weed control practices, and a major factor making weed management still less sustainable.

The High Economic Cost of Herbicide-Resistant Weed Epidemic

EPA should consider how the proposed new use of 2,4-D choline salt as part of Dow's 2,4-D resistant crop system will promote the growth of HR weeds, a significant economic cost to agricultural production. HR crop systems such as 2,4-D resistant corn and soybeans involve post-emergence application of one or more herbicides to a crop that has been bred or genetically engineered to survive application of the herbicide(s). These HR crop systems promote more rapid evolution of herbicide-resistant weeds than non-HR crop uses of the associated herbicides. This is explained by several characteristic features of these crop systems.

HR crops foster more frequent use of and overreliance on the herbicide(s) they are engineered to resist. When widely adopted, they also lead to more extensive use of HR crop-associated herbicide(s). Herbicide use on HR crops also tends to occur later in the season, when weeds are larger. Each of these factors contributes to rapid evolution of resistant weeds by favoring the survival and propagation of initially rare individuals that have genetic mutations lending them resistance. Over time, as their susceptible brethren are killed off, these rare individuals become more numerous, and eventually dominate the weed population.

High frequency of use means frequent suppression of susceptible weeds, offering (at frequent intervals) a competition-free environment for any resistant individuals to thrive. Overreliance on the HR crop-associated herbicide(s) means little opportunity for resistant individuals to be killed off by alternative weed control methods, thus increasing the likelihood they will survive to propagate and dominate the local weed population. Widespread use of the

HR crop system increases the number of individual weeds exposed to the associated herbicide(s), thus increasing the likelihood that there exists among them those individuals with the rare genetic predisposition that confers resistance. The (late) post-emergence use of herbicides fostered by HR crop systems means more weeds become larger and more difficult to kill; thus, a greater proportion of weeds survive to sexual maturity, and any resistant individuals among them are more likely to propagate resistance via cross-pollination of susceptible individuals or through deposition of resistant seeds in the seed bank; in short, a higher likelihood of resistance evolution.

Below, we discuss these resistant weed-promoting features of HR crop systems in more detail, with particular reference to systems involving glyphosate-resistance (Roundup Ready) and 2,4-D-resistance.

GE seeds in general, including HR seeds, are substantially more expensive than conventional seeds (Benbrook 2009b). Their higher cost is attributable to a substantial premium (often called a technology fee) for the herbicide-resistance trait. This premium constitutes a financial incentive for the grower to fully exploit the trait through frequent and often exclusive use of the associated herbicide(s), and a disincentive to incur additional costs by purchasing other, often more expensive herbicides.

For example, “the cost of RR [Roundup Ready] alfalfa seed, including the technology fee, is generally twice or more than that of conventional alfalfa seed. Naturally, growers will want to recoup their investment as quickly as possible. Therefore, considerable economic incentive exists for the producer to rely solely on repeated glyphosate applications alone as a weed control program.” (Orloff et al. 2009, p. 9).

Dow has not revealed its pricing for Enlist corn or soybean seed, but it is likely to be considerably more expensive than currently available GE varieties, based on Dow’s profit projections. Dow CEO Andrew Liveris estimates that its 2,4-D resistance trait “is worth two to three times more than Smartstax corn seed, developed with Monsanto, which has a net present value of $500 million…” (Kaskey 2010). GE SmartStax corn is the most expensive corn seed on the market (Tomich 2010). In order to capture this $1 to $1.5 billion in revenue, Dow would likely have to charge a substantial premium for Enlist corn and soybean seeds beyond that charged for current GE seeds.

Overreliance is especially favored when the associated herbicide(s) are effective at killing a broad range of weeds, which tends to make other weed control practices less needed, at least until weed resistance emerges. Glyphosate and to a lesser extent 2,4-D are both such “broad-spectrum” herbicides. However, it should be noted that glyphosate has more fully displaced other herbicides in HR soybean and cotton, but to a much lesser extent in HR corn, systems. As discussed above, although glyphosate use has increased dramatically on corn with adoption of Roundup Ready corn, utilization of other major corn herbicides like atrazine and acetochlor has remained relatively steady. Corn growers who have adopted Roundup Ready corn have greatly increased their use of glyphosate, but have also continued to use substantial amounts of other herbicides. Interestingly, this continued use of other modes of action has not prevented rapid emergence of glyphosate-resistant weeds in corn, suggesting that use of multiple herbicides is not as effective as commonly believed at forestalling emergence of resistant weeds, and that greater use of non-chemical weed control tactics is required, as suggested above.

Frequent use and overreliance are also fostered when the HR crop-associated herbicide(s) are inexpensive relative to other herbicides. Monsanto lowered the price of Roundup herbicide in the late 1990s to encourage farmers to adopt Roundup Ready crop systems and rely exclusively on glyphosate for weed control (Barboza 2001),[67] and the price has fallen further since then (DAS 2011c, Figure 1.2).[68] 2,4-D is even cheaper than glyphosate, and in fact is one of the least inexpensive herbicides on the market (U of Tenn 2011, p. 94). CFS has not seen any price projections for 2,4-D choline. As suggested by Orloff et al. (2009), quoted above, overreliance on HR crop-associated herbicide(s) is particularly favored when the HR trait premium is high and the herbicide's price is low, the likely scenario with Enlist corn and soybeans.

One of the key changes wrought by herbicide-resistant crop systems is a strong shift to post-emergence herbicide application, which generally occurs later in the season on larger weeds, versus early-season use on smaller weeds or prior to weed emergence that is more characteristic of conventional crops. It is important to understand that facilitation of post-emergence herbicide use as the sole or primary means of weed control is the *sine qua non* of HR crop systems, not an incidental feature. Early-season uses include soil-applied herbicides put down around time of planting; these herbicides have residual activity to kill emerging weeds for weeks after application.

Weed scientist Paul Neve has simulated the rate at which weeds evolve resistance to glyphosate under various application regimes (Neve 2008). His results show unambiguously that the post-emergence use of glyphosate unique to glyphosate-resistant crop systems fosters resistant weeds much more readily than traditional uses ("prior to crop emergence") typical of conventional crops. This is consistent with the massive emergence of glyphosate-resistant weeds only after glyphosate-resistant crops were introduced (see below):

> "Glyphosate use for weed control prior to crop emergence is associated with low risks of resistance. These low risks can be further reduced by applying glyphosate in sequence with other broad-spectrum herbicides prior to crop seeding. Post-emergence glyphosate use, associated with glyphosate-resistant crops, very significantly increases risks of resistance evolution" (Neve 2008)

GR crop systems promote not just post-emergence use, but <u>delayed</u> post-emergence application to larger weeds:

> "Growers rapidly adopted glyphosate-resistant crops and, at least initially, did not have to rely on preventive soil-applied herbicides. Growers could wait to treat weeds until they emerged and still be certain to get control. <u>Many growers waited until the weeds were large in the hope that all the weeds had emerged and only</u>

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[67] Monsanto has greatly increased the price of RR seed to compensate for reduced income from sale of Roundup.

[68] This and other "DAS" references refer to submissions to APHIS by Dow AgroSciences, which may be found in the bibliography of APHIS's DEA.

> one application would be needed. Today, experts are challenging this practice from both an economic and a sustainability perspective." (Green et al. 2007, emphasis added)

> "Following the widespread adoption of glyphosate-resistant soybean, there has been a subtle trend toward delaying the initial postemergence application longer than was once common. Because glyphosate provides no residual weed control and application rates can be adjusted to match weed size, producers hope that delaying the initial postemergence application will allow enough additional weeds to emerge so that a second application will not be necessary" (Hagar 2004, emphasis added)

University of Minnesota weed scientist Jeff Gunsolus notes that: "Larger weeds are more apt to survive a postemergence application and develop resistance" (as quoted in Pocock 2012). University of Arkansas weed scientist Ken Smith notes that application of Ignite (glufosinate) to cotton plants with dual resistance to glyphosate and glufosinate (Widestrike) in order to control large glyphosate-resistant weeds risks generating still more intractable weeds resistant to both herbicides (as quoted in Barnes 2011, emphasis added):

> "Many growers who use Ignite on WideStrike varieties do so after they discover they have glyphosate-resistant weeds, according to Smith. To combat this, growers will make an application of Ignite on weeds that, on occasion, have grown too big to be controlled by the chemistry. This creates a dangerous scenario which could possibly encourage weeds to develop resistance to glufosinate, the key chemistry in Ignite. The end-result, according to Smith, would be disastrous."

It should be noted that Dr. Smith's concern is that weeds will evolve resistance to the same two herbicides to which the HR crop is resistant, which both undermines the utility of the crop and generates a potentially serious HR weed population that becomes extremely difficult to control.

Overview of Glyphosate-Resistant Crops and Weeds

The epidemic of glyphosate-resistant weeds from the registered use of glyphosate on glyphosate-resistant crop systems (Roundup Ready) demonstrates the environmental and economic costs that EPA should consider in its risk assessment of Dow's New Use Registration Applications.

First, the rapid emergence of GR weeds in Roundup Ready crop systems is evidence of the resistant weed-promoting effect of HR crop systems in general, as discussed above, and provides insight into the risks of resistant weed evolution in the context of Enlist corn and soybean systems. Second, the prevalence of glyphosate-resistant weeds is the motivating factor in Dow's introduction and farmers' potential adoption of Enlist crops.

Glyphosate was first introduced in 1974.[69] Despite considerable use of the herbicide, for the next 22 years there were no confirmed reports of glyphosate-resistant weeds. A few small and isolated populations of resistant weeds – mainly rigid and Italian ryegrass and goosegrass – emerged in the late 1990s, attributable to intensive glyphosate use in orchards (e.g. Malaysia, Chile, California) or in wheat production (Australia).

Significant populations of glyphosate-resistant weeds have only emerged since the year 2000, four years after the first Roundup Ready crop system –Roundup Ready soybeans—was introduced in 1996, followed by RR cotton & canola in 1997 and RR corn in 1998 (Monsanto History undated). According to the International Survey of Herbicide-Resistant Weeds (ISHRW), multiple populations of 23 weed species are resistant to glyphosate in one or more countries today; of these, 26 populations of ten species are also resistant to herbicides in one to three other families of chemistry in addition to glyphosate (ISHRW GR Weeds 4/22/12). Based on acreage infested, glyphosate-resistant weeds have emerged overwhelmingly in soybeans, cotton and corn in countries, primarily the U.S., where Roundup Ready crop systems predominate (*see* CFS RRSB 2010, which has further analysis of glyphosate-resistant weeds).

The first glyphosate-resistant weed population confirmed in the U.S., reported in 1998, was rigid ryegrass, infesting several thousand acres in California almond orchards (ISHRW GR Weeds 4/22/12). Beginning in the year 2000 in Delaware, glyphosate-resistant horseweed rapidly emerged in Roundup Ready soybeans and cotton in the East and South. Just twelve years later, glyphosate-resistant biotypes of 13 species are now found in the U.S., and they infest millions of acres of cropland in at least 27 states (ISHRW GR Weeds 4/22/12).

Based on CFS's periodic compilation of data from the ISHRW website over the past four years, glyphosate-resistant weeds in the U.S. have evolved at an accelerated rate in recent years. As of November 2007, ISHRW recorded eight weed species resistant to glyphosate, covering up to 3,200 sites on up to 2.4 million acres. By early 2012, as many as 239,851 sites on up to 16,683,100 acres were documented to be infested by glyphosate-resistant weeds (CFS GR Weed List 2012). This astonishing proliferation of resistant weeds – an over 70-fold increase in number of sites and 7-fold increase in acreage – is portrayed in the figure at the end of this section. This chart and two additional charts portraying glyphosate-resistant weeds by crop setting and farm production region are found in the file entitled at CFS GR Weed Charts (2012). The true extent of glyphosate-resistant weeds is almost certainly greater than even the maximum figures shown in the graph, because "...the voluntary basis of the contributions likely results in underestimation of the extent of resistance to herbicides, including glyphosate" (NRC 2010, p. 2-12). Many examples could be cited to illustrate to what extent ISHRW underestimates the extent of glyphosate-resistant weed populations, but one will suffice. Illinois weed scientist Bryan Young recently reported 5-6 million acres of Illinois cropland infested with glyphosate-resistant waterhemp (as quoted in Lawton 2012, confirmed with Dr. Young, personal communication). Yet ISHRW lists glyphosate-resistant waterhemp as infesting just 100 acres in Illinois (ISHRW Illinois Waterhemp). Inclusion of this single updated report in the ISHRW system would raise the glyphosate-resistant weed infested acreage by one-third. It appears that much or all of this waterhemp is resistant ALS inhibitors as well, with a significant portion also resistant to PPO inhibitors and/or triazine herbicides (Tranel 2010).

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[69] *See* Benbrook (2009s) for the following discussion.

Early on, most resistant weed populations were driven by intensive glyphosate use associated with Roundup Ready soybeans and Roundup Ready cotton. However, adoption of corn with the Roundup Ready trait has increased sharply in recent years, from 20% to 72% of national corn acres from just 2004 to 2011. The increasing reliance on glyphosate associated with the growing use of Roundup Ready soybean/ Roundup Ready corn rotations is likely responsible for the rapid emergence of resistant weeds in the Midwest and Northern Plain states. In general, more glyphosate-resistant weeds are emerging on agricultural land planted to several crops that are predominantly Roundup Ready in the U.S., which since 2008 includes sugar beets. One recent example is the emergence of glyphosate-resistant common waterhemp on land planted to corn, soybeans and sugar beets in North Dakota (ISHRW GR Weeds 4/22/12). A brief, documented overview of the adverse consequences of GR weeds – which include increased use of glyphosate and more toxic herbicides as well as soil-eroding tillage operations, reduced yield, sharply increased weed control costs, widespread reversion to manual weeding, and in extreme cases abandonment of cropland, is provided in Benbrook (2009a, Chapter 4).

Synthetic Auxin-Resistant Crops and Weeds

2,4-D is the most important and widely used member of the synthetic auxin class of herbicides, which act by mimicking plant growth hormones such as indole acetic acid. Dow scientists maintain that deployment of Enlist corn and soybeans under the proposed registrations would be unlikely to foster evolution of weeds resistant to 2,4-D for several reasons: 1) Very few weeds have thus far evolved resistance to the herbicide; 2) 2,4-D's mode of action is complex, suggesting that multiple mutations would be needed to confer resistance; and 3) 2,4-D would be used in combination or rotation with glyphosate, which would require weeds to evolve resistance to both at once, which is regarded as unlikely (Wright et al. 2010).

There are several serious flaws in these arguments, which were persuasively rebutted by Mortensen et al. (2012). First, the ISHRW website lists 43 biotypes of 29 different weed species with resistance to synthetic auxin herbicides (ISHRW SynAux Weeds 4/22/12). Of the 21 herbicide classes to which weeds have evolved resistance, synthetic auxin-resistant weeds rank fourth in terms of number of resistant biotypes (ISHRW HR Weed Ranking 4/22/12). The majority of the 29 auxin-resistant species (17) are resistant to 2,4-D (Mortensen et al. (2012) report 16 species, but an additional one has arisen since publication of that paper, discussed further below). This is hardly "very few 2,4-D–resistant weed species" (Wright et al. 2010).

The second argument is equally specious. In most cases, scientists have not elucidated the precise mechanisms by which weeds evolve resistance, making predictions about the likelihood of weed resistance on this basis extremely hazardous. Indeed, the precise mechanisms by which auxin herbicides kill weeds remains unclear even today. Monsanto scientists likewise predicted very little chance of glyphosate-resistant weed evolution in the 1990s (Bradshaw et al. 1997), and for much the same reasons as put forward by Dow's scientists. These predictions were of course disastrously wrong, but they did help quell concerns about GR weed evolution and weaken momentum for serious weed resistance management programs for RR crop systems (Horne 1992), which leading weed scientists deemed necessary (Gressel 1996), as Monsanto was introducing its Roundup Ready crops. Interestingly, only one GR weed had been identified by the time the first RR crop was introduced in 1996 (ISHRW GR Weeds 4/22/12), in contrast to the 17 weed species with biotypes resistant to 2,4-D today.

Dow's third argument, that use of both 2,4-D and glyphosate on Enlist corn and soybeans will hinder evolution of weeds resistant to either one, also lacks merit. This argument ignores the fact that the huge extent of existing GR weed populations – with many billions of individual weeds on millions of infested acres – make it near certain that some among them will have the rare genetic mutations conferring resistance to 2,4-D as well. Penn State weed scientists Mortensen et al. (2012) provide the mathematical exposition (emphasis added):

> "First, when a herbicide with a new mode of action is introduced into a region or cropping system in which weeds resistant to an older mode of action are already widespread and problematic, the probability of selecting for multiple target-site resistance is not the product of two independent, low-probability mutations. In fact, the value is closer to the simple probability of finding a resistance mutation to the new mode of action within a population already extensively resistant to the old mode of action. For instance, in Tennessee, an estimated 0.8–2 million ha of soybean crops are infested with glyphosate-resistant horseweed (C. canadensis) (Heap 2011). Assuming seedling densities of 100 per m^2 or 10^6 per ha (Dauer et al.. 2007) and a mutation frequency for synthetic auxin resistance of 10^{-9}, this implies that next spring, there will be 800–2000 horseweed seedlings in the infested area that possess combined resistance to glyphosate and a synthetic auxin herbicide ((2×10^6 ha infested with glyphosate resistance) x (10^6 seedlings per ha) x (1 synthetic auxin–resistant seedling per 10^9 seedlings) = 2000 multiple-resistant seedlings). In this example, these seedlings would be located in the very fields where farmers would most likely want to plant the new stacked glyphosate- and synthetic auxin–resistant soybean varieties (the fields where glyphosate-resistant horseweed problems are already acute). Once glyphosate and synthetic auxin herbicides have been applied to these fields and have killed the large number of susceptible genotypes, these few resistant individuals would have a strong competitive advantage and would be able to spread and multiply rapidly in the presence of the herbicide combination."

The upshot is that 2,4-D-resistant crop systems like DAS-40278-9 will very likely foster rapid evolution of weeds resistant to 2,4-D and glyphosate. In those cases where glyphosate-resistant weed populations in 2,4-D crop fields already have resistance to one or more additional modes of action, the result will be evolution of still more intractable weeds with multiple-herbicide resistance, including to 2,4-D.

The experience with glyphosate-resistant weeds demonstrates that neither a narrow focus on the biochemical nuances of resistance mechanisms, nor the frequency of resistance evolution in the past, nor the presumed rarity of resistance alleles, provide an accurate basis for forecasting what will happen when the herbicide in question is used in the context of a widely adopted herbicide-resistant crop system. What it does demonstrate is that the characteristic ways in which HR crop systems are used in the field, as discussed above, make them far more likely to trigger evolution of resistance weeds than non-HR crop uses of those same herbicides.

Mutations conferring resistance to glyphosate are regarded as extremely rare, much more so than mutations lending resistance to other classes of herbicides. It is significant to observe that weed populations have evolved the most widespread resistance (in terms of acreage infested) to two modes of action – ALS inhibitors and glyphosate – that stand at the extreme poles of resistance-conferring mutation frequency (with mutations conferring resistance to ALS inhibitors regarded as relatively common). This provides a striking illustration of how enormous selection pressure – particularly as exerted by herbicide use in the context of an HR crop system – can "overcome" initial rarity of resistance alleles, and foster widespread evolution of resistant weeds to the same extent as weeds resistant to a mode of action for which resistance alleles are relatively common.

Multiple Herbicide-Resistant Crops and Weeds

Mortensen et al. (2012) note that there are currently 108 biotypes of 38 weed species possessing simultaneous resistance to two more classes of herbicide, and that 44% of them have appeared since 2005. Since herbicide-resistant weeds began to emerge in a significant way around 1970 (triazine-resistant weeds),[70] this means that nearly half of multiple HR weed biotypes have emerged in just the past seven years of our 40-year history of significant weed resistance. This global trend is also occurring in the U.S., where acreage infested with multiple HR weeds has increased by 400% over just the three years from November 2007 to November 2010 (Freese 2010, p. 15). There are at least 12 biotypes of weeds resistant to glyphosate and one or more other herbicide families in the U.S. (11) and Canada (1) that are attributable to RR crop systems, all but one having emerged since 2005 (ISHRW GR Weeds 4/22/12).

There is already evidence that the scenario of 2,4-D resistance evolving in weeds already resistant to one or more herbicide classes, as depicted by Mortensen et al. (2012), will occur with four especially problematic species of weeds: horseweed, Palmer amaranth, waterhemp and kochia.

Horseweed

Horseweed, or marestail, is the most prevalent GR weed. First discovered in 2000 in Delaware, glyphosate-resistant horseweed has emerged in just over a decade to infest up to 8.4 million acres in 20 states (CFS GR Weed List 2012[71]), up from 3.3 million acres in 16 states in February 2009 (Benbrook 2009a, p. 35). It is particularly prevalent in Tennessee, Kansas and Illinois, with populations infesting up to 5 million, 2 million and 1 million acres, respectively. Glyphosate-resistant horseweed in Mississippi is also resistant to paraquat, the first time multiple resistance to these two herbicides has been documented, while Ohio has glyphosate/ALS inhibitor-resistant[72] horseweed.

Weed scientists regard GR horseweed as a "worst-case scenario" in Roundup Ready cropping systems because this weed is well adapted to no-tillage planting systems popular among glyphosate-resistant crop growers. It also producers up to 200,000 seeds per plant, and its

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[70] Although a few auxin-resistant biotypes emerged in the 1950s and 1960s.

[71] Consult this chart for data in the following discussion.

[72] CFS suspects that glyphosate-resistant weeds that are also resistant to ALS inhibitor herbicides are greatly underreported by ISHRW; this is certainly the case with waterhemp (see discussion below).

seeds can disperse extremely long distances in the wind (Owen 2008), which may partly explain the prevalence of glyphosate-resistant horseweed.

Glyphosate-resistant horseweed can reduce cotton yields by 40 to 70% (Laws 2006), and is also problematic in soybeans. As long ago as 2003, Arkansas weed scientist Ken Smith estimated that Arkansas growers would have to spend as much as $9 million to combat glyphosate-resistant horseweed in 2004 (AP 2003). An uncontrolled outbreak of glyphosate-resistant horseweed in Arkansas could reduce the income of cotton and soybean farmers by nearly $500 million, based on projected loss in yield of 50% in 900,000 acres of cotton and a 25% yield loss in the over three million acres of soybeans (James 2005). Tennessee is especially hard hit, with up to 5 million acres of both cotton and soybeans infested with glyphosate-resistant horseweed.

Because glyphosate-resistant horseweed is often controlled with tillage, it has led to abandonment of conservation tillage practices on substantial cotton acreage in Tennessee and Arkansas, with similar trends reported in Mississippi and Missouri (Laws 2006) and perhaps other states. This in turn increases soil erosion. An NRC committee reported that increased tillage as well as increased herbicide use are common responses to glyphosate-resistant weeds (NRC 2010). Evolution of multiple herbicide-resistance reduces options for chemical control and so increases the chances for still more soil-eroding tillage.

The many farmers with glyphosate-resistant and multiple-HR horseweed would be prime candidates for Dow's Enlist soybeans and corn. Yet Purdue University weed scientists have flagged horseweed as a weed with the genetic "plasticity" to readily evolve resistance to multiple herbicides:

> "Multiple-resistant and cross-resistant horseweed populations have evolved to various combinations of the previous herbicide modes of action in Israel, Michigan, and Ohio (Heap 2009), providing evidence for the plasticity of this weed." (Kruger et al. (2010a).[73]

These same scientists have already founded increased tolerance to 2,4-D in some horseweed populations, demonstrating the potential for horseweed to evolve additional resistance to 2,4-D in the context of heavy postemergence use of 2,4-D, as enabled by the proposed registrations, in Enlist weed control systems:

> "With the announcement that Dow AgroSciences intends to insert genes which convey 2,4-D resistance into corn (Zea mays L.), soybean [Glycine max (L.) Merr.), and cotton (Gossypium hirsutum L.) (Dow AgroSciences 2007), <u>the use of 2,4-D postemergence on agronomic crop areas could dramatically increase.</u> This increased 2,4-D use will increase selection pressure for more tolerant weed populations such as horseweed population 34, potentially leading to the evolution of creeping resistance similar to that described by Gressel (1995) (Kruger et al. 2008, emphasis added)"

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[73] As noted above, horseweed has also evolved dual resistance to glyphosate and paraquat in Mississippi.

The Purdue team further underscore two common practices employed by farmers, particularly in the context of (multiple) HR weed systems, that would further increase the risks of 2,4-D resistance evolution in horseweed: reducing rates of herbicides when used in combination in tank mixes; and delaying application until weeds become larger, more difficult to kill, and hence more likely to propagate resistance.

> "The use of 2,4-D in conjunction with glyphosate is often accompanied by a reduction in the rate of 2,4-D, further increasing the likelihood that horseweed plants will survive the application" (Kruger et al. 2008, emphasis added).

According to the same team:

> "With the announcement of 2,4-D resistance traits being transformed into corn and soybean (Wright et al.. 2005), it is likely that POST selection pressure with 2,4-D will increase. Additionally, if 2,4-D is used POST, the herbicide applications will be applied to larger plants, creating a need for understanding the impact of horseweed size on the efficacy of 2,4-D." (Kruger et al. 2010a, emphasis added)

Follow-up research addressed this very question – "the impact of horseweed size on the efficacy of 2,4-D" – and found that larger weeds became much more difficult to control:

> "While it is realistic to expect growers to spray horseweed plants after they start to bolt, the results show that timely applications to [small] horseweed rosettes are the best approach for controlling these weeds with growth regulator herbicides [2,4-D and dicamba]. Growers should be advised to control horseweed plants before they reach 30 cm in height because after that the plants became much more difficult to control." (Kruger et al. 2010b, emphasis added)

As discussed above, increased survival of more difficult-to-control weeds means a greater likelihood of resistant individuals surviving to propagate resistance via cross-pollination or seed production. And as the authors acknowledge, it is "realistic" to expect late application of 2,4-D with Enlist crops, because that is precisely the point of these crop systems, as also demonstrated with the history of Roundup Ready crops. Illinois agronomist E.L. Knake confirms that even now, with conventional corn: "some later postemergence applications are made because 2,4-D is more effective on larger weeds than are most other herbicides" (Knake undated, emphasis added).

This tendency to delay application to kill larger weeds will be greatly facilitated by the proposed registrations, which would expand the window for direct, over-the-top POST use of 2,4-D on DAS-40278-9 to much later in the season (48" vs. 8" corn), and enable entirely new POST use on Enlist soybeans; and of course, delayed application will also be facilitated by the high-level 2,4-D resistance of the Enlist crops themselves, permitting many-fold higher rates without risk of crop injury, higher rates which are needed for larger weeds. Thus, advising growers to spray weeds when they are small will likely not be any more effective with Enlist corn and soybeans than were similar recommendations made for glyphosate with Roundup

Ready crops.

Waterhemp

Waterhemp is regarded as one of the worst weeds in the Corn Belt. It grows to a height of 2-3 meters, and emerges late into the growing season. Controlled trials in Illinois demonstrated that late-season waterhemp reduced corn yields in Illinois by 13-59%, while waterhemp emerging throughout the season cut yields by up to 74% (Steckel-Sprague 2004).

ISHRW lists 11 biotypes of glyphosate-resistant waterhemp, all of which have emerged since 2005 in corn, soybeans, cotton and/or sugar beets, almost certainly all in Roundup Ready crop systems (CFS GR Weed List). While ISHRW records up to 1.1 million acres infested with glyphosate-resistant waterhemp, this is a vast underestimate. As noted above, Illinois weed scientist Bryan Young estimates an astounding 5-6 million acres infested with glyphosate-resistant waterhemp in his state.

Waterhemp has an astounding ability to evolve resistance to herbicides. Biotypes resistant to one to four herbicide families have been identified in several Midwest and Southern states, from North Dakota to Tennessee (*see* CFS GR Weed List 2012 and ISHRW GR Weeds for those resistant to glyphosate). Triple herbicide-resistant waterhemp infests up to one million acres in Missouri, while populations resistant to four herbicide classes, sardonically called "QuadStack Waterhemp" (Tranel 2010), have arisen in Illinois. Tranel's investigations suggest that the 5-6 million acres of GR waterhemp in Illinois noted above are all resistant to ALS inhibitors, with some additionally resistant to PPO inhibitors and/or triazines.

Tranel states that multiple herbicide-resistant waterhemp "appears to be on the threshold of becoming an unmanageable problem in soybean," and is quite concerned that if already multiple herbicide-resistant waterhemp evolves resistance to additional herbicides, "soybean production may not be practical in many Midwest fields" (Tranel et al. 2010). Corn is often rotated with soybeans, and so could be similarly affected.

In early 2011, waterhemp was identified as the first weed to have evolved resistance to a relatively new class of herbicides, HPPD inhibitors, the fifth "mode of action" to which waterhemp has evolved resistance (Science Daily 2011), prompting weed scientist Aaron Hagar to comment that "we are running out of options" to control this weed. Populations of waterhemp in Iowa and Illinois are resistant to HPPD inhibitors and two other modes of action (ISHRW Waterhemp 2012).

Just months later, waterhemp resistant to its sixth mode of action, 2,4-D, was discovered, and it is potentially resistant to the popular corn herbicides atrazine and metolachlor as well, which would make it particularly difficult to manage (UNL 2011). The weed scientists who discovered this resistant weed population clearly understand the likelihood that 2,4-D resistant crop systems – "if used as the primary tool to manage weeds already resistant to other herbicides," the hallmark of these systems – will lead to still more intractable, multiple herbicide-resistant weeds:

> "New technologies that confer resistance to 2,4-D and dicamba (both synthetic auxins) are being developed to provide additional herbicide options for postemergence weed control in soybean and cotton. The development of 2,4-D resistant waterhemp in this field is a reminder and a caution that these new technologies, if used as the primary tool to manage weeds already resistant to other herbicides such as glyphosate, atrazine or ALS-inhibitors, will eventually result in new herbicide resistant populations evolving." (UNL 2011)

Palmer amaranth

Perhaps the most destructive and feared weed in all of U.S. agriculture is glyphosate-resistant Palmer amaranth (see Benbrook 2009a, Chapter 4). Second only GR horseweed in prevalence, glyphosate-resistant Palmer amaranth is estimated to infest 112,000 to over 220,000 fields covering up to 7.0 million acres in 12 states, all but one in corn, cotton and/or soybeans (CFS GR Weed List 2012). Best known for plaguing cotton and soybean growers in Southern states, this weed is rapidly emerging in Corn Belt states like Illinois and Missouri; a small population was even reported recently in Michigan (ISHRW GR Weed List 4/22/12). Palmer amaranth is feared chiefly because of its extremely rapid growth – several inches per day – which means it can literally outgrow a busy farmer's best attempts to control it while still small enough to be killed. It also produces a huge number of seeds, so just one mature weed can ensure continuing problems in future years by pouring hundreds of thousands of resistant weeds into the "weed seed bank." Left unchecked, its stem can become baseball bat breadth, and is tough enough to damage cotton pickers. Glyphosate-resistant Palmer amaranth can dramatically cut yields by a third or more, and occasionally causes abandonment of cropland too weedy to salvage. In Georgia, Arkansas and other states, farmers have resorted to hiring weeding crews to manually hoe this weed on hundreds of thousands of acres, tripling weed control costs (Haire 2010). Herbicide regimes of six to eight different chemicals, including toxic organic arsenical herbicides such as MSMA otherwise being phased out (EPA 2009, p. 3), are recommended to control it (Culpepper-Kichler 2009).

At least three states (Mississippi, Georgia and Tennessee) have Palmer amaranth resistant to both glyphosate and ALS inhibitors; the most recent one, reported in 2011, infests over 100,000 sites covering up to 2 million acres in Tennessee (CFS GR Weed List 2012). Palmer amaranth belongs to the same genus as common waterhemp (*Amaranthus*), and to some extent can interbreed with it. Both have considerably genetic diversity. The demonstrated ability of waterhemp to evolve resistance to 2,4-D suggests that a similar potential likely exists in Palmer amaranth. Growers with GR and multiple HR Palmer amaranth would be prime candidates to adopt Enlist weed control systems, and utilize them under the proposed registrations. The likely emergence of 2,4-D resistance in glyphosate-resistant Palmer amaranth under the proposed registrations would seriously undermine the efficacy of existing, pre-emergence use of 2,4-D in battling this serious weed threat.

Kochia

Kochia is a fourth serious weed, described further at CFS (2010). It has evolved widespread resistance to many different herbicides, and is on the ISHRW's list of the top ten most important herbicide-resistant weed species (ISHRW Worst HR Weeds). Limited population of glyphosate-resistant kochia first emerged in Kansas in 2007, but recent reports suggest that it is now likely prevalent in the entire western third of Kansas, as well as parts of Colorado (Stahlman et al. 2011). A second population identified in Nebraska (2009) was first listed on ISHRW in December of 2011, and a third in South Dakota (2011), infesting up to 10,000 acres, was first listed in May of 2012. In addition, kochia resistant to both glyphosate and ALS inhibitors was recently identified in Alberta, Canada (2012). All of the US populations emerged in corn, soybeans and/or cotton (almost certainly Roundup Ready versions), while the Canadian population emerged in cereals and "cropland" that may also include Roundup Ready crops.

Stahlman et al. (2011) state that the original four populations in Kansas likely evolved glyphosate-resistance independently, but the rapid emergence across such a broad swath of the state suggests the potential for spread of the original populations, perhaps by resistant seed dispersal, as kochia "tumbleweed" can disperse seeds at considerable distances (see CFS 2010). CFS (2010) also documents that kochia is a serious weed of both alfalfa and sugarbeets, Roundup Ready versions of which have been recently introduced and are widely grown. Glyphosate-resistant kochia infesting these Roundup Ready crops would seriously impair the efficacy of the Roundup Ready trait; likewise, selection pressure from glyphosate use with these crop systems (especially in rotation with other Roundup Ready crops, as seen particularly with Roundup Ready sugar beets, which are frequently rotated with Roundup Ready corn and/or Roundup Ready soybeans) could rapidly lead to still more extensive emergence of glyphosate-resistant kochia.

Four biotypes of kochia have also evolved resistance to synthetic auxin herbicides, the class to which 2,4-D belongs (ISHRW Kochia 2012). While none are listed as resistant to 2,4-D, all are resistant to dicamba, a closely-related auxin herbicide, which may indicate that kochia is a likely candidate for evolution of resistance to 2,4-D. The rapid emergence of glyphosate-resistant biotypes in Roundup Ready crop systems may induce growers to adopt Enlist corn and/or soybeans to control it; and kochia's demonstrated propensity to evolve resistance to auxin herbicides may make it more likely to also evolve resistance to 2,4-D.

Stewardship

In its review of Dow's New Use Registration Applications, EPA should also take into account the failure of voluntary industry stewardship on weed management and consider the imposition of mandatory weed resistant management requirements. In his September 30, 2010 testimony before the House of Representatives' Domestic Policy Subcommittee, Deputy Assistant Administrator Mr. Jim Jones stated that the inclusion of "mechanism of action information on herbicide labels" is "critical" to "preventing or delaying development of [weed] resistance."[74] Indeed, EPA itself has admitted, in the context of the agency's regulation of transgenic *Bacillus thuringiensis (B.t.*) crops, that development of resistance to pesticides "as a result of unmitigated exposure" constitutes an "adverse effect on the environment."[75]

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[74] Testimony of Jim Jones, Deputy Assistant Administrator for Chemical Safety and Pollution Prevention, EPA, before the Domestic Policy Subcomm. Oversight and Gov't Reform Comm. of the U.S. House of Rep. (Sept. 30, 2010).

[75] *Id.*

Recognizing the importance of B.t. formulations in organic farming, EPA has consistently required B.t. crop registrants to "market B.t. crops with mandatory insect resistant management (IRM) requirements."[76] EPA should consider taking the same regulatory actions here with regards to herbicide-resistant weeds. Indeed, for at least 15 years, companies and weed scientists have touted voluntary stewardship guidelines and best management practices as the chief bulwark against evolution of resistant weeds in the context of HR crop systems. These programs and exhortations have demonstrably failed with Roundup Ready crops, or there would not be an epidemic of glyphosate-resistant weeds. A critical assessment of Monsanto's failed stewardship messages and practices may be useful to inform an assessment of Dow's similar approach.

Monsanto insisted that weeds would not evolve glyphosate resistance to any serious extent when Roundup Ready crops were first being introduced (Bradshaw et al. 1997), in direct contradiction to concerns expressed by weed scientists, many of whom understood that serious measures were called for to forestall it (Freese 2010, question 1). Even several years after glyphosate-resistant weeds had emerged, Monsanto promoted "glyphosate-only" weed control programs in farm press advertisements that leading weed scientists castigated as irresponsible for promoting weed resistance (Hartzler et al. 2004). Monsanto continues to tout voluntary stewardship programs as an effective means to forestall or manage glyphosate-resistant weeds, despite their obvious failure.

Dow scientists have similarly denied that weeds will evolve resistance to 2,4-D to any significant degree, based on the molecular nuances of 2,4-D's mode of action (Wright et al. 2010), quite similar to the fallacious arguments of Monsanto's scientists 15 years ago. When their assessment was effectively challenged (Egan et al. 2011), these same scientists fell back on the argument that stewardship recommendations (chiefly, use multiple modes of action) would effectively prevent emergence of 2,4-D resistance (Wright et al. 2011). Yet there is little or nothing to distinguish Dow's stewardship program (DAS Stewardship) from Monsanto's failed approach.

Increase Use of Other Herbicides

EPA should also consider that Dow's proposed registered use of 2,4-D on DAS-40278-9 corn may, and DAS-68416-4 soybeans apparently will, be introduced with additional resistance to glufosinate. As noted above, glufosinate is very little used on corn, applied to just 2% of acres in 2010. USDA-NASS (2006) does not report any glufosinate use with soybeans.[77] Whether growers would choose to use glufosinate on glufosinate-resistant Enlist corn or soybeans is questionable. However, there is already reason to question the efficacy of glufosinate in forestalling resistance to 2,4-D and/or glyphosate in the event that it were to be used.

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[76] *Id.*

[77] This is true despite the availability of glufosinate-resistant, LibertyLink corn since the mid-late 1990s, and the more recently introduced SmartStax corn. We are not aware of any figures on glufosinate-resistant corn adoption. Glufosinate use provides some indication. USDA-NASS data show that from 1998-2005, just 2-5% of corn acres were sprayed with glufosinate, suggesting very low adoption rates of any glufosinate-resistant corn varieties. LibertyLink soybeans have been introduced recently, but it is not clear to what extent.

Avila-Garcia and Mallory-Smith (2011) have recently discovered Italian ryegrass resistant to both glyphosate and glufosinate in an orchard where little or no glufosinate was used, and suspect a common, non-target site mechanism – reduced translocation – for resistance to both herbicides. They regard the potential for evolution of resistance to both herbicides where both glyphosate- and glufosinate-resistant crops are grown as an "alarming weed management issue." In Illinois, Tranel et al. (2010) find that glufosinate may soon be the only effective post-emergence herbicide option for control of already multiple-HR waterhemp in soybeans; that glufosinate is not well-suited to control this weed; and that "there is no reason to expect [waterhemp] will not evolve resistance to glufosinate if this herbicide is widely used."

Dow touts its Enlist corn and soybean systems as the "solution" to weeds resistant to glyphosate as well as other modes of action, just as RR crop systems were regarded as the solution to prior resistance, particularly epidemic ALS inhibitor-resistant weed populations in soybeans. As documented above, dual resistance to glyphosate and ALS inhibitors is quite common in weeds, particularly common waterhemp and Palmer amaranth. If HR crop systems really did "solve" resistant weed problems, as Dow maintains, one would certainly not expect multiple HR weeds to expand dramatically with their use – yet that is precisely what has happened with its predecessor Roundup Ready system. As also discussed above, there are already very good scientific reasons to suspect that the major mid-range consequence of widespread use of Enlist corn and soybeans under the proposed registrations would be to foster additional resistance to 2,4-D, with extremely serious consequences for farmers, the agricultural economy, the environment and public health.

Spread of Weed resistance and Tragedy of the Commons

Weeds evolve resistance through strong selection pressure from frequent use and overreliance on particular herbicides, especially when applied late in the context of HR crop systems. However, once resistant populations of outcrossing weeds emerge, even small ones, they can propagate resistance via cross-pollinating their susceptible counterparts (Webster & Sosnoskie 2010). It is estimated that common waterhemp pollen can travel for one-half mile in windy conditions, and so spread resistance to neighbors' fields via cross-pollination (Nordby et al. 2007). And whether out-crossing or inbreeding, those resistant individuals with lightweight seeds can disperse at great distances. Dauer et al. (2009) found that the lightweight, airborne seeds of horseweed, the most prevalent glyphosate-resistant weed (CFS GR Weed List 2012), can travel for tens to hundreds of kilometers in the wind, which might partially explain its prevalence. Hybridization among related weeds is another potential means by which resistance could be spread, for instance by weeds in the problematic *Amaranthus* genus (Gaines et al. 2012).

Thus, even farmers who employ sound practices to prevent emergence of herbicide-resistant weeds themselves can have their fields infested with resistant weeds from those of other farmers. With reference to glyphosate-resistant weeds, Webster & Sosnoskie (2010) present this as a tragedy of the commons dilemma, in which weed susceptibility to glyphosate is the common resource being squandered. Since responsible practices by individual farmers to prevent evolution of weed resistance in their fields cannot prevent weed resistance from spreading to their fields as indicated above, there is less incentive for any farmer to even try to undertake such prevention measures.

The weed science community as a whole has not even begun to grapple with the implications of the spread of resistance, particularly as it relates to the efficacy of weed resistance management recommendations based solely on individual farmers reducing selection pressure. It may not be effective or rational for farmers to commit resources to resistance management in the absence some assurance that other farmers in their area will do likewise. This suggests the need for a wholly different approach that is capable of ensuring a high degree of area-wide adoption of sound weed resistance management practices.

Volunteer Corn and Corn Rootworm Resistance to Bt Toxins

EPA should also consider how the proposed new use of 2,4-D choline salt on 2,4-D resistant corn would make it more difficult for farmers to effectively control volunteer corn, Corn volunteers can be troublesome weed in the following season's crop (e.g. soybeans). Just two to four volunteer corn plants per square meter can reduce yields in soybeans by 20% (Morrison 2012). Control of volunteer corn becomes much more problematic when it is herbicide-resistant. In 2007, volunteer glyphosate-resistant corn (Roundup Ready) was rated as one of the top five weeds in Midwest soybean fields. Things have become worse with adoption of SmartStax corn, which like DAS-42078-9 is resistant to two herbicides – in this case glyphosate and glufosinate (Brooks 2012, Morrison 2012). When volunteer corn emerges in soybeans, one tactic is to apply "grass" herbicides like quizalofop to kill it (effective on corn since corn is a grass family crop). This tactic would no longer be effective on DAS-40278-9 volunteers, since it is resistant to quizalofop and other "fops" herbicides like cyhalofop. In addition, Dow plans to market DAS-40278-9 with resistance to three modes of action (i.e. stacked with glyphosate resistance), and possibly even four (Scherder et al. (2010) report that DAS-40278-9 has been stacked into SmartStax corn, lending additional resistance to glufosinate). Such quad-resistant volunteer corn plants would present still more serious control problems.

Moreover, EPA should also take into account the potential interplay between DAS-42078-9 corn varieties stacked with Bt and corn rootworm resistance to Bt toxins. Like most HR corn, DAS-40278-9 will likely be stacked with insect-resistance, including Bt for corn rootworm, an extremely damaging corn pest that feeds on corn roots. Bt-resistant corn rootworm is already an emerging problem in Illinois and other states, in part because the corn produces lower levels of Bt toxin that tends to foster evolution of resistance (Gray 2011, Porter et al. 2012). Volunteer corn produces still less of the insect-resistance toxin, in many cases insufficient levels to kill rootworm. The lower-level Bt toxin expression of volunteer corn allows many corn rootworm to persist into the next season, and also fosters evolution of resistance in them, regarded by agronomists as a serious emerging problem (Morrison 2012).

Chemical control options for volunteer Enlist corn varieties with resistance to two to four major modes of action will be greatly diminished; this may mean that such volunteers are not controlled as well. If stacked with Bt targeting corn rootworm, such Enlist corn volunteers could exacerbate corn rootworm resistance to Bt toxins

d. EPA Should Consider Any Unreasonable Adverse Effects Stemming from the Interactions Between the Proposed New uses of 2,4-D Choline Salt and the AAD-1 Enzyme in Genetically Engineered 2,4-D Resistant Corn and Soybeans.

EPA should carefully consider the impacts of the accumulation of novel molecules with similarity to known toxins under the proposed new use of 2,4-D choline on DAS-40278-9 corn and DAS-68416-4 soybeans.

There are differences in the composition of DAS-40278-9 corn and DAS-68416-4 soybeans compared to non-2,4-D resistant varieties that result from the *activity* of their respective novel AAD-1 and AAD-12 proteins. The AAD-1 and AAD-12 proteins are enzymes that act on 2,4-D and other substrates likely to be encountered by DAS-40278-9 corn and DAS-68416-4 soybeans to produce metabolites missing or at much lower levels in non-engineered corn and soybeans (Fueng et al. 1978, Hamburg et al. 2001, Laurent et al. 2000), and some of these metabolites are suspected of being toxic to animals via ingestion (Pascal-Lorber et al. 2012, Edwards and Hutson 1986).

Specifically, the AAD-1 protein in DAS-40278-9 corn and AAD-12 protein in DAS-68416-4 soybeans are enzymes that break down several herbicides into their corresponding phenols. The herbicide substrates include some that are highly likely to be present in the environment of these crops, either because the herbicides are applied directly to the corn and soybeans, or contact the corn and soybeans via drift. Dow claims that “AAD-1 is able to degrade the R-enantiomers (herbicidally active isomers) of chiral phenoxy auxins (e.g., dichlorprop and mecoprop) in addition to the achiral phenoxy auxins (e.g., 2,4-D, MCPA, 4-chrophonoxyacetic acid. See Table 1. Multiple mixes of different phenoxy auxin combinations have been used globally to address specific weed spectra and environmental conditions in various regions. Use of the AAD-1 gene in plants would afford protection to a much wider spectrum of phenoxy auxin herbicides, thereby increasing the flexibility and spectra of weeds that can be controlled, protecting from drift or other off-site phenoxy herbicide injury for the full breadth of commercially available phenoxy auxins.” (DAS patent 2009, p. 4 – 6) The enzyme also degrades “…a host of commercial and non-commercial graminicidal compounds of the general class aryloxyphenoxypropionates (AOPPs). See Table 2.” (DAS patent 2009, p. 6). The AAD-12 enzyme somewhat different activity, but also degrades 2,4-D and related phenoxy auxin herbicides into their corresponding phenols.

Although the AAD-1 and AAD-12 enzymes degrade multiple phenoxy herbicides, Dow has only applied for registration at this time of 2,4-D choline in the phenoxy auxin group for direct use over the top of DAS-40278-9 corn and DAS-68416-4 soybeans. Other herbicide substrates may be present from drift or off-label use, though.

To assess risk to non-target organisms of registering 2,4-D choline, then, EPA needs to know if these new AAD-1 and AAD-12 enzymes alter *metabolism* in DAS-40278-9 corn and

DAS-68 416-4 soybeans such that the plants have a new composition after 2,4-D is used, and thus have the potential to harm non-target species.

This is not a new concern. The issue of toxins resulting from engineered 2,4-D resistance was raised in 1992 by Dr. Rebecca Goldburg, then at Environmental Defense Fund:

> Both the degradation products and accumulation of herbicides in tolerant plants need to be considered before plants can be accepted as safe.
>
> First, 2,4-D resistance can be achieved by transforming plants with a gene coding the enzyme that catalyzes the first step in the bacterial 2,4-D degradative pathway. Degradation of 2,4-D results in the formation of 2,4-dichlorophenol (2,4-DCP)", a toxic substance. (Goldburg 1992, p. 650; internal citations removed).

Since then, there has been a series of peer-reviewed, independent studies on whether 2,4-DCP or other potentially toxic metabolites from the breakdown of 2,4-D do accumulate differently in 2,4-D resistant crops than conventional ones, and whether these metabolites could pose a risk to animals ingesting the plants (Laurent et al.. 2000, Laurent et al.. 2006, Pascal-Lorber et al.. 2012.

Cotton has been engineered with an enzyme similar to AAD-1 - tfdA – that also breaks down 2,4-D into 2,4-DCP, and the metabolism of 2,4-D was followed in this cotton compared to non-engineered wild-type cotton (Laurent et al.. 2000, Laurent et al.. 2006). Both engineered and wild-type cotton converted 2,4-D to 2,4-DCP, but in engineered cotton "2,4-D was entirely transformed into DCP, whereas in wild[-type] cotton almost no DCP appeared." (Laurent et al.. 2006) This is the first important fact, then: DCP is a major metabolite in 2,4-D resistant cotton, but not in cotton that lacks the engineered enzyme.

Also, there was a new metabolite in the engineered cotton treated with 2,4-D: DCP-glucosyl sulfate. This did not appear in wild-type cotton treated with 2,4-D but did when wild-type cotton was fed DCP directly. These researchers showed that DCP metabolism was similar in transgenic cotton plants whether it came from metabolism of 2,4-D by the novel enzyme, or from DCP supplied in the nutrient solution. They deduced that they could study the fate of DCP in different non-transformed species by just adding DCP to leaves via their petioles, and that the metabolites that form will predict what would have happened had the plants been engineered to convert 2,4-D to DCP. This allowed them to study the types of metabolites that would form if plants other than cotton were given enzymes similar to AAD-1 and tfdA, without injuring the experimental subjects with 2,4-D. They examined DCP metabolism in tomato, sugar beet, potato, and rapeseed (Laurent et al.. 2006); wheat and soybean (Pascal-Lorber et al.. 2003); and radish, lettuce and spinach (Pascal-Lorber et al.. 2008).

Combining results of these studies, it is clear that when 2,4-D is metabolized to 2,4-DCP by the its use on 2,4-D resistant crops with the engineered enzyme, this DCP is rapidly converted into conjugated forms – sugars and other molecules are added onto the DCP, depending on the plant species. These conjugated forms of DCP are stable in the plants, and might be converted back to free DCP during the digestive process in animals, posing a possible health risk:

> Offsetting the agronomic benefits of this [engineering for resistance] 2,4-D tolerant [i.e., resistant] crops could increase the food safety risk, even though free DCP has not been directly found in plants since it is rapidly metabolised to glucoside conjugates. However, after ingestion by humans or animals, these latter could be hydrolysed by intestinal microflora in the intestinal lumen, thus liberating the toxic aglycone in the gastrointestinal tract, with subsequent absorption by intestinal mucosa. Moreover, DCP could be converted into a more toxic compound in animals. The use of 2,4-D for transgenic tolerant crops would increase the risk of health effects from exposure to this herbicide as compared with 2,4-D treatments of wild[-type] crops." (Laurent et al.. 2006, p. 563; internal citations omitted)

In the latest work from the Laurent lab, the ability of animals to absorb conjugates of DCP from plants in their diet was tested directly (Pascal-Lorber et al.. 2012). They first supplied radioactive DCP to radish plants via their roots. Various extracted fractions of the radishes were then fed to rats to see what happened to the DCP and DCP conjugates afterwards. They conclude:

> This study clearly demonstrates that the soluble fraction of DCP residues present in plants is bioavailable in mammals, whereas bound residues are not absorbed**.** Plant DCP conjugates are likely to contribute substantially to the exposure of the general population to DCP. This observation may be probably expanded to several categories of chemicals, including pesticides. Accordingly, our data suggest that extractable residues should then be taken into account in occurrence data regarding residues of pesticide treatment in plants. ...
>
> In conclusion, the present work focused on the comparison of oral administration to rats of DCP with plant residues, DCP- (acetyl)glucose, soluble, total, and bound residues from radish plants. DCP was rapidly absorbed and eliminated in urine equally in the form of sulfate and glucuronide conjugates. A new metabolite was also detected and characterized as a dehydrated glucuronide conjugate of DCP. DCP-(acetyl)glucose exhibited a urinary metabolic profile similar to that of DCP. Plant conjugates of DCP were absorbed in the digestive tract of rats, and the major part was eliminated in urine subsequent to biotransformation in sulfate and glucuronide conjugates. Living organisms are thus exposed to DCP through the food chain. The vegetal matrix seemed to influence the metabolic profiles derived from soluble and total residues as urinary elimination proceeded predominantly through glucuronidation. In addition, a plant matrix effect was also evidenced because the behavior of total residues was different (less absorption occurred) from that expected from soluble and bound residues. Bound residues seemed to be unabsorbed under our conditions and consequently should be not bioavailable and of limited toxicological concern. (Pascal-Lorber et al.. 2012, p. 1734 - 1735; emphases added).

Given these results, as part of its risk assessment to determine whether to approve the new use of 2,4-D choline, the EPA must consider whether DCP and its conjugates are present in soluble fractions of DAS-40278-9 corn and DAS-68416-4 soybeans after the AAD-1 and AAD-12 enzymes, respectively, act upon 2,4-D in order to fully assess the impacts to non-target organisms.

Some information about 2,4-D metabolism in DAS-40278-9 corn, including levels of DCP and DCP-conjugates from the breakdown of 2,4-D, is present in Dow's studies (Ma and Adlelfinskaya 2010, Rotondaro and Balcer 2010, Stagg et al.. 2010, Culligan 2010; DAS Petition 2011, p. 18). Such studies are clearly relevant to an assessment of non-target impacts of the proposed new use of 2,4-D on DAS-40278-9 corn and DAS-68416-4 soybeans.

These studies of residues and metabolites in DAS-40278-9 corn are available on the Australia New Zealand Food Standards website[78] We assume these same studies were submitted to the EPA for evaluation as part this "new use" registration, and we also assume similar studies have been submitted to the EPA for DAS-68416-4 soybeans, but we have not had access to the soybean studies, so base our comments on the corn results.

The "nature of residue" studies (Ma & Aldelfinskaya 2010, Rotondaro and Balcer 2010) show that the use of 2,4-D formulations on DAS-40278-9 corn plants (and a different transformation event with the same enzyme) do result in measurable herbicide residues in the corn plant, that DCP levels are low, but that DCP-conjugates make up a significant portion of the metabolites in forage and fodder (e.g., Rotondaro and Balcer 2010, p. 12), as expected from the independent studies discussed above. And although Dow claims that these DCP conjugates from the breakdown of 2,4-D are no different from those in conventional corn, there are no data or cited references to support their assertion (e.g., Rotondaro and Balcer 2010, p. 31-32).

To analyze any unreasonable adverse effects stemming from the proposed new use of 2,4-D, EPA should consider requiring that Dow submit a study with a conventional corn control (with and without 2,4-D) in their residue and metabolism studies. It would be surprising if conventional corn made much DCP at all after application of 2,4-D (Feung et al.. 1978, Hamburg et al.. 2001), and therefore DCP conjugates would be an unlikely metabolite.

Note that in their reports Dow did not cite or discuss any of the independent studies of metabolites that we rely on here.

Although DCP conjugates were identified as major metabolites in Dow's "nature of residue" studies using radioactive tracers, this information was not incorporated into the "magnitude of residue" studies looking at total residue and metabolite levels and used to determine whether DAS-40278-9 corn would meet tolerance requirements for residues in forage and fodder (Culligan 2010). Conjugates were simply not measured in the "magnitude of residue" studies. However, the DCP levels in forage were actually higher in the "magnitude of residue" studies than the levels of 2,4-D, in contrast to the results from the "nature of residue" studies (Culligan 2010, p. 113). Even without considering the DCP conjugates, if the DCP levels

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[78] http://www.foodstandards.gov.au/foodstandards/applications/applicationa1042food4758.cfm; click on the "Application" zip file.

Dow reports for DAS-40278-9 corn were added to the total residue of 2,4-D in forage and fodder, tolerance levels would be exceeded (Stagg et al.. 2010, Culligan 2010, p. 113).

For example, the tolerance level of 2,4-D in forage is 6 µg 2,4-D per g of forage (Stagg et al.. 2010, p. 29). Dow measured 3.124 µg/g 2,4-D in forage after labeled 2,4-D applications, and 3.899 µg/g of 2,4-DCP (Highest Average Field Trial measurements, Culligan 2010, p. 113). If DCP were included in the current tolerances, there would be 7.029 µg/g of residues. We have no idea what the level of DCP conjugates is in these forage samples, but we expect them to be much higher than DCP itself given the activity of the AAD-1 enzyme, so if conjugates were included in the tolerances, 2,4-D use on DAS-40278-9 corn would require a major change in tolerances.

We ask EPA to examine the issue of tolerances and to consider including both DCP and DCP conjugates along with 2,4-D as residues of concern.

However, particularly for wild animals, the Dow nature and magnitude of residue studies are not adequate for determining the impacts of 2,4-D use on DAS-40278-9 corn. Dow designed their studies to simulate field conditions assuming application rates and timings according to the label, and product use by livestock and humans, not by the insects, birds, reptiles, amphibians, and other animals that visit cornfields.

Dow applied the last 2,4-D treatment at the V-8 stage, as per label, and then waited about a month before taking their first samples of forage at the customary time. Wild animals would not necessarily wait a month after an application before ingesting corn tissues. Residues and metabolites of 2,4-D are likely to be higher, and present in more soluble and thus digestible form closer to the time of application, so the food safety studies underestimate exposure for wildlife.

It is also possible that DAS-40278-9 corn could be sprayed later than the V-8 stage if farmers decide to do an off-label salvage treatment of uncontrolled weeds, as sometimes occurs; or DAS-40278-9 corn could be exposed to drift from a variety of herbicide substrates of the engineered enzyme, as suggested by Dow (DAS patent 2009, p. 6). The nature and magnitude of residue studies did not take into account any scenario other than "on label" applications, but we ask the EPA to consider these reasonable possibilities since they are likely to result in higher levels of 2,4-D residues and DCP conjugates.

We expect Dow's studies of DAS-68416-4 soybeans to be similar to these residue and metabolite studies in corn, and we have the same concerns as for DAS-40278-9 corn. In particular, the types and levels of DCP and DCP conjugates in DAS-68416-4 soybean forage and hay after 2,4-D applications need to be compared with independent research on 2,4-D and DCP metabolism in conventional soybeans (Pascal-Lorber et al.. 2003), and any differences explained. We ask the EPA to consider adjusting tolerance levels to incorporate all expected toxic residues and metabolites; and to assess impacts to non-target organisms of the novel, potentially toxic constituents expected to result when 2,4-D choline is used with DAS-68416-4 soybeans under a variety of anticipated application scenarios.

e. The Proposed New Use of 2,4-D on DAS-40278-9 Corn and DAS-68416-4 Soybean Could Harm Honey Bees and Vital Pollinators Due to the AAD-1 and AAD-12 Transgene. EPA Should Analyze This Significant Environmental Cost.

Impacts of using 2,4-D Choline Salt on DAS-40278-9 Corn and DAS-68416-4 Soybeans Due to Expression of AAD-1 and AAD-12 in Pollen and Nectar

To properly consider any unreasonable adverse effects of the proposed new use of 2,4-D choline salt exclusively on DAS-40278-9 corn and DAS-68416-4 soybeans, EPA must consider how the proposed new use of 2,4-D choline on DAS-40278-9 corn and DAS-68416-4 soybeans may have an unreasonable adverse effect on pollinators. At a minimum, EPA must request and examine Dow's own studies on translocation of 2,4-D into floral tissues and subsequent compositional changes due to metabolism of such 2,4-D in the pollen and nectar of engineered plants.

Dow has measured levels of the engineered gene product AAD-1 in different parts of DAS-40278-9 corn, sprayed with 2,4-D, or not (DAS Petition 2011, p. 60, Table 8). In general, average AAD-1 protein levels were between ~3 and 14 nanograms per milligram of tissue dry weight in leaves, roots, and whole plants. However, pollen had much higher levels, with averages between 108 and 127 ng/mg dw. Thus, gene expression in pollen was between 8- and 42-fold higher than in other plant parts.

EPA must investigate whether this high level of expression in pollen might be of significance to the characteristics of DAS-40278-9 corn in various 2,4-D application scenarios. In Roundup Ready cotton, low transgene expression in pollen and other male reproductive cell types limits the window when glyphosate applications can be made and also the maximum rate that can be used, and is seen as a problem for effective season-long weed control (Chen et al.. 2006; Yasuor et al.. 2006, 2007). Companies touted the fact that a second-generation glyphosate resistance trait in cotton has better expression of the EPSPS enzyme in pollen, and thus can withstand higher rates of glyphosate during more of the growing season (Chen et al.. 2006, May et al.. 2004, Monsanto 2005).

Levels of gene expression in pollen have also been of great interest for Bt crops. Corn pollen expressing cry proteins is toxic to some insects should they happen to ingest the pollen in sufficient quantities (Malone and Pham-Delègue 2001). Expression levels in pollen of different corn Bt events have been compared, and there is a wide range of cry protein levels and specificities, and thus potential for harm to butterflies, for example (e.g., Mattila et al.. 2005). The potential risk of exposure to Bt via pollen has been investigated for the endangered Karner Blue butterfly (Peterson et al.. 2006), identifying counties where butterfly sites are located near cornfields and thus need further study.

These precedents demand that EPA must analyze, in deciding whether or not to register 2,4-D choline salt for use on DAS-40278-9 corn and DAS-68416-4 soybeans as part of a 2,4-D resistant crop system, whether the high AAD-1 levels in pollen of DAS-40278-9 corn and potentially high levels of AAD-12 in DAS-68416-4 soybean pollen are correlated with good reproductive tolerance to 2,4-D, and if so, what consequences this might have for how farmers use herbicides on the crop and subsequent impacts.

Specifically, assuming that the AAD-1 protein is metabolically active in pollen, it is important to know whether pollen has the same composition in DAS-40278-9 corn as in conventional corn, particularly when applied with the proposed 2,4-D choline salt. Whether this pollen contains residues and metabolites not found in conventional pollen that might make it toxic to any of the wide array of organisms that feed on corn pollen (Lundgren 2009, Section II: Pollinivory, Ch.6, Ch. 8), such as honey bees, is an environmental cost that EPA must take into account in its determination of Dow's new use registration application. A similar assessment must be made in the case of DAS-68416-4 soybeans.

Consequences of Reproductive Tolerance to 2,4-D

Surprisingly, Dow does not report whether or not DAS-40278-9 corn can be sprayed after the V8 stage of development without injury (DAS Petition 2011). Although V8 is the latest stage that Dow proposes for 2,4-D applications, this is well before tassel maturation and pollen shed, and is also early enough in the season that there could be weed problems after that in some conditions. If later applications of 2,4-D are safe for DAS-40278-9 corn, and weed pressure occurs, surely some growers will figure this out and will take the risk of doing an application that is not warranted by Dow or allowed in the label.

Applications later in the season may result in higher 2,4-D residues and metabolites in forage and fodder, grain, and also in pollen itself. Drift from later applications may impact different crops and wild species than earlier applications. (Olszyk et al.. 2004)

Dow is undoubtedly aware that growers will use the technology in ways that are most useful to them (Anderson 2005). In 2005, Dow introduced a Bt cotton event called "WideStrike", often stacked with a Roundup Ready trait in popular PhytoGen varieties. At this time glyphosate-resistant weeds were becoming a problem in cotton, and "[m]ostly by accident, and often serendipitously, some cotton growers found they could take a shortcut and use Widestrike-containing Phytogen varieties and spray them with glufosinate" (Roberson 2011). Dow had used a glufosinate-resistance gene as a selectable marker in the engineering process, but had not intended it to be used agronomically, so had not advertised this property. Glufosinate is now used, sometimes in addition to glyphosate, to control glyphosate-resistant Palmer amaranth and giant ragweed (Robinson 2010). Growers are willing to risk some injury to their cotton, and the loss of warranty from Dow, to manage these intractable weeds. Both Dow and Bayer, the maker of the herbicide, strongly condemn this practice, but farmers still do it because it is useful. It is also not technically illegal, apparently ("It's controversial. It breaks rules, but not laws." Golden 2010), since glufosinate is approved by the the EPA for use in cotton at these rates (Roberson 2011).

With such high levels of AAD-1 protein in pollen, it is reasonable to assume that there will be good reproductive tolerance to 2,4-D, although it is not certain without results of tolerance tests. For example, Thomas et al.. (2004) reported high levels of EPSPS in pollen of the Roundup Ready corn event NK603, but pollen of that corn was still negatively affected when glyphosate was applied after the V4 stage. We request that EPA ask for results of reproductive tolerance tests, and discuss the implications for impacts of DAS-40278-9 corn that allow it to be sprayed at or closer to pollen shed.

Implications for Honey Bees of Effective AAD-1 Levels in Pollen

EPA must consider the potential harmful effects of the interaction of 2,4-D use on DAS-40278-9 corn and DAS-68416-4 soybeans on honeybees and the honey produced from the collection of corn pollen. Corn produces a prodigious amount of large, protein-rich pollen (Lundgren 2009, p. 85; Roulston et al.. 2000), and honey bees near cornfields collect this pollen to feed their developing brood. Recent research from USDA scientists at Purdue University in Indiana found that "[m]aize pollen was frequently collected by foraging honey bees while it was available: maize pollen comprised over 50% of the pollen collected by bees, by volume, in 10 of 20 samples." (Krupke et al.. 2012, p. 2). A synthesis of 114 data sets in Switzerland showed corn to be the most common pollen source for honey bees there, too, reporting corn in the top five most common pollen sources for over half of the studies, followed by clover and dandelions (Keller et al.. 2005).

Many honey bees do live near cornfields during pollination. According to Krupke and Hunt (2012) "…[m]ost commercial pollinator honey bees in the US spend May through October in the Upper Midwest where these crops [e.g., corn] dominate the landscape."

Since corn pollen can make up the bulk of pollen collected by a substantial population of honey bees, it is even more important to know whether pollen of DAS-40278-9 corn accumulates 2,4-D or other herbicide residues and metabolites differently than does conventional corn. However, information on 2,4-D levels in corn pollen was not found in the scientific literature.

If corn encountered 2,4-D during pollen development from direct application or drift, or if 2,4-D or metabolites were redistributed in the plant - from earlier applications - during growth, presence in pollen would be expected. Note that tassels begin to form just two weeks after corn emergence (Thomas et al.. 2004, p. 732, citing Kiesselbach 1992). Other phloem-translocated herbicides, such as glyphosate, do accumulate in pollen along with nutrients, because developing anthers and pollen are strong "sinks." There is evidence that 2,4-D also travels to anthers because it causes male-sterility (Hsu and Kleier 1990), similar to the action of glyphosate (Yasuor et al.. 2006). Other systemic pesticides are common contaminants of corn pollen (Mullin et al.. 2010, Burlew 2010).

Pollen of DAS-40278-9 corn may be protected from the toxic effects of 2,4-D because of the high expression of AAD-1, and so it may accumulate more 2,4-D and other herbicide substrates than conventional corn: if the pollen remains viable, it will be a stronger sink for a longer period of time (Geiger and Bestman 1990, Chen et al.. 2006). Also, the profile of metabolites is likely to be different, with more DCP-conjugates, able to release free DCP during use by developing bees.

There have been a few studies showing toxicity of 2,4-D itself to bees. According to Burlew (2010), "…Papaefthimiou et al.. (2002) found cell death in the isolated atria of the honey bee heart (*Apis mellifera macedonica*) after exposure to the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). Only 1 µM (micro mol) of 2,4-D was required to reduce the force and frequency of heart contractions by 70% in 20 minutes. The honey bee is much more sensitive to this chemical than other insects tested, including the beetle *Tenebrio molitor*, which required more than 1000 µM of 2,4-D to produce the same result." (Papaefthimiou C., V. Pavlidou, A. Gregorc and G.Theophilidis. 2002. The action of 2,4-dichlorophenoxyacetic acid on the isolated heart of insect and amphibian. Environmental Toxicology and Pharmacology 11: 127–140; as cited in Burlew 2010, p. 49.) Also, the EPA describes a study feeding 2,4-D-formulation added to sugar water to young bees, and uses the LD50 values from that study in their risk assessments for terrestrial invertebrates (US-EPA 2009, p. 112). EPA also cites a study showing that earthworms are more sensitive to 2,4-DCP than to 2,4-D acid (US-EPA 2009, p. 112). However, because 2,4-DCP is not normally a major degradation product of 2,4-D, EPA discounts the importance of DCP for toxicity (US-the EPA 2009, p. 100, citing Wahl and Ulm, 1983). They do not consider DCP conjugates since these also will be at very low levels in conventional plant tissues.

Finally, the AAD-1 enzyme itself may retain its activity in honey, even during digestion by immature bees, able to degrade herbicides brought in from sources other than DAS-40278-9 corn into possible toxins (Grogan and Hunt 1979).

Taken together, the fact that honey bees are likely to collect pollen of DAS-40278-9 corn after it has been sprayed with 2,4-D (and other herbicides that are substrates of the engineered AAD-1 protein), and that resulting residues and metabolites are likely to be different from those in conventional corn, we request that the EPA consider the impacts to honey bees and other pollinators, as in the guidelines for analyzing impacts of transgene products on bees set out by Malone and Pham-Delègue, for example (2001, p. 299 – 300). Impacts of 2,4-D use on DAS-40278-9 corn to other animals that are likely to use corn pollen should also be examined in light of the activity of these high levels of AAD-1 in DAS-40278-9 corn pollen.

Soybeans are also visited by honey bees that are located near soybean fields, and honey bees gather both nectar and pollen (Chiari et al.. 2005, see references cited in introduction). Surprisingly, very recent research in Iowa has shown that many species of wild pollinators also frequent soybean fields (Anonymous 2011, O'Neal and Dill 2012). The resultant cross-pollination many even boost yields under some conditions in this mainly self-pollinating crop. Therefore, impacts of the proposed new use of 2,4-D with DAS-68416-4 soybean on pollinators need to be considered, as well.

Increased Ingestion of 2,4-D Residues and Metabolites from DAS-40278-9 Corn and DAS-68416-4 Soybeans

Higher application rates with DAS-40278-9 corn, and new applications on post-emergent DAS-68416-4 soybeans, will also leave higher levels of 2,4-D residues and metabolites in the corn and soybean tissues (see the Comments-metabolism, pollen), and also higher concentrations of 2,4-D in runoff. Postemergence sprays at higher rates and without drop nozzles are highly likely for DAS-40278-9 corn, so we ask the EPA to consider potential risks to animal communities from eating DAS-40278-9 corn foliage or drinking runoff, including the unique metabolites as well as the parent 2,4-D residues (see metabolism, these Comments). We have the same concerns regarding 2,4-D choline use on DAS-68416-4 soybeans.

Impacts to Biodiversity of Using 2,4-D on DAS-40278-9 Corn and DAS-68416-4 Soybeans

1. Biodiversity in Corn and Soybean Fields

An example of harm to biodiversity in corn fields from an herbicide-resistant crop system is the recent decline in milkweed populations in Midwestern fields with probable impacts on monarch butterflies, as described in a series of studies (Hartzler and Buhler 2000, Hartzler 2010, Brower et al.. 2011, Pleasants and Oberhauser 2012). The basic conclusions are well stated in the abstract of the most recent publication by Pleasants and Oberhauser (2012):

> Abstract. 1. The size of the Mexican overwintering population of monarch butterflies has decreased over the last decade. Approximately half of these butterflies come from the U.S. Midwest where larvae feed on common milkweed. There has been a large decline in milkweed in agricultural fields in the Midwest over the last decade. This loss is coincident with the increased use of glyphosate herbicide in conjunction with increased planting of genetically modified (GM) glyphosate-tolerant corn (maize) and soybeans (soya).
>
> 2. We investigate whether the decline in the size of the overwintering population can be attributed to a decline in monarch production owing to a loss of milkweeds in agricultural fields in the Midwest. We estimate Midwest annual monarch production using data on the number of monarch eggs per milkweed plant for milkweeds in different habitats, the density of milkweeds in different habitats, and the area occupied by those habitats on the landscape.
>
> 3. We estimate that there has been a 58% decline in milkweeds on the Midwest landscape and an 81% decline in monarch production in the Midwest from 1999 to 2010. Monarch production in the Midwest each year was positively correlated with the size of the subsequent overwintering population in Mexico. Taken together, these results strongly suggest that a loss of agricultural milkweeds is a major contributor to the decline in the monarch population.
>
> 4. The smaller monarch population size that has become the norm will make the species more vulnerable to other conservation threats.

Here, 16 years after the introduction of Roundup Ready soybeans, major impacts of their widespread adoption are just now surfacing, with only a handful of researchers doing this kind of "post-market" ecological research. We call on EPA to consider these kinds of harms before rather than after registration of 2,4-D use on DAS-40278-9 corn and DAS-68416-4 soybeans.

The DAS-40278-9 corn cropping system will result in higher rates and more applications per season of 2,4-D, also a systemic herbicide, and likely to be used in addition to full rates of glyphosate. It is also reasonably foreseeable that in the future engineered soybeans will be treated with both 2,4-D and glyphosate, in rotation with DAS-40278-9 corn. Weed biodiversity, such as small populations of milkweed, will be dramatically reduced. Tolerant and resistant weeds will come to dominate, simplifying the number of plant species in the fields, and this by definition is a decrease in biodiversity. Also, with specialist herbivores, such as the monarch butterfly that rely completely on particular plant species, other kinds of plants will not substitute for their requirements.

Besides the direct toxicity of the increased herbicides used on DAS-40278-9 corn to plant population diversity within corn and soybean fields and ramifications for animals from changes in plant diversity, there will also be an increase in herbicide exposure from residues and their metabolites in DAS-40278-9 corn and DAS-68416-4 soybeans tissues (see metabolism, these Comments). A wide variety of animals feed on corn and soybean leaves, flower parts, and seeds, including many beneficial organisms such as honey bees (see pollen, these Comments).

Also, some animals may be over-sprayed during applications of herbicides, and others may brush against newly sprayed foliage, receiving higher herbicide doses in DAS-40278-9 corn and DAS-68416-4 soybeans with possible toxic impacts (US-EPA 2009, Freemark and Boutin 1995).

We ask the EPA to consider the full range of peer-reviewed ecological literature, in addition to any studies on ecological impacts that Dow provides.

2. Biodiversity Around Corn and Soybean Fields

In many areas of the country corn and soybean fields dominate the landscape, so it is important to manage field edges for biodiversity in order to maintain beneficial insects, birds, and other wildlife in the agroecosystem. Drainage ditches, hedgerows, riparian areas, and adjacent woodlots are vital habitat for a range of wild plants and animals in these heavily managed areas.

EPA needs to take into account the impacts that increased 2,4-D use in DAS-40278-9 corn and DAS-68416-4 soybean crop systems would have on those nearby habitats by using a realistic analysis of changes in 2,4-D use, in addition to usual assessments based on maximum label applications.

Increased drift and runoff from the greater use of 2,4-D with DAS-40278-9 corn and DAS-68416-4 soybeans crop systems is likely to alter the very habitats identified as being important for biodiversity (Freemark and Boutin 1995, Boutin and Jobin 1998, Olszyk et al.. 2004). Particular species of plants are more or less sensitive to these herbicides, and at different times of the year, so that a specific drift event is likely to change the population dynamics in affected areas. For example, 2,4-D drift in mid-spring may kill sensitive dicotyledonous wildflowers at seedling stages, cause male sterility in less sensitive grasses about to flower, and have little effect on younger grasses or still-dormant perennials (Olszyk et al.. 2004). These impacts may result in long-term changes in the mix of plant species, favoring annual weeds over native plants, for example (Boutin and Jobin 1998, Boutin et al.. 2008). And if there are 2,4-D resistant plants in these habitats, they will of course be better able to withstand drift and may become more abundant (Watrud et al.. 2011).

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).

There are studies of species composition in field margins (Kleijn and Snoeijing 1997) and hedgerows that border conventional fields compared with fields managed organically without herbicides (Boutin et al.. 2008) showing differences in plant populations that indicate just these sorts of species shifts from herbicide exposure. Also, "[i]n controlled experiments with plant communities, Pfleeger and Zobel (1995) demonstrated that variable species responses to herbicide exposure [including 2,4-D] may alter the competitive interactions within a community. Such shifts in a community could result in changes in frequency and production and even extinction of desired species…" (Olszyk et al.. 2004).

Recent experiments by EPA scientists have shown that drift levels of the broad-spectrum herbicide glyphosate alter population structures of plants that include some herbicide-resistant individuals, favoring an increase in those with the glyphosate-resistance trait. Differences in the populations persist years after the last "drift" incident, affecting the kinds of beneficial soil fungi present and growth of subsequently planted species, for example (Watrud et al.. 2011).

Animals depend on plant biodiversity for most of their needs, so it would be surprising if herbicide induced changes in plant populations had no effects on animal biodiversity around corn and soybean fields. Freemark and Boutin (1995) reviewed the literature on how herbicide use has affected wildlife, and found that, as expected, biodiversity has been affected in areas adjacent to sprayed crop fields, including types and abundance of small mammals and birds. An example of how drift levels of 2,4-D may impact animals has to do with the ability of 2,4-D to cause sterility in grasses that are in early stages of reproduction, and "…reproduction is critical for the ability of non-crop native plants to pass along their traits. Furthermore, many wildlife species depend upon seed production of non-crop plants for their food source." (Olszyk et al.. 2004). Many insects depend on abundant pollen, as well (Lundgren 2009).

Based on experiences with 2,4-D sensitive crops, natural areas miles from agricultural applications of 2,4-D may also be at increased risk from the use of greater amounts of the herbicide in corn and soybeans, since it can volatilize under certain conditions.

It is clear, then, that increased use of 2,4-D with the DAS-40278-9 corn and DAS-68416-4 soybean crop systems is likely to have negative impacts on biodiversity around corn and soybean fields, perhaps at some distance. 2,4-D choline, although designed to have less drift, will still move off-site, and the substantial increase in its use will likely more than offset whatever lower lower drift potential it may have.

VI. The Proposed New Use of 2,4-D Choline Salt on DAS-40278-9 Corn and DAS-68416-4 Soybeans May Affect Threatened and Endangered Species. Thus EPA Must Consult with Expert Agencies Pursuantto Section 7 of the ESA.

Section 7 of the ESA makes clear that Congress intended all federal agencies to participate in the conservation and recovery of threatened and endangered species. Section 7(a)(2) of the Act requires that "[e]ach Federal agency shall … insure that any action authorized, funded, or carried out by such agency … is not likely to jeopardize the continued existence of any endangered species or threatened species or result in destruction or adverse modification of habitat of such species which is determined … to be critical … ."[79]

Pursuant to Section 7 of the ESA, EPA has an independent duty to "insure" that Dow's proposed new use of 2,4-D on 2,4-D resistant corn and soybean will neither jeopardize any threatened or endangered species, nor harm any critical habitat, anywhere the proposed new use of 2,4-D may be applied.[80] As part of its risk assessment of Dow's Proposed New Use Registration Applications, EPA must determine whether the proposed use of 2,4-D "may affect" any listed species or critical habitat; if so, EPA must consult the expert wildlife agencies (FWS and/or NMFS) in making its final decision regarding whether to register the proposed new use of 2,4-D.

EPA's consultation duties under 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.

Harm from Increased 2,4-D Use on DAS-40278-9 Corn and DAS-68416-4 Soybeans to Threatened & Endangered Species

All of the harms from increased use of 2,4-D on DAS-40278-9 corn and DAS-68416-4 soybeans to plants, animals, and other organisms, and to their habitats, discussed above, apply to species that are at risk of extinction. Endangered species near fields planted to DAS-40278-9 corn and DAS-68416-4 soybeans 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.

However, the stakes of herbicide exposure are higher, especially for plants: "Determination of herbicide effects to threatened and endangered plant species in native plant communities is especially critical. In the US, the federal government has listed over 500 plant species as threatened and endangered and the Nature Conservancy considers 5,000 of the 16,000 native species to be at risk. Almost 50% of these species are annuals that are dependent on seed production or the seed bank for survival, thus any reproductive effects of herbicides could affect their survival." (Olszyk et al.. 2004).

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[79] 16 U.S.C. § 1536(a)(2) (emphasis added).

[80] *Wash. Toxic Coal. V. EPA*, 413 F.3d 1024, 1035 (9th Cir. 2005) (agency has burden to prove its action is non-jeopardizing.).

Not only will more endangered species be exposed to the 2,4-D used with DAS-40278-9 corn and DAS-68416-4 soybeans as they are grown on land already planted to corn and soybeans, but because cultivation of these crops could well expand to new land given the expansion of cropland devoted to corn and soybeans. More endangered species are likely to find themselves near DAS-40278-9 corn crop systems, because at least some of the expansion is occurring by conversion of natural areas and Conservation Reserve Program land not recently farmed. These areas are more likely to harbor wild native organisms than land intensively farmed every year for decades (Brooke et al. 2009).

2,4-D was recently assessed in a Pesticide Effects Determination by the EPA (US-EPA 2009) and Biological Opinion from the National Marine Fisheries Service (NMFS 2011), both finding adverse impacts to several specific endangered species. The detailed information in these reports leads to the reasonable conclusion that almost all threatened and endangered species would be similarly impacted by 2,4-D use at rates like those proposed for DAS-40278-9 corn and DAS-68416-4 soybeans.

Specifically, EPA evaluated the risks of 2,4-D use to the threatened California red-legged frog (CRLF) and Alameda whipsnake (AW) and their critical habitats. This frog lives in both coastal and interior mountain ranges, using both water bodies and riparian and upland sites; and eats wide variety of plant and animal foods during its aquatic and terrestrial phases, including insects, other amphibians and an occasional small mammal. The Alameda whipsnake is found in scrub and chaparral, as well as riparian areas, grasslands and savannas; also has a varied diet that includes insects, amphibians, other reptiles, small mammals and birds (US-EPA 2009, p. 55).

Just about all of these habitats and prey types are potentially impacted by use of 2,4-D at agricultural rates, either directly or indirectly (US-EPA, summary of effects p. 11 – 25). Looking at specific use of 2,4-D applied with ground equipment on field corn or popcorn, for example, the “level of concern” is exceeded for direct effects on the terrestrial habitat of CRLF and with aerial applications for AW. “Level of concern” is exceeded for indirect effects on prey, including terrestrial invertebrates and plants, frogs, small mammals (CRLF and AW), and also for birds (AW). Small mammals were also likely to be directly impacted, based on incident reports. After going through the whole assessment process, EPA concluded that use of 2,4-D in a variety of scenarios, including on corn, was “likely to adversely affect” both the CRLF and AW via indirect effects on prey, and was likely to modify critical habitat (US-EPA 2009, p. 175 – 179). They initiated a formal consultation with FWS based on these conclusions.

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. This leads to the reasonable expectation that the EPA would find that use of 2,4-D on DAS-40278-9 corn and DAS-68416-4 soybeans would similarly be “likely to adversely affect” prey and habitats of threatened and endangered animals found near these cornfields.

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). 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 and soybean cultivation and thus could be impacted by the increased use of 2,4-D on DAS-40278-9 corn and DAS-68416-4 soybeans.

Ingestion of DAS-40278-9 Corn and DAS-68416-4 Soybeans

Finally, we ask that EPA take into account the potential toxicity of DAS-40278-9 corn and DAS-68416-4 soybeans, after applications of 2,4-D choline, to listed species that might eat corn and soybean leaves, roots, stems, or flower parts. Migrating birds, for example, eat parts of the corn plant. Bees consume corn and soybean pollen, and soybean nectar (see pollen gene expression, these Comments), 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. Corn and soybeans are planted widely, thus many species are potentially impacted.

VII. EPA Must Critically Analyze the Potential Health Effects of the Proposed 2,4-D Use

EPA has a duty under FFDCA to ensure that the proposed changes in use patterns of 2,4-D choline salt on 2,4-D resistant corn and soybeans will cause "no harm" to humans, particularly infants and children, "from aggregate exposure" to 2,4-D.[81] The FFDCA requires that where use of a pesticide will result in any pesticide residue being left on food, the EPA must either set a "tolerance" level for the amount of allowable pesticide residue that can be left on the food, or set an exemption of the tolerance requirement.[82] The tolerance or exemption requirements apply to raw agricultural commodities such as DAS-402780-9 corn and DAS-68416-4 soybeans.[83] Under the FFDCA, EPA must "establish or leave in effect a tolerance for a pesticide chemical residue in or on a food <u>only if</u> the EPA Administrator determines that the tolerance is safe".[84] For a tolerance level to be "safe," the statute requires EPA determine "that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."[85] "Aggregate exposure" includes not only dietary exposure through food consumption, but also includes "exposures through water and residential uses."[86]

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[81] 21 U.S.C. § 346a(b)(2)(A).

[82] 21 U.S.C. § 346a(1).

[83] 21 U.S.C. § 321(r) defines "raw agricultural commodities" as "any food in its raw or natural state, including all fruits that are washed, colored or otherwise treated in their unpeeled natural form prior to marketing."

[84] 21 U.S.C. § 342(a)(2)(A) (emphasis added); *see also* 40 C.F.R. § 180.1(f).

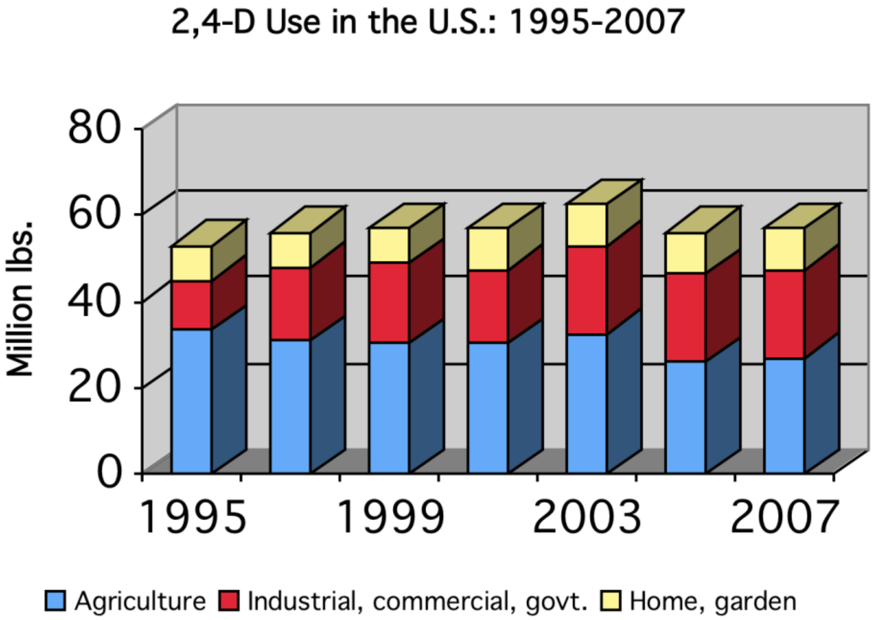
[85] 21 U.S.C. § 346(a)(2)(A)(ii).

[86] *Natural Res. Def. Council v. Whitman*, No. C 99-03701-WHA, 2001 WL 1221774 (N.D. Cal. Nov. 7, 2001).

Existing Use of 2,4-D

2,4-D is the most widely used of at least 10 compounds in the chlorophenoxy class of herbicides, which include 2,4,5-T, MCPA, dichlorprop, and mecoprop.[87] 2,4,5-T, which together with 2,4-D formed the Agent Orange defoliant used in the Vietnam War, was first subject to restrictions in 1970 on the basis of numerous studies demonstrating harm to human health that were generally linked to dioxin contaminants generated during its manufacture. However, Dow was able to extend its use for many applications through legal appeals and injunctions (Trost 1984, p. 169), until its registration was finally cancelled by EPA in 1985.

2,4-D is the main ingredient in over 1,500 pesticide products (EPA 2007). Overall use of 2,4-D in the U.S. has ranged from 53 to 63 million lbs. per year since 1995 (see chart), with the agricultural share declining from roughly 2/3 of overall use in 1995 to somewhat less than one-half by 2007, the latest year for which we have EPA data. 2,4-D has been the most heavily used pesticide in both the home/garden and the commercial-industrial-government sectors since 1995. Home/garden use of 2,4-D has increased slightly from 1995 to 2007 (from 8 to 9.5 million lbs./year), while industrial/commercial/ government use has nearly doubled over this period (11.5 to 20.5 million lbs./year). 2,4-D usage in 2007 is shown in Table 1.



Based on EPA's Pesticide Industry Sales and Usage reports from various years. Figures based on mid-points of ranges reported by EPA.

Use of 2,4-D in the United States (2007)		
Sector	Amount used (min.) (lbs. a.i.)	Amount used (max.) (lbs. a.i)

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[87] http://www.weedscience.org/summary/ChemFamilySum.asp?lstActive=&lstHRAC=24&btnSub2=Go

Home	8,000,000	11,000,000
Industry, commercial, government	19,000,000	22,000,000
Agriculture	25,000,000	29,000,000
TOTAL	52,000,000	62,000,000

Source: EPA Pesticide Use (2011). Note: EPA reports usage in ranges. a.i. = active ingredient.

The leading agricultural uses of 2,4-D in terms of pounds applied are pasture/rangeland and wheat, followed by soybeans and corn (EPA 2005, p. xi). USDA NASS data discussed above show that 7 million lbs. of 2,4-D are applied to corn (3.3 million) and soybeans (3.7 million), roughly ¼ of total agricultural use. This situation would change dramatically if the proposed registrations are granted. Based on the 2,4-D use projections discussed in above, even modest adoption of Enlist corn and soybeans would likely increase agricultural usage of 2,4-D to 100 million lbs.; with widespread adoption and rising rates to control 2,4-D-resistant weeds, 200 million lbs. is a clear possibility. This would represent a four- to nearly eight-fold increase in overall agricultural use of 2,4-D, and a two to over four-fold increase in overall use. While these estimates of increased use may appear high, they are entirely consistent with the six- to seven-fold rise in agricultural use of glyphosate that has in fact occurred since the introduction of Roundup Ready crops: from 25-30 million lbs. in 1995 to 180-185 million lbs. in 2007.[88]

This vastly increased use would result in much greater exposure to 2,4-D, especially for farmers and pesticide applicators.

Impacts on Farmers and Pesticide Applicators

Studies show that farmers from many countries experience higher rates of certain cancers – leukemia, non-Hodgkin's lymphoma, multiple myeloma, soft-tissue sarcoma, and cancers of the skin, lip, prostate, brain and stomach (Blair & Zahm 1995). The excess of certain cancers in farmers is striking in light of their lower mortality from most other causes. Which factors in the farming life might explain the fact that farmers are more likely to contract and die from certain cancers?

Several lines of evidence suggest that exposure to pesticides is one important factor. In broad terms, increased cancer risk coincides with pesticide use in time and space. The overall incidence of cancer in the U.S. population has risen sharply over the period of extremely rapid growth in the use of pesticides and other industrial chemicals, by 85% from 1950 to 2001 (Clapp et al. 2006). Significant associations have been found between agricultural chemical use and cancer deaths in 1,497 rural U.S. counties (Steingraber 2010, p. 64).

Because direct human experimentation is unethical, the chief means to determine whether exposure to pesticides has adverse health effects is epidemiological studies. The rate or incidence of a disease in a population exposed to a particular pesticide is compared to that of a

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[88] Glyphosate use in agriculture almost certainly exceeds 200 million lbs. today, given the sharp rise in Roundup Ready corn adoption from 2007 (52%) to 2011 (72%).

reference population of those not exposed to it. Any excess disease in the exposed population suggests that the pesticide is a risk factor that increases the likelihood of contracting the disease.

2,4-D and Non-Hodgkin's Lymphoma

Numerous epidemiological studies have reported an association between exposure to 2,4-D and non-Hodgkin's lymphoma,[89] a cancer of the white blood cells that kills 30% of those afflicted. The first studies linking 2,4-D with non-Hodgkin's lymphoma were published in Sweden thirty years ago.[90] Some of these studies also found an association with soft-tissue sarcoma, a rare and frequently fatal cancer.[91] More recently, studies published in Canada and Italy have supported these results, as have studies performed by researchers at the National Cancer Institute.[92,93,94]

Evidence from other occupational groups exposed to 2,4-D support the association found in studies of farmers. A recent study by The Dow Chemical Company of their pesticide production workers reported a 36% increase in non-Hodgkin's lymphoma in workers classified as exposed to 2,4-D, but the authors concluded the result was not statistically significant.[95]

A retrospective study of golf course superintendants (based on death certificates) revealed a proportionate mortality ratio for NHL of 237, meaning that death from NHL was 2.37 times more likely in this group than in the general population (Kross et al. 1996). Many golf course superintendants have a history of pesticide application. 2,4-D is heavily used on golf courses. For instance, the authors note that 2.4-D is the most common herbicide applied to Iowa golf courses, representing about 42% of the total amount of herbicide applied.

Additional evidence of a link between 2,4-D and NHL comes from studies of canine malignant lymphoma conducted by National Cancer Institute scientists, which showed increased

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[89] *See, e.g.*, Hardell L, Eriksson M. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. Cancer 85:1353-1360, 1999. Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, Fraumeni JF. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 256:1141-1147, 1986. McDuffic HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW. Non-Hodgkin's lymphoma and specific pesticide exposures in men: Cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev. 10(11):1155-63, 2001; Mills PK, Yang R & Riordan D. Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988-2001. Cancer Causes and Control 16: 823-830, 2005. Selected studies included in supporting materials.

[90] Hardell L, Eriksson M, Lenner P, et al.. Malignant lymphoma and exposure to chemicals especially organic solvents, chlorophenols and phenoxy acids: A case-control study. Br J Cancer 43:169-176, 1981.

[91] Hardell L, Sandstrom A. Case-control study: Soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Br J Cancer 39:711-717, 1979.

[92] McDuffie HH, Pahwa P, Robson D, Dosman JA, Fincham S, Spinelli JJ, McLaughlin JR. Insect repellents, phenoxyherbicide exposure, and non-Hodgkin's lymphoma. J Occup Environ Med 47(8):806-16, 2005.

[93] Miligi L, Costantini AS, Veraldi A, Benvenuti A; WILL, Vineis P. Cancer and pesticides: an overview and some results of the Italian multicenter case-control study on hematolymphopoietic malignancies. Ann N Y Acad Sci 1076:366-77, 2006.

[94] Chiu BC, Blair A. Pesticides, chromosomal aberrations, and non-Hodgkin's lymphoma. J Agromedicine 14(2):250-5, 2009. Zahm SH, Blair A. Pesticides and non-Hodgkin's lymphoma. Cancer Res 1;52(19 Suppl):5485s-5488s, 1992.

[95] Burns C, Bodner K, Swaen G, Collins J, Beard K, Lee M. Cancer Incidence of 2,4-D Production Workers. Int J Environ Res Public Health 8:3579-3590, 2011.

incidence of the canine equivalent of NHL in dogs exposed to 2,4-D-treated lawns (Hayes et al. 1991, 1995).

In light of this abundant evidence, it is not surprising that scientists at the National Cancer Institute regard the link between 2,4-D and NHL as "the strongest association" yet found in "epidemiological investigations focusing on pesticides" (Zahm & Blair 1995).

NHL is a disease of the lymphocytes, or white blood cells. Cancer involves uncontrolled cell growth, or proliferation. Exposure to 2,4-D increases lymphocyte replication in humans. One study of pesticide applicators found increasing lymphocyte proliferation of 11 to 14 percent greater than normal in the applicators in a manner that was directly related to 2,4-D absorbed dose (Figgs et al. 2000). This finding was confirmed in a follow-up study, showing a 12-15% rise in lymphocyte proliferation, with a further indication that higher-dose exposures may cause direct damage to white blood cells, thereby increasing the risk of lymphoid cancer in humans (Holland et al. 2002). These findings are consistent with, and provide mechanistic support for, the frequently-reported epidemiologic evidence linking 2,4-D exposure to non-Hodgkin's lymphoma in humans discussed above.

In 2010, approximately 65,540 people in the United States were diagnosed with non-Hodgkin's lymphoma. The incidence of this disease in the United States has increased to about double the rate seen in the 1970s, even when adjusted for population size and age.[96] While this epidemic rise in NHL has slowed since 1990, the incidence rate continues to increase (see SEER chart below). As noted above, studies from around the world have shown that farmers are more likely to contract NHL than the general population, despite having a lower incidence of cancer overall, while numerous epidemiology studies have found significant associations between 2,4-D exposure and NHL. Other occupational groups exposed to 2,4-D have also been found to suffer higher rates of NHL, and animal epidemiology provides further support. In addition, several studies demonstrating increased lymphocyte proliferation with exposure to 2,4-D offer mechanistic support for this epidemiology. Based on these multiple, mutually supporting lines of evidence, it is reasonable to conclude that exposure to 2,4-D is very likely responsible for some portion of non-Hodgkin's lymphoma cases each year.

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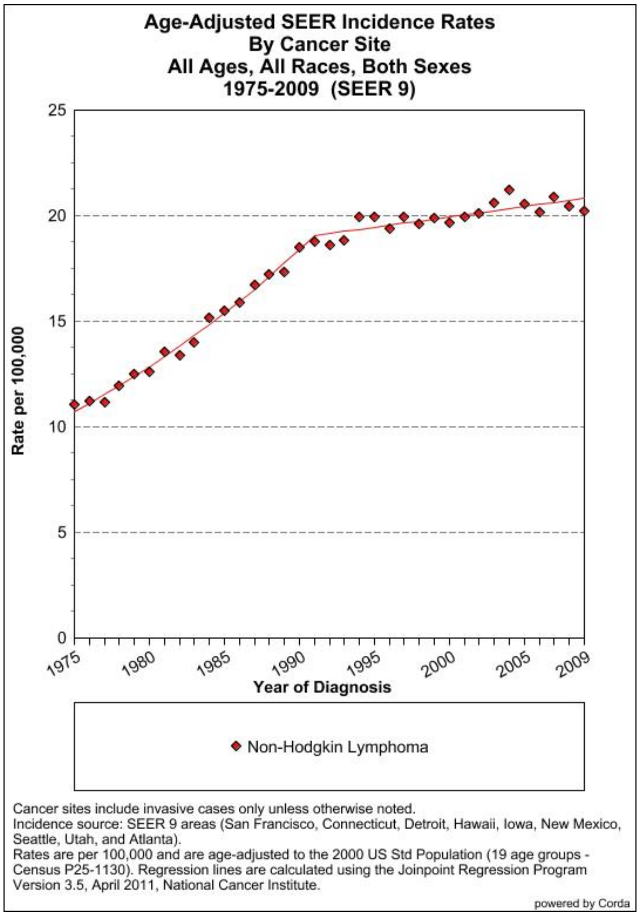
[96] Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.


Age-Adjusted SEER Incidence Rates
By Cancer Site
All Ages, All Races, Both Sexes
1975-2009 (SEER 9)

Cancer sites include invasive cases only unless otherwise noted.
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.5, April 2011, National Cancer Institute.

Downloaded from http://seer.cancer.gov/, 6/21/12.

It should be noted that EPA's classification of 2,4-D as a Category D chemical ("not classifiable as to human carcinogenicity") is out of line with assessments by other authoritative bodies that take epidemiology more seriously, not to mention those by leading epidemiologists at our National Institutes of Health. For instance, the governments of Norway, Sweden and Denmark have banned 2,4-D use (Boyd 2006), together with 2,4,5-T, largely on the basis of the epidemiological associations to non-Hodgkin's lymphoma and related cancers. The World Health Organization's International Agency for Research on Cancer (IARC) classifies the chlorophenoxy herbicide group, of which 2,4-D is by far the most widely used member, as "possibly carcinogenic to humans" (IARC 1987). WHO IARC finds "limited evidence in humans" for chlorophenoxy herbicides as causative agents for multiple cancers (i.e. "multiple sites") (IARC 2012). EPA incorrectly states that IARC has not assessed chlorophenoxy herbicides for carcinogenicity (EPA 2007).

The Institute of Medicine (IOM) of the National Academy of Sciences has conducted biennial reviews of the toxicity of Agent Orange compounds (2,4-D, 2,4,5-T and dioxins) for the Veteran's Administration for many years. Recognizing the difficulty in separating out the effects due to each, the IOM's approach is to assesses the toxicological evidence for what it terms "chemicals of concern," which encompass all three components of Agent Orange – 2,4-D, 2,4,5-T and the class of dioxin compounds. Like WHO's IARC, the IOM Committee seriously considers and gives substantial weight to human epidemiological evidence, in stark contrast to EPA's dismissal of the same.

In consequence, the IOM Committee's most recent review (IOM 2012) concludes as follows:

There is sufficient evidence of an association between exposure to the chemicals of interest and the following health outcomes:

- Soft-tissue sarcoma (including heart)
- Non-Hodgkin's lymphoma
- Chronic lymphocytic leukemia (CLL) (including hairy cell leukemia and other chronic B-cell leukemias)
- Hodgkin's disease
- Chloracne

Finally, EPA's assessment of the cancer risks posed by 2,4-D conflicts with the views of leading U.S. epidemiologists at the National Cancer Institute, part of the National Institutes of Health. As noted above, Dr. Aaron Blair and Dr. Sheila Hoar-Zahm regard the link between 2,4-D and NHL as "the strongest association" yet found in "epidemiological investigations focusing on pesticides" (Zahm & Blair 1995).

Parkinson's Disease

Exposure to 2,4-D (an organochlorine compound) has been associated with a significant, more than 2-fold increased risk of Parkinson's disease (odds ratio = 2.59 (1.03-6.48)) in subjects occupationally exposed to it (Tanner et al 2009). The authors of this paper note that other organochlorines have also been associated with increased risk of Parkinson's disease (PD), that excessive amounts of organochlorines have been found in the brains of people with PD, and that 2,4-D is known to affect dopaminergic neurons in experimental settings, all of which strengthen the association of 2,4-D with PD found in this study.

Spermatic Abnormalities and Birth Defects

Male pesticide applicators who applied 2,4-D exhibited lower sperm counts and more spermatic abnormalities than men who were not exposed to this herbicide.[97] In Minnesota**,** children of pesticide applicators in wheat-growing regions of Minnesota with heavy use of chlorophenoxy herbicides like 2,4-D had a disproportionately higher incidence of birth anomalies than in non-crop regions or where these herbicides were less used; moreover, this increased incidence was most pronounced among infants who were conceived in the spring, when herbicide use is greatest (Garry et al 1996). Another study that encompassed agricultural counties in Montana, North Dakota and South Dakota as well as Minnesota found significant increases in malformations of the circulatory and respiratory systems, particularly among infants conceived between April and June in wheat-growing counties where chlorophenoxy herbicides

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[97] Lerda D, Rizzi R. Study of reproductive function in persons occupationally exposed to 2,4-D. Mutation Research 262: 47-50, 1991.

such as 2,4-D are heavily used (Schreinemacher 2003).

Infants and Young Children

It is well-known that infants and young children are more susceptible to adverse effects of toxins, including pesticides, than adults. 2,4-D is often tracked into homes, where it may persist for months on carpets, leading to potentially significant exposures of infants and toddlers who crawl on the floor and consume 2,4-D through hand-to-mouth contact.[98]
Farm children as a group, as well as children of homeowners who use 2,4-D-containing herbicides on their lawns, are at greater risk of exposure to and adverse effects from 2,4-D. As noted above, 2,4-D is the leading herbicide used in the home/garden sector.

Liver Toxicity

Leonard et al (1997) documented a case of acute hepatitis in a golfer who played on a golf course treated with 2,4-D, and who engaged in the common golfer practice of licking his golf balls. After exhaustive analysis of medical tests (e.g. liver enzyme assays) and ruling out other potential causes, the researchers concluded that there was "little doubt that our patient's hepatitis was due to ingestion of 2,4-D from his golf ball." A case of chronic hepatitis tending to cirrhosis was diagnosed in an avid golfer who had for many years frequently licked his golf balls (Johnston et al 1998). Though not confirmed to be due to 2,4-D exposure, the authors found no other cause that might explain the patient's condition.

Epidemiology vs. Animal Studies and Human Exposure Estimates

Because human experimentation is unethical, the medical community relies heavily on epidemiology to assess the potential hazards of environmental causes of disease in humans. EPA relies much more heavily on extrapolation from animal experiments to assessments of human exposure based on ideal world assumptions. Canadian physicians reviewing the toxicology of 2,4-D expressed the frustration that many medical professionals must feel regarding the EPA's approach:

> "…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."[99]

The strength of using animal studies to assess pesticide risks is that they permit strict control of the conditions of exposure, including calibrated doses to facilitate identification of dose-response relationships; exclusion of confounding environmental factors, such as exposure to other

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[98] Nishioka MG, Lewis RG, Brinkman MC, Burkholder HM, Hines CE, Menkedick JR. Distribution of 2,4-D in air and on surfaces inside residences after lawn applications: comparing exposure estimates from various media for young children. Environ Health Perspect. 2001 Nov;109(11):1185-91; Marcia G. Nishioka et al., Measuring Lawn Transport of Lawn-Applied Herbicide Acids from Turf to Home: Correlation of Dislodgeable 2,4-D Turf Residues with Carpet Dust and Carpet Surface Residues, 30 ENVTL. SCI. & TECH. 3313 (1996).

[99] Sears, M et al (2006). "Pesticide assessment: protecting public health on the home turf," Paediatr Child Health 11(4): 229-234.

compounds; and sacrifice of animals for histological and other investigations to ascertain mechanisms of action and tissue damage. However, animal studies as they are conducted by industry for EPA have many weaknesses which far outweigh their strengths.

Animal studies generally utilize only the active ingredient of a complex pesticide formulation, and therefore cannot gauge the impacts of the active ingredient under conditions of actual use, which include potential independent, additive or synergistic effects of inert ingredients in the formulation.[100] Likewise, EPA for the most part does not require any animal testing for mixtures of pesticides, or otherwise account for exposure to multiple pesticides. It is also difficult to relate any adverse impacts found in animal studies to humans due to interspecies differences in susceptibility, which may be greater or lesser in human beings. Inferences from animal studies to human beings require a multitude of often highly dubious assumptions. First, safety factors intended to account for potentially greater human susceptibility to a particular effect found in animals are often applied in complete absence of any mechanistic understanding of that effect, and hence may be insufficiently protective in some cases. Second, such inferences rely on highly theoretical human exposure estimates that are often based on ideal-world assumptions. In particular, EPA often prescribes measures (e.g. personal protection equipment, reentry intervals) intended to reduce farmer or applicator exposure to a pesticide, and bases exposure estimates on perfect compliance with such prescriptions, despite abundant evidence that they are often not observed (Jacobs & Clapp 2008). Finally, animal studies are most commonly conducted by the pesticide's manufacturer or by a third party contracted by the manufacturer, introducing conflict of interest concerns.

The strength of epidemiology is that it bypasses these weaknesses of the animal experiment-exposure assessment model to deliver evidence on real world outcomes. For instance, any adverse impacts of a pesticide's inert ingredients are automatically accounted for, as are real-world exposures from imperfect observance or neglect of exposure mitigation measures.

EPA's Treatment of Epidemiological Studies Involving 2,4-D

While EPA does not completely ignore epidemiology, its treatment of the evidence reveals either extreme bias against, or fundamental misconceptions about the nature of, the science. In EPA's 2005 reregistration of 2,4-D, the Agency found that none of the recent epidemiological studies "definitively linked" human cancer cases to 2,4-D (EPA 2005, p. 20). Similarly, in a recent review of epidemiological studies on 2,4-D and cancer (EPA 2004), EPA health statistician Jerome Blondell quotes from a review article on 2,4-D epidemiology: "Overall, the available evidence from epidemiological studies is not adequate to conclude that any form of cancer is causally associated with 2,4-D exposure." As EPA acknowledges, the authors of this deeply flawed review were funded by 2,4-D manufacturers (Garabrant & Philbert 2002).[101] Surprisingly, Dr. Blondell offers no critical comment on this statement. He is

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[100] This is not an inherent liability of animal experiments, but the great majority of animal trials involving pesticides are in fact carried out with the active ingredient alone.

[101] See EPA (2004) for full reference. Garabrant & Philbert, environmental health scientists at the University of Michigan, apparently have no familiarity with modern industrial agriculture. In their zeal to exonerate 2,4-D, they make the following wildly inaccurate statement: "Moreover, herbicides are not used on a substantial proportion of farms." On the contrary, herbicides are ***far*** more widely and heavily used than any other class of pesticides. Scientists who have such

apparently unaware that epidemiology, by its by its very nature, cannot definitively prove causation.[102] Using precisely the same rationale, tobacco industry apologists long denied the epidemiology implicating tobacco smoking as a prime cause of lung cancer based on ignorance of the specific cellular mechanisms involved. While it may be safely assumed that 2,4-D puts far fewer lives at risk than smoking, this fact offers little solace to the farmer who contracts a deadly cancer from use of an EPA-approved pesticide he/she naturally assumes is safe.

In practice, EPA's treatment of epidemiological studies appears to be somewhat more nuanced, but underlying it is the demand for the "definitive link" of mechanistic causation that epidemiology cannot by its very nature deliver. Dr. Blondell repeatedly dismisses epidemiology studies on 2,4-D and cancer on the grounds that exposure to other pesticides cannot be ruled out as potential contributing factors (EPA 2004). It is important to understand that dismissal on this basis effectively excludes ALL epidemiology studies as irrelevant, since one cannot expect to find any farming or other pesticide-exposed population that is not exposed to one or more pesticides in addition to the one of interest (e.g. 2,4-D). This approach is equivalent to demanding that an epidemiological study of a pesticide be what it cannot be, either ethically or in practical terms: a perfectly controlled experiment involving intentional dosing of a human population with that single pesticide.

This review also suggests that EPA does not assess pesticides with common mechanisms of action as a group for the purposes of epidemiology. For instance, EPA (2004) dismisses a Canadian study (McDuffie et al 2001) that found a significant association between exposure to 2,4-D and NHL (adjusted odds ratio = 1.32, 95% confidence interval 1.01 to 1.73) primarily on the grounds that the subjects were also exposed to another, much lesser used, phenoxy herbicide (mecoprop) and the closely related auxin dicamba. The authors apparently utilized common statistical tools used in epidemiology to isolate the effects of 2,4-D, but not to the satisfaction of EPA. Dr. Blondell also discounts the study on the illegitimate grounds that stronger associations were found to other risk factors. It is relevant to note here that 2,4-D is far more widely used than any other phenoxy herbicide. Assuming that phenoxy herbicides have a similar mechanism of action in disease causation, any effects attributed to phenoxy herbicides where more than one is used would in most cases be attributable primarily to 2,4-D. For instance, EPA figures show that the second most heavily used phenoxy in agriculture is MCPA, just 2-4 million lbs. of which were used in contrast to 27 million lbs. of 2,4-D (2007). The magnitude of exposure to 2,4-D would of course increase dramatically under the proposed registrations.

A deeper criticism of the unrealistic demand that epidemiological studies deliver definitive evidence of a causative link between exposure to a single pesticide and a disease outcome is our scientific understanding that disease causation is often multifactorial (see generally Steingraber 2010). What EPA views as "confounding variables" may in some cases be "contributing factors." The removal of a pesticide implicated as a risk factor for a disease will in many cases mitigate or eliminate the adverse health outcomes associated with exposure to it in combination with other pesticides or risk factors.

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ignorance of basic facts about herbicide use in modern agriculture are simply not qualified to conduct an epidemiological review of studies on exposure to an herbicide.

[102] "Epidemiological studies can never prove causation; that is, it cannot prove that a specific risk factor actually causes the disease being studied." http://pmep.cce.cornell.edu/profiles/extoxnet/TIB/epidemiology.html.

If taken seriously, the multifactorial nature of much disease would lead naturally to a very different pesticide assessment regime in which "confounders" were viewed as potential contributing factors rather than grounds for dismissal. Similarly, it is very likely that the multiple factors involved in disease causation helps to explain the inconsistent results in many epidemiological studies, including those involving 2,4-D exposure.

Dioxin Contaminants in 2,4-D

EPA generally appears to believe that any adverse health outcomes associated with 2,4-D by medical science are attributable to dioxin contaminants, and that dioxin levels in 2,4-D have been reduced sufficiently over the past several decades to eliminate such adverse effects.

However, it is not at all clear that dioxins associated with 2,4-D are low enough to be of no concern. First, EPA acknowledges that 2,4-D is the nation's seventh largest source of dioxins, based on industry tests conducted in the early 1990s (EPA 2005, p. 83). This ranking of 2,4-D would likely be considerably higher if EPA were to include dioxins emitted in the 2,4-D production process. While CFS does not have data on dioxin emissions associated with 2,4-D production, the EPA's toxics release inventory does show that two Dow plants (Freeport Facility and Louisiana Operations) rank 3rd and 9th in dioxin emissions (EPA TRI 2010). Under the proposed registrations, 2,4-D use would increase dramatically. The release of dioxins into the environment would be greatly increased by the increased volume of dioxin-contaminated 2,4-D applied to agricultural fields, and through corresponding increases in any dioxins released from manufacturing plants due to expanded production.

Industry-conducted tests ordered by the EPA in a 1987 data call-in show that 2,4-D from early 1990s is still contaminated with significant levels of dioxins (EPA Dioxins in 2,4-D). Based on assurances from the pesticide industry's 2,4-D Task Force, EPA believes that the 2,4-D production process has been improved to sharply reduce dioxin contamination of 2,4-D below the levels reported by industry in 2,4-D from the early 1990s (EPA 2005, pp. 83-84). EPA stated that further dioxin testing on more recent batches of 2,4-D would be required to confirm industry claims of reduced dioxin contamination (EPA 2005, p. 84), an implicit admission that EPA regards those levels as unacceptable. But it is unclear whether such tests have been formally requested by EPA or submitted to the Agency; and the data, if any, have not been made publicly available. CFS is also unaware of any dioxin testing on 2,4-D choline in particular.

Australian researchers recently tested two 2,4-D formulations manufactured in 2005 and 2006, and found dioxin levels comparable to those found in 2,4-D made 10-20 years ago (Holt et al 2010). These findings at the very least cast doubt on industry claims of reduced levels of dioxin contaminants in 2,4-D, and point to the need for EPA to itself perform tests to determine dioxin levels in 2,4-D, or alternately to commission tests by independent laboratories or scientists with no financial ties to 2,4-D manufacturers. Allowing manufacturers to conduct their own tests for dioxin contamination of 2,4-D involves a clear conflict of interest.

As noted above, there are 1,500 formulations containing 2,4-D as the main ingredient, and they are produced by a multitude of different manufacturers. Such independent tests must be undertaken on a broad cross-section of 2,4-D formulations produced by these manufacturers. This is needed because various manufacturers utilize different production processes, and it is well-known that the level of dioxin contamination can vary dramatically, by orders of magnitude, under different production conditions. EPA should also ensure that dioxin testing is conducted on off-the-shelf 2,4-D formulations rather than (or in addition to) batches of 2,4-D provided for testing purposes by 2,4-D manufacturers. The latter approach could lead to provision of 2,4-D batches that are specially manufactured to have low dioxin levels that do not reflect dioxin levels in 2,4-D produced commercially.

Another source of dioxin contamination is the incineration of 2,4-D containers, which are often burned without the recommended triple-rinsing to remove 2,4-D residues. Tests were recently conducted by EPA scientists on standard 2.5 gallon HDPE jugs in which pesticides are commonly sold (Gullett et al 2012). It was determined that about 10 ml of 2,4-D residue remained in unrinsed containers. Incineration of unrinsed containers resulted in many-fold higher levels of PCDD/PCDF formation (both on a TEQ and even more on weight basis) than either clean or triple-rinsed 2,4-D HPDE jugs. Gullett et al note that EPA estimates that 218 million plastic nonrefillable (single use) containers for liquid pesticides are in use (2005). EPA should assess the increased dioxin emissions and exposure associated with incineration of unrinsed 2,4-D containers that would result from the vastly increased use of 2,4-D under the proposed registrations.

Dioxin Contaminants in 2,4-D in Light of EPA's Ongoing Review of Dioxin Toxicity

In February 2012, EPA issued Part 1 of its long-awaited assessment of dioxin toxicity, that pertaining to non-cancer risks (EPA 2012). EPA established a low chronic oral reference dose for dioxins of 7.0×10^{-10} mg/kg-day for non-cancer risks. The chronic oral reference dose is defined as: "An estimate of a daily oral exposure for a chronic duration (up to a lifetime) to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime."[103] The assessment of cancer risks posed by dioxins is still underway.

It is essential that EPA conduct an assessment of the greatly increased exposure to dioxins that would be enabled by the proposed registrations in light of its review of dioxin toxicity, both cancer and non-cancer risks. As indicated above, the assessment should include collection of reliable data on dioxin contaminants in a broad range of 2,4-D formulations, and associated exposure; assessment of dioxin emissions from manufacturing facilities that produce 2,4-D; and dioxin emissions from incineration of 2,4-D containers with 2,4-D residues. The assessment should take particular account of increased exposure of farmers and pesticide applicators to dioxins in 2,4-D (e.g. from mixing and otherwise handling 2,4-D concentrate) and associated with 2,4-D (from incineration of containers with 2,4-D residues).

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[103] http://www.epa.gov/iris/gloss8_arch.htm.

2,4-D and the Proposed Registrations in Light of the Upcoming Registration Review of 2,4-D

EPA is scheduled to begin a registration review of 2,4-D late this year or early next year. The registration review will give EPA the opportunity to examine 2,4-D in light of the latest science on its human toxicity, and to collect and evaluate data to assess the dioxin-related concerns in light of the Agency's ongoing review of dioxin toxicity. The registration review also will also involve a detailed assessment of use patterns, without which human health and other risks cannot be adequately evaluated.

The proposed registrations would enable vastly increased use of 2,4-D, and undoubtedly open the door to off-label use of many other 2,4-D formulations; shift use of 2,4-D to considerably later in the season, with attendant increase in drift-related crop injury; would shift usage of 2,4-D in a manner that is highly likely to foster rapid evolution of 2,4-D resistance in weeds, with consequent harms to the environment and human health from increased herbicide use; may pose serious risks to non-target organisms via 2,4-DCP metabolites; threaten biodiversity through increased damage to field-edge habitats; and threaten endangered species and their critical habitat.

For these reasons, EPA should defer any decision on the proposed registrations until it has completed its registration review of 2,4-D.

VIII. EPA Must Allow Opportunity for Public Comment After EPA Has Published Dow's New Use Applications and Any Supporting Documentation.

In light of the new use patterns of 2,4-D choline salt proposed by Dow's New Use Registration Applications, EPA should allow the public and interested parties an opportunity to comment on Dow's application materials, EPA's risk assessments, and EPA's proposed registration decision regarding Dow's application prior to issuing EPA's final decision.

The availability of Dow's application materials and EPA's proposed registration decision is essential to ensure sufficient public notice and meaningful public participation in EPA's new use registration process. The Federal Circuit identified the following three purposes of the notice and comment, "(1) to ensure that agency regulations are tested via exposure to diverse public comment, (2) to ensure fairness to affected parties, and (3) to give affected parties an opportunity to develop evidence in the record to support their objections to the rule and thereby enhance the quality of judicial review."[104] "To achieve those purposes, … the notice required by the APA ... must disclose in detail the thinking that has animated the form of a proposed rule <u>and the data upon which that rule is based</u>.'"[105]

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[104] *Int'l Union, United Mine Workers of Am. v. Mine Safety & Health Admin*., 407 F.3d 1250, 1259 (D.C.Cir.2005).

[105] *Prometheus Radio Project v. FCC*, 652 F.3d 431, 449 (3d Cir.2011) (holding, *inter alia*, that the F.C.C.'s notice of proposed rulemaking did not contain enough information about its planned overhaul to newspaper broadcast cross-ownership, or the options it was considering, to provide the public with a meaningful opportunity to comment (citing *Home Box Office, Inc. v. FCC*, 567 F.2d 9, 35–36 (D.C.Cir.1977)) (emphasis added).

EPA itself recognized the importance of increased transparency and meaningful public participation in the pesticide registration process: since October 2009, the agency has implemented a new public participation process that allowed the public to "review and comment on the risk assessments and proposed registration decision … for pesticide regulatory actions for which significant public interest is anticipated."[106] The proposed use of 2,4-D will enable 2,4-D to be used, for the first time, on crops genetically engineered to resist 2,4-D, and is significant public interest can be anticipated. Thus, EPA should allow the public to review and comment Dow's application materials, the agency's risk assessments and its draft registration decision prior to issuing its final registration decision on Dow's proposed new use registration of 2,4-D choline salt on 2,4-D resistant corn and soybeans.

CONCLUSION

For the above reasons, we request EPA to comply with FIFRA, FFDCA, NEPA and the ESA by critically considering the unreasonable adverse effects stemming from the change in use patterns of 2,4-D under Dow's proposed new use registration of 2,4-D choline salt applications on 2,4-D resistant, Enlist corn and soybeans.

Submitted by,

Center for Food Safety

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[106] EPA, Public Involvement in Pesticide Registration, http://www.epa.gov/pesticides/regulating/registration-public-involvement.html (last visited June 17, 2012).

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