UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: January 12, 2017
Subject: Response to Public Comments Received Regarding the Evaluation of Enlist Duo™ on Enlist Corn, Cotton, and Soybeans
Product Name: Enlist Duo™
EPA Registration Number: 62719-649
Application Date: July 28, 2014

Response to Comments

The Environmental Protection Agency (the EPA or the agency) received 20,030 comments in response to the October 31, 2016 Proposed Registration Decision of Enlist Duo™ Herbicide for use in 34 states on corn, cotton, and soybeans that have been genetically engineered (GE) to be 2,4-D and glyphosate tolerant, which Proposed Decision was posted for comment to Docket ID: EPA-HQ-OPP-2016-0594 in regulations.gov pursuant to the EPA's Public Participation Process for Registration Actions policy.[1] Comments received were both in favor of and opposed to the Proposed Decision. The EPA welcomes input from the public during the decision process when registering pesticides, and is committed to thoroughly evaluating and mitigating any potential risks from registered pesticides, consistent with applicable statutory standards. Also, the EPA strives to document and explain the basis of its regulatory decisions through these and other public documents.

Because similar issues were raised in multiple comments, the comments are grouped into major topic areas and representative comments are excerpted and paraphrased for each topic area and addressed below. To view these comments in their entirety, visit the docket mentioned above (EPA-HQ-OPP-2016-0594) on regulations.gov.

I. Human health

A common concern expressed in the submitted comments regarded the human health effects of the potential increased use, and therefore exposure of, 2,4-D.

[1] See https://www.epa.gov/pesticide-registration/public-participation-process-registration-actions. These comments included also those comments submitted in response to the Notice of Receipt (NOR) of an application for a new use of 2,4-D on "[c]otton, gin byproducts and cotton, undelinted seed," published at 81 Fed. Reg. 74800 (Oct. 27, 2016) pursuant to section 3(c)(4) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C. § 136a(c)(4).

Most of the comments received were similar to previous comments on the registration of Enlist Duo on GE corn and soybean, and responses have already been provided in a previous document, *Response to Public Comments Received Regarding New Uses of Enlist Duo™ on Corn and Soybeans, October 14, 2014*, herein referred to as the "2014 response document." In those cases, a brief response or summary is provided herein with a reference to the more detailed response provided previously. The complete document can be found on regulations.gov (Document No. EPA-HQ-OPP-2014-0195-2414).

A. Thyroid Toxicity and Endocrine Effects

Comment: *The EPA incorrectly evaluated and dismissed evidence of thyroid toxicity and other endocrine effects; The EPA should consider the possibility that 2,4-D dose-response curves are non-monotonic.*

Response: As noted in the 2014 response document, the agency identified thyroid toxicity as a potential effect of concern and required additional testing. Potential for thyroid toxicity was assessed in the extended one-generation reproduction study (EOGRTS) on 2,4-D, which assessed numerous thyroid parameters. These parameters were assessed in the young animal on postnatal days 4, 22, and 70 and in pregnant females on gestation day 17. At the highest dose tested, the predicted pattern of thyroid hormone changes that could signify a thyroid effect was observed in the adult females (*i.e.*, ↓T3 and ↓T4 with ↑TSH levels). These hormone findings are considered treatment-related, but adaptive and not adverse; i.e., the thyroid responded to the insult and corrected itself. The thyroid findings in the other age groups were not treatment-related because there was no dose-response in the changes, and/or the predicted pattern of thyroid hormone changes was not evident. In this study and in other studies where thyroid effects were observed, clear no observed adverse effect levels (NOAELs) were identified, and the endpoints selected for risk assessment are protective of potential thyroid effects. The EPA has quantified risk of 2,4-D to assure exposures are at least 100-fold lower than levels where renal saturation occurs. In response to the comment that 2,4-D dose-response curves may be non-monotonic, the EPA notes that there is no evidence to support a biological process that would lead to a non-monotonic dose response for 2,4-D affecting the thyroid.

The agency has also comprehensively evaluated the endocrine effects of 2,4-D. The EPA concluded in its review of the data submitted that the rat two-generation reproduction study protocol described in the 1998 test guidelines is valid for the identification and characterization of reproductive and developmental effects, including those due to endocrine disruption, based on the long history of its use, the endorsement of the 1998 test guideline by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP), and acceptance by member countries of the Organisation for Economic Cooperation and Development (OECD). The results of this study were consistent with other toxicity studies in the database showing that toxic effects occur only at doses above levels of renal

saturation (and, again, the EPA has quantified risk of 2,4-D to assure exposures are at least 100-fold lower than levels where renal saturation occurs).

As noted above, in addition to the rat two-generation reproduction study, 2,4-D also has an EOGRTS available. Both studies have been evaluated by the agency and incorporated into the hazard assessment of 2,4-D. In the EOGRT study on 2,4-D, for all of the parameters assessed, a clear NOAEL (21 mg/kg/day) was identified, which was used as the point of departure for risk quantification, and as in other toxicity studies in the database, adverse toxic effects were observed only at levels that exceed the body's ability to excrete 2,4-D (i.e., the level of renal saturation). A more detailed response is provided in the 2014 response document on pages 3-5.

B. Cancer

Comment: *The EPA has ignored IARC's recent cancer finding for 2,4-D and is relying on its outdated carcinogenicity classification for 2,4-D in registering Enlist Duo.*

Response: Several comments noted that the World Health Organization's International Agency for Research on Cancer (IARC) concluded in June, 2015 that 2,4-D is "possibly carcinogenic to humans." The IARC evaluation summary stated that there is inadequate evidence in humans for the carcinogenicity of 2,4-D, and there is limited evidence in experimental animals for the carcinogenicity of 2,4-D. Since there has been no compelling evidence to re-visit the previous EPA classification of the carcinogenic potential of 2,4-D, the classification remains unchanged. As was noted in the 2014 response document, studies in rats and mice showed no statistically significant tumor response in either species for 2,4-D. Furthermore, 2,4-D is not mutagenic, a flag for potential carcinogenicity. The agency determined, based on several reviews of epidemiological studies, in addition to the animal studies, that the existing data did not support a conclusion that links human cancer to 2,4-D exposure. Thus, in accordance with the agency's 1986 "Guidelines for Carcinogen Risk Assessment," 2,4-D was classified as a "Group D Chemical: Not Classifiable as to Human Carcinogenicity."[2] This classification was based on the lack of evidence of carcinogenicity in two well-designed and well-conducted animal studies of adequate power and dose in two species (mice and rats), and on the lack of epidemiological data supporting an association between 2,4-D exposure and cancer. Although 2,4-D's classification has not been evaluated according to the 2005 classification scheme, based on weight of evidence consideration of the available data, 2,4-D would be classified as "Not Likely to be Carcinogenic to Humans." While the agency does not anticipate any changes to that position at this time, a comprehensive evaluation of all available data for 2,4-D will be conducted by the Health Effects Division's Cancer Assessment Review Committee in 2017.

[2] *Carcinogenicity Peer Review (4'th) of 2,4-Dichlorophenoxyacetic acid (2,4-D)* (Jess Rowland, 1/29/97)

Comment: *Several comments noted that the World Health Organization's International Agency for Research on Cancer (IARC) concluded in March, 2015 that glyphosate is "probably carcinogenic to humans" and urged the EPA to refrain from any decision on Enlist Duo until the EPA completes its registration review of glyphosate, which the commenters assert has been delayed due to the EPA's uncertainty about glyphosate's carcinogenic potential. Comments also noted that the EPA recently appointed a panel of experts to assess the evidence of glyphosate's carcinogenicity.*

Response: IARC's cancer classification for glyphosate considers only its cancer hazard. Risk assessment involves both hazard and exposure evaluation. The EPA's current evaluation of glyphosate is more thorough and comprehensive than IARC's evaluation because the EPA estimates risk to consumers based on expected exposure from all potential exposure pathways, including through food, drinking water, residential exposure, and occupational exposure. In 2016, the EPA completed a comprehensive examination of the cancer database for glyphosate and determined that glyphosate is not likely to be carcinogenic to humans (at the expected levels of exposure) (*Glyphosate Issue Paper: Evaluation of Carcinogenic Potential, EPA's Office of Pesticide Programs*, September 12, 2016, Docket EPA-HQ-OPP-2016-0385). This conclusion is based on a thorough review of the open literature and epidemiological database, and an examination of available genotoxicity, mutagenicity, and carcinogenicity studies (including data from over 50 newly submitted studies not previously available to the agency). The EPA's conclusion that glyphosate is not likely to be carcinogenic to humans is also the same conclusion reached by many regulatory authorities in the world, including those in Europe, Australia, Japan, and Canada. More recently, the EPA convened a panel of experts (FIFRA Science Advisory Panel) in December 2016 to discuss the EPA's weight of the evidence approach and the EPA's method for data interpretation with respect to its recent cancer finding for glyphosate. The EPA expects to receive recommendations from the FIFRA Science Advisory Panel in March 2017. The EPA is committed to using the best science available to inform its policy decisions. If the EPA determines at any time that there are urgent human health risks and/or environmental risks from exposure to a pesticide that requires prompt attention, the agency will take appropriate regulatory action, regardless of the status of the pesticide in the review process.

C. Parkinson's Disease

Comment: *Many epidemiology studies have found associations between exposure to chlorophenoxy herbicides in general and 2,4-D in particular and Parkinson's disease.*

Response: The EPA has reviewed key literature regarding the link between 2,4-D exposure and Parkinson's Disease, including the recent epidemiology report sponsored by the European Food Safety Authority (EFSA). The EPA has concluded that the available evidence is not sufficient to link 2,4-D exposure to Parkinson's Disease. The EPA's assessment of 2,4-D exposure as it relates to Parkinson's Disease is discussed in greater detail in the 2014 response document on pages 12 and 13.

D. Synergy

Comment: *Synergistic effects of 2,4-D and glyphosate and/or formulation inerts must be considered. The Enlist formulation is a combination of two herbicides (2,4-D choline salt and glyphosate) as well as adjuvants and inerts. The agency did not address the potential synergistic effects between 2,4-D choline salt and glyphosate nor potential reactions with the other chemical components of the formulation.*

Response: The EPA is issuing a new decision for currently registered Enlist Duo™ for use on genetically engineered (GE) corn and soybean in 15 states (in addition to issuing a decision to register Enlist Duo™ for use on GE corn and soybean in an additional 19 states and to add a use on GE cotton in all 34 states) because after having issued the registration and amendment for use of Enlist Duo™ on GE corn and soybean in 15 states, and while defending that registration decision in the 9th Circuit U.S. Court of Appeals, the EPA discovered that the registrant, Dow AgroSciences LLC (DAS), had filed a patent application with the U.S. Patent and Trademark Office (USPTO) that claimed "synergism" between the two active ingredients in Enlist Duo™ and cited studies in support of that claim. The EPA had granted the registration and amendment based on the data and information provided by the registrant (which did not include the data cited to the USPTO), and found no evidence of synergism. Because the EPA only became aware of previously-existing information about possible synergistic effects after it had made its registration decision, the agency could no longer represent to the Court that its conclusions were correct regarding whether issuance of the registration met the standard in FIFRA and the finding that the registration would have no effect upon threatened or endangered plant species. The EPA therefore moved the Court on November 24, 2015 for remand and vacatur of the decision to register Enlist Duo™ for use on GE corn and soybean in 15 states. On January 25, 2016, the Court granted the motion for remand and denied the motion for vacatur, so that the registration for use on GE corn and soybean in 15 states has remained in effect while the agency determined whether changes to the registration were necessary.

Prior to registering Enlist Duo™ for use on GE corn and soybean in the original 6 states, the EPA evaluated the available data on the two chemicals individually as well as any available formulation-specific information and found no indication of synergism for mammals, freshwater fish and freshwater invertebrates and believed it reasonable to use that determination as to plants as well. In addition, the formulation-specific data did not show greater toxicity to mammals compared to either compound alone. *See* the 2014 response document at pages 7 and 19.

As described above, however, in light of newly discovered information concerning patent claims made by DAS, on October 13, 2015, the EPA directed the registrant to provide to the agency certain information regarding potential "synergy," which ultimately resulted in the registrant's submission of Enlist Duo™ formulation-specific plant vegetative vigor and seedling emergence toxicity test data conducted using OCSPP 850 guideline protocols. For

the combination of choline 2,4-D and glyphosate that is used in the Enlist Duo™ formulation, the standard vegetative vigor and seedling emergence studies were submitted for a suite of commonly tested plant species for which existing single-herbicide testing indicated plant sensitivity to 2,4-D or glyphosate. Surpassing the normal requirement of ten plant species, this testing spanned fifteen commonly tested monocot and dicot crop species: buckwheat, cabbage, corn, cucumber, mustard, oat, oilseed rape, onion, radish, sorghum, soybean, sugarbeet, sunflower, tomato, and wheat. In addition, the agency required and received vegetative vigor and seedling emergence studies with three weed species identified in the data set submitted to the USPTO as having the potential for exhibiting enhanced sensitivity to the 2,4-D choline/glyphosate combination in excess of simple addition of individual active ingredient effects. These species included lambs quarters (*Chenopodium album*), horseweed (*Conyza canadensis*), and quackgrass (*Agropyron repens*). These data were used to better understand the toxicity effects of the combination of 2,4-D and glyphosate on plants, address any uncertainty in the ecological risk assessment, endangered species effects determinations, and critical habitat modification determinations arising due to the "synergistic effects" claims made in patent applications for the two constituent herbicides (2,4-D and glyphosate), and to confirm that the original buffers were still appropriate. These data demonstrate that the combination of 2,4-D choline and glyphosate in Enlist Duo™ does not show any increased toxicity to plants and is therefore not of concern. After reviewing the data submitted by DAS, the EPA has determined that the information supports the original decision. Details of the EPA's review of this data can be found in the document entitled, *2,4-D Choline: Review of Seedling Emergence and Vegetative Vigor Terrestrial Plant Studies for the Formulated Product Enlist Duo*, found in docket EPA-HQ-OPP-2016-0594.

The agency views synergism to be a rare event and intends to follow the National Research Council's recommendation for government agencies to proceed with estimating effects of pesticide mixtures with the assumption that the components have additive effects[3] in the absence of any data to support the hypotheses of a synergistic interaction between pesticide active ingredients. As was discovered post-registration to be the case regarding Enlist Duo™, some USPTO filings suggest that combined mixtures have enhanced activity or synergistic effects. The endpoints in these patent application studies tend to be based on visual observations of weed control and injury, and so are not directly applicable to the EPA's quantitative risk assessment process for plants, in which measures of sublethal effects (plant height and weight) serve as sensitive effects thresholds for risk estimation purposes. The EPA believes this quantitative approach is much more scientifically rigorous and is a very reliable method of assessing risk for the purpose of potential toxicity to plants.

[3] The phrase "additive effects" is used when the effect of the combination of chemicals can be estimated directly from the sum of the scaled exposure levels (dose addition) or of the responses (response addition) of the individual components.

With regards to human health, although the agency does not routinely include a separate evaluation of mixtures of active ingredients and/or formulation inerts, the EPA believes it adequately addressed the issue of synergism between 2,4-D and glyphosate by evaluating data on the chemicals individually as well as with formulation-specific information. Acute oral, dermal, and inhalation data, skin and eye irritation data, and skin sensitization data are available for the 2,4-D choline salt and glyphosate formulation for comparison with the 2,4-D parent compound and glyphosate parent compound data, and these test results show similar profiles. The mixture does not show a greater toxicity compared to either parent compound alone. Although no longer duration toxicity studies are available, toxic effects would not be expected as the maximum allowed 2,4-D exposure is at least 100-fold below levels where toxicity to individual chemicals might occur, and exposure to people is far below even that level. A more detailed response is provided in the 2014 response document on pages 7 and 19.

See also, section II.E., below, regarding "synergy."

E. FQPA Safety Factor

Comment: *The Food Quality Protection Act (FQPA) "additional tenfold margin of safety" to protect infants and children should be retained because the agency's toxicity and exposure assessments do not adequately protect childrens' health.*

Response: The decision of whether a margin of safety different from the tenfold margin of safety should be applied was determined in a manner consistent with all pesticide assessments. Major considerations include the completeness of the 2,4-D database with respect to toxicity and exposure, whether the assessment is protective for any observed sensitivity in infants and children (including developing fetuses), and whether the exposure data are protective for exposure to infants and children (including fetuses). Based on these three considerations – a complete database for toxicity and exposure, adequate protection for sensitivity in infants and children, and an exposure assessment which will not underestimate childrens' exposures – sufficient reliable information is available showing that risks to infants and children will not be underestimated. The EPA determined that the 10X FQPA safety factor could be reduced to 1X, consistent with the requirements of the Food Quality Protection Act. A more detailed response is provided in the 2014 response document on pages 9-10, and in the response to a Natural Resources Defense Council (NRDC) petition (Taylor, et al. 2012) found in docket EPA-HQ-OPP-2008-0877-0446.

F. Dioxins

Comment: *2,4-D is a major source of dioxins presenting risk concerns for use of the chemical; some of the toxic effects of 2,4-D are attributable in whole or in part to dioxin contamination.*

Response: As noted in the 2014 response document, as a result of changes in the manufacturing processes for 2,4-D over the past 15-20 years, dioxins are no longer found at detectable levels in 2,4-D products sold and used in the United States. The agency has required testing of all 2,4-D products for dioxins using very sensitive methods. Additionally, the agency conducted an assessment assuming that dioxins were present at the detection limit in all 2,4-D products – an implausible situation, but a very protective assumption. Human health risks assessed with this assumption were insignificant.

G. Neurological and other health impacts

The comments regarding neurological and other health impacts in research papers in the open literature have been addressed previously in the agency's response to the NRDC petition[4] (EPA-HQ-OPP 2008-0877-0446) in 2012 and are not reiterated here. Other studies cited (in vitro; mechanistic) do not provide information relevant to establishing a point of departure for human health risk assessment. A recent agency literature search of the open literature identified several articles, which have been screened and were found not to impact endpoint selection.

H. Reference Doses/Population Adjusted Doses

Comment: *The EPA must set reference doses (RfDs) or population adjusted doses (PADs) for 2,4-D that are adequately protective of sensitive developmental endpoints (e.g, brain development) and of human health; the EPA's current point of departure, 25 mg/kg/day, is not adequately protective against thyroid toxicity and population health*

Response: The point of departure (POD) suggested by the comment (a LOAEL of 5 mg/kg/day) is not appropriate for an acute exposure scenario as the data are not reflective of an acute exposure. As noted previously, the predicted pattern of thyroid hormone changes that could signify a thyroid effect was observed at the highest dose tested in adult females (*i.e.*, ↓T3 and ↓T4 with ↑TSH levels). These hormone findings are considered treatment-related, but adaptive and not adverse; i.e., the thyroid responded to the insult and corrected itself. The thyroid findings in the other age groups were not treatment-related because there was no dose-response in the changes, and/or the predicted pattern of thyroid hormone changes was not evident. In this study and in other studies where thyroid effects were observed, clear no observed adverse effect levels (NOAELs) were identified, and the endpoints selected for risk assessment are protective of potential thyroid effects.

I. Dietary Assessment

[4] Natural Resources Defense Council's Petition to Revoke All Tolerances and Cancel All Registrations for the Pesticide 2,4-D (November 6, 2008).

Comment: The *dietary risk assessment does not adequately capture all reasonable exposure risks (assumptions were not adequately articulated; not clear what unrefined means; it was not clearly demonstrated that breast milk was considered in dietary exposure assessment; must incorporate increased use of 2,4-D into the assessment)*

Response: The dietary exposure estimates are unrefined, meaning that conservative, health protective assumptions were included in the assessment that result in a screening level determination of risk which overestimates exposure. That risk estimate could be further refined if necessary. The assumptions included primarily tolerance-level residues in food, 100% of the crop is treated with the proposed product, and upper-bound drinking water estimates based on modeling. Wherever tolerance-level residues were not used, a value higher than the tolerance was used to account for metabolites. Drinking water estimates used in the dietary assessment were derived from modeling using modeling inputs designed not to underestimate residues in drinking water. Modeled residue estimates are far higher than residues found in monitoring data. These residue estimates will not underestimate exposures to anyone in the U.S. population, and will be far higher than those to which the vast majority of the population will be exposed. All aspects of these comments are fully addressed in the 2014 response document on pages 13-14.

J. Volatilization

Comment: *The agency did not properly account for volatility of 2,4-D (did not consider available monitoring data; it's unclear if reasonable worst-case assumptions were used in the assessment; surfactants and solvents can alter 2,4-D volatility; temperature and field conditions can alter 2,4-D volatility; not enough information was provided on the 2,4-D flux data)*

Response: As discussed on pages 14-15 of the 2014 response document, the agency conducted a volatility assessment using health-protective assumptions. 2,4-D specific flux monitoring data were used for the volatility assessment. Trials were conducted at different sites (Indiana, Arkansas, and Georgia) to reflect a range of temperature and field conditions. Trials were conducted with applications to bare soil, soybean (30 cm crop height with 80% canopy closure), soybean (15 cm crop height with 15% canopy cover), and cotton (50 cm crop height with 40% canopy cover). These flux studies used products with differing formulations: 2,4-D choline-specific flux study was completed using the experimental formulations (both 2,4-D choline alone and 2,4-D choline plus glyphosate end use products). Results showed that 2,4-D choline salt has lower volatility than 2,4-D esters and other salts. The maximum application rate was used for the assessment.

Volatilization modeling was completed by the agency using the Probabilistic Exposure and Risk model for fumigants (PERFUM). Approaches the EPA has used previously to assess inhalation exposures to fumigant pesticides were used for the assessment, consistent with the

recommendations of the December 2009 Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) meeting on the scientific issues associated with field volatilization of conversional (semi-volatile) pesticides. The PERFUM modelling results are based on Bradenton, FL; Yakima, WA; Flint, MI; and Ventura, CA weather datasets which have been used in the past for other volatilization analyses and represent a range of conditions including those which have consistently provided the highest risk estimates.

The portal-of-entry inhalation toxicity endpoint was used in the volatilization assessment, the most sensitive inhalation toxicity observed for 2,4-D. By using this endpoint, the agency assumed that bystanders are exposed every day for 28 consecutive days at the maximum, day-of-application volatilization exposure near the field – this is a very health-protective assumption. Combining this protective assumption with the exposure assumptions discussed above which reflect the highest exposure scenario results in a very health protective assessment.

Estimated risks from volatility will not increase if there is increased use of 2,4-D; the current assessment assumes that bystanders are exposed to air concentrations at the edge of a field treated using the use pattern likely to result in the highest residues possible. Based on these assumptions, airborne concentrations of 2,4-D at the edge of the treated field are not of concern.

K. Spray Drift

Comment: *Invalid assumptions were used for spray drift (assumption of compliant applications; an increased frequency of applications will cause increase in exposure)*

Response: The approach used to quantitatively incorporate spray drift exposure into the 2,4-D risk assessment was based on the agency's current policy on drift (https://www.epa.gov/reducing-pesticide-drift). The assumption is that applications will not result in direct exposures to individuals, since such contact would constitute a misuse. Direct exposures would include inhalation of the spray plume or being directly sprayed. The exposures addressed for 2,4-D, as with other conventional chemicals, are assumed to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. For agricultural pesticides, the Worker Protection Standard (WPS) prohibits the application of a pesticide such that it contacts, either directly or through drift, any worker or other person. This WPS prohibition mitigates the potential for bystander exposure to active drift, but not the residues of drift that are deposited on surfaces to which bystanders may be exposed. The spray drift methodologies were developed based on the premise of compliance with label guidance and with the requirements of the Worker Protection Standard

Some comments indicated that residential exposure to 2,4-D would increase as a result of the proposed use. Since there is no change in the residential use patterns, the only potential for

increased residential exposure is to bystanders exposed through drift or volatility, neither of which have risk concerns. A detailed response regarding the 2,4-D spray drift assessment is provided in the 2014 response document on pages 15-17.

L. Dioxins

Comment: *Dioxins are known to be formed during the manufacturing process of 2,4-D. The increased use of 2,4-D associated with herbicide-tolerant corn and soybean will lead to an increase in dioxins, as well as other impurities formed during the manufacturing process, in the environment.*

Response: As noted in the 2014 response document (page 11), dioxins are no longer found at detectable levels in 2,4-D products sold and used in the United States as a result of changes in the manufacturing processes for 2,4-D over the past 15-20 years. The agency has required testing of all 2,4-D products for dioxins using very sensitive methods. Additionally, the agency conducted an assessment assuming that dioxins were present at the detection limit in all 2,4-D products – an implausible situation, but a very protective assumption. Human health risks assessed with this assumption were insignificant.

II. Environment

Another area of concern expressed in many comments was the risk of adverse environmental impacts from the increased application of 2,4-D. As with comments regarding human health issues, many comments expressed similar concerns involving the environment, so they are grouped into major topic areas and addressed below.

A. Data Gaps and Uncertainty

Comment: *Given the significant data gaps, uncertainties, and limitations identified in the EPA's risk assessments, the EPA cannot reach the required "no unreasonable adverse effects" finding necessary to support new use approvals under FIFRA. As a result, the EPA's approval of these new uses will be unlawful without further adequate study.*

Response: See specific data gap and study classification comments below that support the EPA's finding.

<u>Environmental Fate Data Gap</u>

Comment: *A comment claims that an example of inadequate data involves dissipation studies of 2,4-D. Without dissipation studies, it is unclear whether 2,4-D will persist or dissipate in the environment. The Ecological Risk Assessment acknowledges that there is no terrestrial field dissipation study to determine the environmental fate behavior of 2,4-D*

choline salt to 2,4-D acid. Furthermore, there is no environmental chemistry method (ECM) in soil and water to support the terrestrial field dissipation study. That means there are no studies to confirm the dissipation of 2,4-D in terrestrial fields or water. This data gap prohibits the EPA from making a finding that its approval will not have unreasonable adverse effects on the environment.

Response: The ecological risk assessment (DP Barcode 428301) acknowledged a number of environmental fate data gaps related to terrestrial field dissipation and environmental chemistry method (ECM) in soil and water studies for 2,4-D choline salt. These are generic data gaps for 2,4-D choline salt. The bridging strategy developed for other salt and amine forms of 2,4-D was assumed applicable to 2,4-D choline salt. Therefore, the requested terrestrial field dissipation and ECM fate studies for 2,4-D choline would be potentially useful to confirm a long-standing bridging strategy. Given that terrestrial field dissipation and ECM studies are not used quantitatively for calculating estimated environmental exposures, these studies were not critical to the quantitative risk estimations performed for the ecological risk assessment of 2,4-D choline on GE corn, cotton, and soybean.

<u>Supplemental Data Unsuitable for Risk Assessment Purposes</u>

Comment: *A comment notes that much of the data and studies that the EPA possesses are not "acceptable," and therefore, unknowns remain. As an example, the comment notes that the toxic effects on fish and amphibian populations for chronic toxicity remain unknown because there are no data. The acute freshwater amphibian study was deemed "supplemental" rather than "acceptable." Similarly, a study regarding oral acute toxic effects in honeybees was deemed "supplemental." The commenter believes these do not qualify to supply the EPA with the requisite data.*

Response:

The EPA applied a bridging strategy to characterize the chronic effects potential of 2,4-D choline through the use of available chronic effects data for fish using other rapidly dissociating 2,4-D salt moieties (page 43 of DP Barcode 428301). Data for fish is commonly used as a surrogate for aquatic phase amphibians. Table 17 of DP Barcode 428310 shows that available effects data for amphibians and fish for bridged compounds are not different. Further, the low risk quotient results for fish (acute and chronic are an order of magnitude or more less than the EPA's listed species levels of concern) indicate that a substantial margin of safety is in place, even without consideration of the effects of spray drift mitigation.

The EPA has established a policy for classifying registrant submitted studies in support of guideline study requirements (Bradbury 2005). As noted in that policy, studies that do not meet the guideline study requirements but are scientifically sound are classified as supplemental. Supplemental is a broad category. Studies in this category are scientifically valid; however, they were either performed under conditions that deviated from

recommended guideline protocols or certain critical data necessary for complete verification are missing. Supplemental studies may be useful in a risk assessment and can, at the scientist's discretion, fulfill the corresponding data requirement in 40 CFR Part 158. A subset of these studies might be referred to as Upgradeable. These studies may be upgraded to Core/Acceptable with additional information. Other Supplemental studies may be referred to as Ancillary. These studies appear to provide scientifically sound information, but the data cannot be verified under the EPA's criteria, and/or the study is not upgradeable. In the case of Enlist Duo and the studies discussed in the comment, the EPA scientists concluded that the studies were scientifically sound and provided data that could be used quantitatively in the risk assessment.

Effects Data Gaps

Comment: *Comments noted that other examples of data gaps and uncertainties identified by the EPA include:*

- *Estuarine/Marine Invertebrate Chronic Toxicity Test (850.1350): No data from acceptable studies are available for chronic toxicity of 2,4-D choline salt to marine/estuarine invertebrates. This assessment estimated a chronic value based on an acute-to-chronic ratio using freshwater invertebrate data.*

- *Acute and Chronic Larval Honeybee Toxicity Tests: No data are available for larval honeybee toxicity endpoints involving short-term survival and long-term development. The toxicity data for honey bees described here may apply to situations where exposure of bees to the pesticide is considered likely. It is uncertain whether larval stages are more or less sensitive to the pesticide and whether prolonged exposure to the pesticide would alter developments of the larval stage. These gaps are evident for all 2,4-D formulations and testing has been required through the Registration Review Process Chronic Adult Honeybee Toxicity Test: No data are available for long-term exposure effects in adult honeybees. The toxicity data for honey bees described here may apply to situations where exposure of bees to the pesticide is considered likely. While acute data are available for adults, there are no data to address the uncertainty associated with prolonged exposure and subsequent effects to the pesticide for the adult insect. This gap is evidence for all 2,4-D formulations and testing has been required through the Registration review process.*

Response: While the comment identifies data gaps, it fails to take into consideration the additional characterization in the risk assessment associated with the data gaps. The data gap concerning estuarine marine invertebrate chronic effects testing was addressed in a manner consistent with the EPA guidance (Pease et al. 2005). That guidance recommends the use of acute to chronic ratios to describe the potential effects thresholds for chronic effects when data are missing. The risk assessment concluded that the margins between estimated

exposure and the estimated chronic effects endpoints were so large that confidence in the endpoint estimate was sufficient to evaluate risks.

The EPA has provided guidance to risk assessors to characterize the importance of the bee testing data gaps (USEPA 2016a). Consistent with that guidance, the risk assessment DP 428301 documents the conclusion that the bee data gaps would only limit the confidence of the risk assessment in one crop and in within field locations, stating on page 105:

> "The application timing of Enlist duo is in the early development phases of corn and soybeans so the likelihood that bees would be using these crops at times contemporary with pesticide application is very low. Additionally, given the short foliar half-life of 2,4-D and the low root uptake of the chemical it is likely that the coincidence of foraging bees to residues in corn and soybean is low."
>
> Additionally, recognizing that cotton applications could coincide with bee attractive blooming of the crop, the EPA concluded on pages 105 and 106:
>
> "Spray drift analyses in this document, coupled with the risk assessment for terrestrial invertebrates would suggest, on the basis of available bee data, that the spray drift mitigations labeled for Enlist Duo place exposures off the treated crop at levels well below existing toxicity endpoints. It is therefore concluded that the utility of additional effects testing lies mostly in enhanced characterization for the cotton crop."

B. Monarch Butterfly

Comment: *The agency must consider the substantial adverse impacts that Enlist Duo will have on monarch butterflies, insofar as both glyphosate and 2,4-D destroy milkweed, which is critical to the monarch life cycle.*

Response: The EPA has conducted a risk assessment for the combined toxic effects to non-target plants (a grouping that includes plants important to monarchs) for glyphosate and 2,4-D choline in Enlist Duo. The risk assessment DP 428301 uses effects data for the Enlist Duo formulation. The conclusion of that risk assessment (page 67) was that effects to non-target plants, under application conditions prescribed on the label, would be limited to the treated field itself.

Comment: *The EPA has never considered, as part of any pesticide registration, the impacts that either of Enlist Duo's active ingredients has on monarchs. Without analyzing how Enlist Duo would impact milkweed and monarchs, the EPA lacks an adequate basis to conclude that registration of Enlist Duo will not cause unreasonable adverse effects on the environment, as required by FIFRA.*

Response: The EPA completed a non-target direct effects risk assessment for terrestrial invertebrates, specifically referencing monarch butterflies as a member of this taxa. This analysis is presented in DP Barcode 428301 and finds no concerns for terrestrial invertebrates (including monarchs). Again, the EPA has also conducted a risk assessment for the combined toxic effects to non-target plants (a grouping that includes plants important to monarchs) for glyphosate and 2,4-D choline in Enlist Duo. The risk assessment used effects data specific to the Enlist Duo formulation. The conclusion of that risk assessment was that effects to non-target plants, under application conditions prescribed on the label, would be limited to the treated field itself.

C. Other Pollinators

Comment: *Comments noted that data for chronic toxicity to adult honeybees is required for all pesticides, as outlined in the EPA's Pollinator Risk Assessment Framework. One study, How Herbicides Affect Honey Bees (Morton and Moffett, 1972), found that phenoxy herbicides, when fed at concentrations of 10 ppm, caused no adverse effect on brood development, but reduced amount of brood when fed at concentrations of 100 ppm. The eggs did not hatch at all in colonies fed the higher levels of phenoxy herbicides. According to the Risk Assessment, the data suggested a potential for adverse effects in the hive that are either mediated by toxicity to young or reduced by care and feeding by adults, but additional data is needed to fully assess the potential risk from 2,4-D on honey bees, solitary bees, and other terrestrial invertebrates. The data available coupled with the lack of data should indicate that the use of Enlist Duo will have unreasonable adverse effects on the environment.*

Response: The EPA has reviewed Morten and Moffett (1972). The study is quite old, and honey bee brood rearing for toxicity testing has advanced since the time period of the article. Consequently, it is important to understand the response of control broods in this study to ascertain the baseline performance and variance to which treatment response can be compared. Unfortunately, Morten and Moffett failed to report their individual replicate responses for controls or treatments and did not provide statistical methods or summary statistics to minimally provide the reviewer with needed information on comparisons with controls. Therefore, the EPA considers the data unusable in a quantitative context (i.e., for calculating risk quotients).

Comment: *Risks to pollinators and other organisms beneficial to agriculture are inadequately assessed by the EPA in the proposed registration. The following studies that show impacts on beneficial insects from over-control of weeds in agricultural fields and the threats to pollinators from the proposed new use of Enlist Duo should be considered: de Menezes and Soares 2016, DiTommaso et al. 2016.*

Response: The agency has reviewed de Menezes and Soares (2016). The document secondarily cites the results of one identifiable study of 2,4-D impacts on beneficial insects, Carmo et al. (2009). Carmo et al. (2009) investigated the effects of a 2,4-D dimethylamine

acid formulation (Nortox 806 SL) on *Trichogramma pretiosum*, a parasitoid wasp. However, the study has no control data and as such it would not pass open literature data quality evaluation and cannot be considered appropriate for risk assessment use. The agency has reviewed DiTommaso et al. (2016). The paper discusses implications of milkweed control as it relates to provision of resources to support beneficial insects and the balancing of positive effects on promotion of beneficial insects with negative impacts of resource competition of milkweed with crop species. Given that the agency has determined that Enlist Duo impacts to non-target plants off a given treated crop field are not a concern for the product when used as labeled, the paper is not material to an assessment of risks off the treatment area for non-target species. It may be applicable to cost/benefit calculations a grower may wish to consider when determining if a milkweed pest within a crop field constitutes an overall positive or negative impact on crop yield.

D. Reptiles and Amphibians

Comment: The *EPA uses birds as surrogate species for reptiles and terrestrial phase amphibians, in spite of large differences in their biological characteristics. For example, reptiles and amphibians are much more likely than birds to absorb pesticides through direct contact (Weir et al. 2014, Van Meter et al. 2014, 2015, 2016), with dermal intake of 2,4-D and glyphosate formulations shown to change biochemical markers of health in a toad (Lajmanovich et al. 2015). The EPA only considers consumption of 2,4-D-contaminated food in the risk assessments, underestimating risk significantly.*

Response: The EPA has reviewed Weir et al. (2014) and Van Meter et al. (2014, 2015, 2016). While the comment suggests that the conclusions of these works indicate that dermal absorption is greater in amphibians and reptiles, the papers make no such comparisons.

Weir et al. (2014) compares the relative concentrations of three phthalate compounds (substantially different in chemical properties from 2,4-D) in various tissue compartments of lizards exposed via the diet or via dermal exposure. The authors concluded that the relative importance of dermal versus dietary exposure to resulting chemical residues in tissue were not consistent across tissue type. However, the study authors did conclude:

> "Our findings suggest that given similar doses, dermal and oral exposure to phthalates will result in relatively similar body residues, with oral exposure having generally greater residues."

Consequently, the agency reasons that risk analysis and mitigation based on oral exposure should be protective of the dermal route.

The Van Meter et al. papers (2014, 2015, 2016) present the calculation of amphibian bioconcentration factors (BCFs) for pesticide uptake from soil. None of the papers provided

measurements for any form of 2,4-D and the BCF values for any of the pesticides studies never reached unity.

E. Synergy

Product

Comment: *Effects of the whole product, Enlist Duo (including not only the active ingredients but also the additional unidentified ingredients) have not been assessed.*

Response: Additional terrestrial plant toxicity data conducted with the Enlist Duo formulation were used in the EPA's assessment of plant risk. These data were conducted according to agency protocols for vegetation vigor and seedling emergence and directly represent toxicity of the applied product to plants. These data were then used for risk assessment, rather than relying on 2,4-D active ingredient test data. Establishing effects endpoints using the Enlist Duo formulation would address any potential combined toxicity from the two active ingredients.

See also, section I.D., above, regarding "synergy."

Extra- Formulation Mixtures

Comment: *Synergistic or additive effects of Enlist Duo when applied with other commonly used herbicides such as atrazine have not been assessed.*

Response: The EPA has evaluated combined effects of active ingredients where available data allow. As explained in the Proposed Decision Document, the agency views synergism to be a rare event and intends to follow the National Research Council's recommendation for government agencies to proceed with estimating effects of pesticide mixtures with the assumption that the components have additive effects[5] in the absence of any data to support the hypotheses of a synergistic interaction between pesticide active ingredients. As was discovered post-registration to be the case regarding Enlist Duo™, some USPTO filings suggest that combined mixtures have enhanced activity or synergistic effects. The endpoints in these patent application studies tend to be based on visual observations of weed control and injury, and so are not directly applicable to the EPA's quantitative risk assessment process for plants, in which measures of sublethal effects (plant height and weight) serve as sensitive effects thresholds for risk estimation purposes. The EPA believes this quantitative

[5] The phrase "additive effects" is used when the effect of the combination of chemicals can be estimated directly from the sum of the scaled exposure levels (dose addition) or of the responses (response addition) of the individual components.

approach is much more scientifically rigorous and is a very reliable method of assessing risk for the purpose of potential toxicity to plants.

Taxa other than Plants

Comment: *One comment notes that in reviewing the rest of the EPA's assessment, it is unclear whether assessment of synergy was conducted for other organisms. Even though prompted by label claims of synergy for certain plant species, the fact remains that other non-target organisms, including humans, can and will be exposed to a chemical mixture that has not been properly evaluated. The current risk assessment document has assessed risks based on the 2-4-D choline salt only for mammals, birds, and other required organisms. It does not appear that assessments, based on exposure to both glyphosate and 2,4-D choline, have been conducted to properly assess whether synergistic effects can occur in non-plant organisms.*

The decision by the EPA to do toxicity tests on plants with the Enlist Duo formulation rather than a surrogate active ingredient alone is not adequate for determining risks from interactions between pesticide components in the proposed registration. There are other ingredients added by the end user just before application – other pesticide active ingredients (Donley 2016), and various adjuvants that change qualities of pesticide solutions (e.g. Curran and Lingenfelter 2009) – that also may change the toxicity of 2,4-D choline to plants and also to other taxa (Tornisielo et al. 2013). For example, in a recent study of herbicide toxicity to a beneficial lady beetle, a particular 2,4-D formulation was almost as toxic as the insecticide added as a positive control, and the toxicity was due mostly to an undisclosed "inert" ingredient (Freydier and Lundgren 2016).

Response: The decision to conduct toxicity tests using standard guideline protocols for a formulation containing both 2,4-D choline and glyphosate was based on two considerations: 1) a need to address patent information for that combination of active ingredients that suggested, with considerable uncertainty, more than additive combined toxic effects for 2,4-D in some plant species, and 2) a need for data to allow the agency to assess risk using the effects endpoints the agency's risk assessment methodology relies upon. The EPA was not in possession of other claims of effects in other taxa.

The comments suggest that there are additional mixtures in Donley (2016) for which patent information are available and should be assessed in this case before the risk assessment would be complete. The agency has reviewed Donley (2016), particularly the summary of information provided in Appendix B of the publication. A number of patents are said to involve 2,4-D mixed with other pesticides in the summary table. However, close scrutiny finds: 1) patent references for mixtures of 2,4-D and glyphosate (a mixture already addressed in the risk assessment through direct testing), 2) patent application references for 2,4-D in combination with mecoprop-p, and indaziflam for which no empirical data are available to support any combined toxicity claims, 3) patent references for 2,4-D and picloram for which

no information relative to the patent are provided at all, 4) patent application references for 2,4-D mixed with aminopyralid where a review of the US Patent and Trademark Office database finds no application with a matching identification number, and 5) reference to a patent application with mixtures of 2,4-D, isoxaben mecoprop-p and dicamba for which a search of the US Patent and Trademark Office database reveals no application with a matching identification number. In summary, despite the inclusion of the citation in the above comment, the reference to Donley (2016) does not serve to demonstrate any need for additional mixture investigations.

The EPA disagrees with the commenter's claim that the Freydier and Lundgren (2016) paper demonstrates a formulation with greater toxicity than the active ingredient tested alone. The basis for our disagreement is rooted in review of the article and the finding that the formulation tested (Albaugh LV4) has a different form of herbicidal active ingredient from technical 2,4-D acid. LV4 contains 2,4-dichlorophenoxyacetic acid 2-ethylhexyl ester, while the tested active ingredient is 2,4-dichlorophenoxyacetic acid. As discussed in DP Barcode 428301, ester forms of 2,4-D are not considered by the EPA to be appropriate chemical surrogates for the toxicity of acid forms to terrestrial invertebrates. The degree to which the formulation and the acid as tested differ in toxicity may in large part be the result of this difference in tested 2,4-D form and not to constituents of the formulation. Freydier and Lundgren (2016), in its most accurate representation, does not support a contention of synergistic activity for 2,4-D and other formulation components.

Similarly, Curran and Lingenfelter (2009) presents a variety of adjuvants and claims for their activity, but provides no data, specific to 2,4-D or any other pesticide, about the degree to which any increase in pesticidal activity has been empirically demonstrated. As such, Curran and Lingenfelter (2009) does not advance or suggest any quantitative basis for synergy with 2,4-D and other tank mixture additives.

Finally, a careful read of Tornisielo et al. (2013) discovered not a single reference to 2,4-D (in any chemical form) and its effect on any living organism when tested alone or mixed with any other chemical.

On the basis of our review of the citations listed in the comment, the agency finds no supporting evidence for the claim that the risk assessment was insufficient in scope with respect to mixtures.

Comment: *Based on scientific studies showing that some mixtures are significantly more toxic to particular organisms than the active ingredient alone, comments argue that toxicity of end-use pesticide formulations must be determined and taken into account when assessing risks. The following studies were referenced: Risolli et al. 2016, Wagner et al. 2016; insects, Ciarlo et al. 2012, Freydier and Lundgren 2016, Mullin et al. 2015, 2016; grapes, Mosheni-Moghadam et al. 2016. The comments note that this is especially important for determining*

whether mitigations such as in-field buffers during applications are protective of non-target organisms.

Response: The agency has considered the citations identified in this comment with respect to the comment contention that they provide evidence that mixtures can be more toxic than individual active ingredients. Because the present registration action involves a product containing 2,4-D choline and glyphosate, it is logical to evaluate the cited material in the context of those chemicals. The agency notes that Risolli et al. 2016 deals solely with glyphosate formulations, none of which include 2,4-D in any form, nor are there any data in the publication that address mixtures of glyphosate with 2,4-D. Similarly, Wagner et al. (2016) also presents data solely on glyphosate formulations and nothing either in formulation or as tank mixtures related to additions of glyphosate with 2,4-D in any form. Ciarlo et al. (2012) research centers on pesticidal adjuvants and their effects on honeybees, and again contains no data on mixtures of these compounds with any form of 2,4-D. Freydier and Lundgren (2016) has been discussed earlier, and again the agency finds no evidence of extra toxicity for suitable toxicological surrogates of 2,4-D choline in formulation versus active ingredient alone in this document. Mullin et al. (2015 and 2016) provide no data relevant to a combined effects analysis for 2,4-D in any form when mixed with any other chemical.

Mosheni-Moghadam (2016) does present data relevant to a consideration of potential enhanced toxicity of 2,4-D and glyphosate combination. However, the study investigated the effects of these compounds and combination upon plants using a visual signs of damage measurement endpoint. This study endpoint is the same as measured in patent data for 2,4-D and glyphosate. The agency concludes that Mosheni-Moghadam (2016) provides data with endpoints not suitable for direct use in the ecological risk assessment, consistent with the conclusion for the patent data evaluated. At best the study might provide rationale for the performance of guideline plant toxicity studies with the Enlist Duo formulation. Because these guideline studies have already been performed and the results incorporated into the draft risk assessment, the agency concludes that Mosheni-Moghadam (2016) provides no evidence that mixture toxicity has not been adequately characterized in the draft ecological risk assessment.

F. Endangered Species Process

<u>Updated Effects Determinations</u>

Comment: *Comments asserted that the EPA is seeking to expand the use of Enlist Duo on additional crops and additional states without rectifying its improper "no effect" determinations for use of Enlist Duo on GE corn and soybean in the original fifteen states.*

Response: The EPA considered all new relevant data provided to the agency when updating all of the species effects determinations in DP Barcodes 428301 and 436497**.**

See also, section I.D., above, regarding "synergy."

On-Field / Off-Field Criteria

Comment: *The EPA identified 531 listed species inside the "action area" (area of concern where use of pesticides may result in exposure to endangered species).*

Response: The comment is in error for the following reasons.

1. DP Barcode 428301 states (page 76):

   "As indicated in the risk assessment sections of this document, the above spray drift mitigation label requirements and analyses of volatility and runoff loadings result in a screening risk assessment conclusion that any risks of effects to non-target organisms will be confined to the treated field. As a consequence of this spatial limitation of effects to the treated site, the action area for the registration of Enlist Duo (the area where effects are reasonably expected to occur) is considered to be limited to the sites of application of Enlist Duo on corn, cotton, and soybean fields."

2. DP Barcode 428301 states which species may be within the action area (page 102):

   "Of the 531 listed species within the states proposed for 2,4-D choline uses on corn, cotton, or soybean, there are 508 species identified as not using corn, cotton or soybean fields and 23 species using these fields."

Comment: *Comments asserted that the EPA has erroneously and unilaterally determined that it "expects" spray drift to remain confined to the Enlist Duo treated field, and concluded that the action area is therefore limited to only the field, as opposed to areas surrounding the field. Consequently, the EPA determined that 508 of the 531 species originally identified as potentially at-risk can be given a "no effect" determination. The EPA misinterprets its statutorily defined duties, conflating the "may affect" standard with the "no effect" standard.*

Response:

The EPA does not agree that it has "conflated" a "may affect" finding with a "no effect" finding. The following explains the EPA's assessment process starting with a screening-level risk assessment followed by a species-specific Effects Determination. The agency begins with a screening-level assessment that includes a basic ecological risk assessment based on its 2004 Overview of the Ecological Risk Assessment Process document.[6] That

[6] http://www.epa.gov/oppfead1/endanger/litstatus/riskasses.htm.

assessment uses broad default assumptions to establish estimated environmental concentrations of particular pesticides. If the screening-level assessment results in a determination that no levels of concern are exceeded, then the EPA concludes its analysis. On the other hand, where the screening-level assessment does not rule out potential effects (exceedances of the level of concern) based on the broad default assumptions, the EPA then uses increasingly specific methods and exposure models to refine its estimated environmental exposures. At each screening step, the EPA compares the more refined exposures to the toxicity of the pesticide active ingredient to determine whether the pesticide exceeds levels of concern established for listed aquatic and terrestrial species. The EPA determines that there is no effect on listed species if, at any step in the screening-level assessment, no levels of concern are exceeded. If, after performing all of the steps in the screening-level assessment, a pesticide still exceeds the agency's levels of concern for listed species, the EPA then conducts a species-specific refined assessment to make effects determinations for individual listed species. The refined assessment, unlike the screening-level assessment, takes account of species' habitats and behaviors to determine whether any listed species may be affected by use of the pesticide.

The screening-level ecological risk assessment generates a series of taxonomic (e.g., mammals, birds, fish, etc.) risk quotients (RQs) that are the ratio of estimated exposures to acute and chronic effects endpoints. These RQs are then compared to the EPA established levels of concern (LOCs) to determine if risks to any taxonomic group are of concern. The LOCs address risks for both acute and chronic effects. Acute effects LOCs range from 0.05 for aquatic animals that are federally-listed threatened or endangered species (listed species) to 0.5 for aquatic non-listed animal species and 0.1 to 0.5 for terrestrial animals for listed and non-listed species. The LOC for chronic effects for all animal taxa (listed and non-listed) is 1. Plant risks are handled in a similar manner, but with different toxicity thresholds (NOAEC/EC_{05} and EC_{25}, respectively) used in RQ calculation for listed and non-listed species and an LOC of 1 used to interpret the RQ. When a given taxonomic RQ exceeds either the acute or chronic LOC, a concern for direct toxic effects is identified for that particular taxon. If RQs fall below the LOC, a no effect determination is identified for the corresponding taxon.

The EPA does not expect "spray drift to remain confined to the Enlist Duo treated field." The EPA states in DP Barcode 428301 (page 76) that "spray drift mitigation label requirements and analyses of volatility and runoff loadings result in a screening risk assessment conclusion that any risks of effects to non-target organisms will be confined to the treated field." The EPA used these findings to ascertain the extent of the action area in accordance with the Endangered Species Consultation Handbook (USFWS and NMFS 1998), which defines the action area on page *x* as "all areas to be affected directly or indirectly by the Federal action."

The EPA does not agree that there has been a misinterpretation of its statutory duty relative to effects determinations. In DP Barcode 428301, the EPA 1) considered Enlist Duo use as

described on the proposed label, 2) applied conservative exposure/effects endpoints, and 3) concluded the direct and indirect effects to any taxa would be limited to areas within the confines of the treated fields. Therefore, the action area was logically limited to the treated fields. The 531 species mentioned in the comment were part of the total number of listed species that DP Barcodes 428301 and 436497 identified as being present in the states of proposed Enlist Duo use. A subset of these species were found not to be in the action area. The remaining subset of species were determined to exist within the action area and these were subject to further risk assessment to support an effects determination. The EPA has applied the "no effect" determination consistent with the criteria outlined by the National Marine Fisheries Service (NMFS 2014). In that document (page 1), NMFS states that a "no effect" determination can be reached for a species and action when:

1. The species does not occur at all in the action area *(For Enlist Duo, the EPA described the action area boundaries as being within the treated field and species that were considered not to occur in treated fields were outside the action area and so no effect);*

2. The species occurs in the action area seasonally, and the project will be timed to avoid their presence *(The EPA did not apply this criterion for Enlist Duo though did consider the timing of use of treated fields for exposure analysis for some species*); or

3. The species occurs in the action area and may be present at the time of the project, but there are no plausible (i.e., no credible) routes of effects (beneficial or adverse) to the species. (*In the case of Enlist Duo, the EPA conducted an analysis of exposure and effects to determine if exposures were sufficient to indicate a plausible and credible route to effects for any species determined to exist within the treated field action area. Species for which this process excluded exposure at or above effects thresholds received a "no effect" determination. Species with exposures exceeding effects thresholds received a "may affect" determination and the EPA considered all available lines of evidence to determine whether those effects were "likely to adversely affect" or "not likely to adversely affect."*

Pursuant to USFWS (2016), consistent with NMFS criteria, for species co-occurring or exposed to effects in the action area:

1. If the best available data indicate that the species and critical habitat will not respond in any manner, conclude "no effect" and document your finding. No further consultation required. (*Note: this is similar to NMFS number 3 above*).

2. If data indicate the species and habitat may respond upon exposure, or if data are equivocal or lacking to justify a determination of "no effect," conclude "may affect." (The *EPA has already outlined above the approach taken for "may affect" above.*)

If the agency saw no avenue to change the nature of the action area in localities where species occurrence overlapped and that overlap resulted in a "may affect" determination, then the EPA sought consultation with the United States Fish and Wildlife Service (USFWS). However, the EPA believes it is in the best interest of a listed species to modify a proposed action so as to avoid effects to the organism altogether, when practical. Therefore, if the agency could incorporate modifications to the action (i.e., prohibit select areas of application to avoid listed species occurrence areas), then the EPA could modify the effects determination at that point to a "no effect" because the action no longer co-occurred with the listed species.

Comment: *Comments asserted that the EPA's assumption that spray drift simply will stop at field boundaries and never extend beyond those boundaries is wholly unjustified, and undermines its argument that none of the 157 plant and animal species identified in its previous analysis could be adversely affected. The argument also ignores the possibility that some species could be within the field or moving in and out of the field at time of spraying. By relying on this faulty assumption, the EPA appears to be taking a shortcut to avoid assessing the potential harms to each of these 157 species of exposure not only to 2,4-D, but to the whole product, Enlist Duo.*

Response: The EPA made no assumption that spray drift will stop at field boundaries. On the contrary, the EPA used the best available information to quantitatively evaluate the extent of spray drift under the use conditions described on the Enlist Duo label. The EPA then compared those results to available effect thresholds for the new active ingredient and the product (where data were available). This comparison indicated that non-target organism exposures would be expected to be below effects thresholds off the treated field. This logically resulted in the confinement of the area where effects could reasonably be expected to occur to the treated field itself. The EPA's evaluation of habitat requirements and biological information available through NMFS and USFWS (Services) publications allowed the agency to determine whether a species could be reasonable be expected to occur on fields. The documents DP Barcode 428301 and 436497 present the rationale for occurrence on or off the field for each species identified as present in the states where the GE corn, cotton, and soybean crops would be cultivated.

<u>Direct Effects RQ Use</u>

Comment: *Comments expressed that it is improper for the EPA to use FIFRA-based risk quotients and levels of concern to make ESA-based effects determinations and that the EPA is not the expert agency on the biology of listed species, so it must consult with FWS and/or NMFS if there may be any effect at all. The comments assert that it is arbitrary and contrary to law for the EPA to base its ESA conclusions on its own internal—and fatally flawed—assumptions regarding FIFRA risk quotients and levels of concern.*

Response: Consistent with the Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, U.S. Environmental Protection Agency – Endangered and Threatened Species Effects Determinations (USEPA 2004),[7] the EPA established conservative effects thresholds for plants and animals based on effects to survival, growth, and reproduction.[8] With labeled mitigation measures in place, exposures to the product or the 2,4-D choline active ingredient under registration consideration fall below the direct effect thresholds established by the agency for threatened and endangered species. Below these thresholds, the agency concludes that exposures are not reasonably expected to affect individuals of a species (i.e., a "no effect" determination). For situations where the EPA's effects determination was "no effect," not entering into consultation with the Services is consistent with Services' guidance on "no effect" determinations. For example, **"**If the best available data indicate that the species and critical habitat will not respond in any manner, conclude "no effect" and document your finding. No further consultation required." (USFWS 2016).

Indirect Effects

Comment: *Indirect effects such as loss of critical food, forage and nesting sites resulting from reduced plant diversity associated with increased spraying of the whole product, Enlist Duo (separately and in combination with other pesticide products), in these 34 states, have not been assessed, but could further stress vulnerable species.*

Response: The EPA determined that exposures to Enlist Duo off of the treated field do not affect non-target organisms including non-target plants. Therefore, the diversity of the vegetative community outside the treated field would suffer no adverse impacts from the action. The EPA therefore concluded that the possibility of any effects would be limited to only those species within the treated field, an area managed to maintain a monoculture of the crop species.

Specific Effects Determinations

Comment: *The EPA's Determination that the New Use Approvals Are "Not Likely to Adversely Affect" Two Species and "Likely To Adversely Affect" One Species Is Contrary to Law…. After making "no effect" determinations for 527 of the 531 species, the EPA determined that its new use approvals "may affect" the four remaining species. However, the EPA may not unilaterally determine that its action is "not likely to adversely affect" (NLAA)*

[7] https://www.epa.gov/sites/production/files/2014-11/documents/ecorisk-overview.pdf.

[8] As explained above, acute effects LOCs range from 0.05 for aquatic animals that are federally-listed threatened or endangered species (listed species) to 0.5 for aquatic non-listed animal species and 0.1 to 0.5 for terrestrial animals for listed and non-listed species. The LOC for chronic effects for all animal taxa (listed and non-listed) is 1. Plant risks are handled in a similar manner, but with different toxicity thresholds (NOAEC/EC05 and EC25, respectively) used in RQ calculation for listed and non-listed species and an LOC of 1 used to interpret the RQ.

a listed species without first engaging in Section 7 consultation, undertaking at least informal consultation, and culminating in a written concurrence from one of the expert wildlife agencies on that NLAA decision. That is, once the EPA determines that a listed species "may be present" in the action area, it must stop and consult with the expert agency and enter into some form of consultation.

Formal consultation is only not required if through informal consultation the expert wildlife agency agrees, in writing, that the EPA's action will "not likely adversely affect" a listed species. Accordingly, failure to consult and receive written concurrence is a violation of the procedures and substance of the ESA.

For the remaining four species—Eskimo curlew, Sonoran pronghorn antelope, Audubon's crested caracara, and Spring Creek bladderpod— the EPA only initiated informal consultation for the Eskimo curlew. The EPA determined that its action may affect the Sonoran pronghorn antelope in cotton in certain Arizona counties and Audubon's crested caracara in cotton in one Florida county, but concluded its action is "not likely to adversely affect" either species. The EPA determined that its action would "likely adversely affect" the Spring Creek bladderpod. Nonetheless, the EPA did not consult the Services regarding the Sonoran pronghorn antelope, Audubon's crested caracara, or the Spring Creek bladderpod. Instead, once the EPA determined that the species would be present in the action area and affected by the new use approvals, the EPA relied exclusively on its own assessment that a label precluding the use of the product in certain counties would allow it to make a "no effect" determination. The EPA may not unilaterally decide that its action is "not likely to adversely affect" a listed species, nor may it unilaterally determine that a label would reduce the effects to "no effect," and failure to consult the Services is arbitrary and contrary to law.

Response: In the effects determinations documented in DP Barcodes 428301 and 436497, the EPA discussed options to reach a "no effect" determination and so avoid continuation to formal or informal consultation with the Services for each species that was determined to be "may affect" and "likely" or "not likely" to be adversely affected (LAA or NLAA). The mitigation suggested in all cases was to reduce the action area to avoid the species altogether. This could be accomplished by the prohibition of one or more uses of Enlist Duo in the counties where the Services have indicated a particular LAA or NLAA species exists and where overlap with the non-reduced action area lead to a LAA or NLAA determination. The Enlist Duo Final Decision and approved Enlist Duo product label confirm that the federal action has been modified in response to those suggestions and the Enlist Duo product is now prohibited in the counties where DP Barcodes 428301 and 436497 indicated NLAA or LAA determinations for one or more species. Therefore, the removal of Enlist Duo from those counties eliminates those corresponding portions of the action area, thus changing the effects determination to "no effect" for the listed species in those counties. The only case where such prohibitions were not made is for action area overlap with occurrence of the Eskimo Curlew, where the EPA has concluded consultation and FWS concurred with the agency's effects determination in a memorandum included as Appendix N of DP Barcode 428301.

Endangered Terrestrial Invertebrate Comments

Comment: *For insects, the EPA determined that for 2,4-D there will be "no direct toxic effects to terrestrial insects, even within the treated fields" based on acute toxicity studies with honeybees as a surrogate species. However, studies with some 2,4-D formulations have shown toxicity similar to insecticides on another beetle (Freydier and Lundgren 2016). Therefore, calculations of risks to the American burying beetle that do not take into account direct toxic effects of whole formulations may greatly underestimate actual risks.*

Response: Freydier and Lundgren (2016) tested a formulation of 2,4-D (Albaugh LV4) that contains the ethylhexyl ester of 2,4-D. The agency has determined (DP 424054) that ester forms of 2,4-D are not toxicologically equivalent to the acid or its salts because the non-polar nature of un-dissociated ester forms are much more bioavailable. Therefore, the agency concludes that data available for the LV4 formulation are not applicable to characterization of effects and risk associated with the choline salt of 2,4-D. Freydier and Lundgren also present terrestrial invertebrate data for 2,4-D acid and found that the survival, development, sex ratio, weight, feeding behavior and righting behavior of the tested invertebrates exposed to 2,4-D was indistinguishable from controls.

G. Spray Drift Analysis

The Effect of Mitigation for Drift

Comment: *The threshold triggering a finding of "may affect" is extremely low. A triggering effect need not be significant; rather, "any possible effect, whether beneficial, benign, adverse, or of an undetermined character, triggers the formal consultation requirement." Here, the EPA acknowledges that the pesticide may have direct and indirect acute and chronic effects on listed species, yet "expects" that spray drift mitigation language on labels will confine the spray drift to the treated field. This assumption is flawed and not based on the best available scientific and commercial data available.*

In its 2013 Risk Assessment, the EPA acknowledged that 2,4-D is toxic to birds and mammals, and identified 53 endangered species (including mammals and birds) that could potentially be at risk from direct or indirect effects caused by the increased application of 2,4-D in Midwest states where 2,4-D resistant crops are most likely to be planted. The EPA downplayed these risks, arguing—without sufficient evidence—that Enlist Duo would not drift off-field.

Response: The EPA did not make a finding that exposure would not occur off the field. The EPA reviewed the available empirical data regarding the droplet spectra of labeled spray nozzles operated under restrictive label conditions, with the product formulation, and with requirements for tank mixture components to demonstrate no departure for the formulation-

derived droplet spectra. From these data, the agency developed an empirically-based spray drift deposition function that allowed the agency to predict drift downwind from the treated field. This downwind deposition function was then compared to available toxic effect thresholds to determine a distance downwind from an application event where the agency could confidently predict that deposition of drift was no longer sufficient to trigger a concern for effects to any non-target organism. This distance was then compared to the label requirements for spray drift setbacks within the field. The setback distances exceeded the downwind distances for triggering effects concerns, providing an extra margin of safety. Therefore, the agency confidently concludes that, with spray drift mitigation requirements on the label, the lawful use of Enlist Duo will not result in drift levels that reach toxic effect levels for off-field listed or non-listed organisms and that the area of expected toxic effects is limited to the treated field itself.

Comment: *There is an expectation that the EPA label use restrictions for Enlist Duo will mitigate the potential (non-target) risks from exposure. But, pesticide product label directions have been shown to have no effect on decreasing spray drift. The EPA has stated that Enlist Duo's label spray drift mitigations "would reduce exposures off site to levels well below the agency's level of concern." These mitigation measures include 30-foot in-field buffers, applications nozzle restrictions, and a 24-hour rainfast period to reduce runoff. These are not novel mitigation measures and are not effective in reducing non-target impacts from drift.*

Response: The technical analysis provided in DP Barcode 428301 supports the conclusion that legal use of Enlist Duo (i.e., use according to the conditions required on the label) will not result in off-site transport of pesticide at levels meeting or exceeding effects thresholds for listed and non-listed plants and animals. The comment provides no evidence to the contrary.

<u>Tank Mixture and Spray Drift</u>

Comment: *USDA encourages the continued evaluation of pesticide active ingredients as tank mix partners to determine the combinations do not impact spray quality.*

Response: USDA concurred that the approach taken by the EPA in evaluating tank mix partners was consistent with standard EPA practice.

H. Vapor Drift

Comment: *The major marketing spin for Enlist Duo is the promise that the choline salt of 2,4-D is significantly less volatile than other forms of 2,4-D. The EPA's information regarding this is based on a field study submitted by the registrant that is still "preliminary.""" The vapor pressure for the 2,4-D acid is 1.4x10-7mmHg, DMA salt: 1x10-7mmHg, and EHE salt: 3.6x10-6mmHg, while that of 2,4-D choline salt is not provided, but*

the EPA concludes that its volatility flux rate is lower than the EHE and DMA salts. However, it is still not clear what field conditions existed during the study reviewed by the EPA, e.g. temperature, soil moisture content etc., and so this data does not provide meaningful information, and has not been independently corroborated.

Response: The review of the field volatility study was completed on November 18, 2013 (USEPA, 2013) and found adequate for quantitative use in risk assessments. The field volatilization of 2,4-D choline, 2,4-D ethylhexyl ester (EHE), and 2,4-D dimethylamine salt (DMA) was conducted to evaluate vapor phase drift. Trials were conducted at different sites (Indiana, Arkansas, and Georgia) to reflect a range of temperature and field conditions. The 2,4-D choline-specific flux study was completed using the experimental formulations (both 2,4-D choline alone and 2,4-D choline plus glyphosate end use products). Field studies were performed during the months of July to September and the temperature ranged from 48.6 to 90.6°F in IN, 76.1 to 100°F in AR and 65.6 to 96.7°F in GA. Percents of relative humidity were between 26% and 100%. Trials were conducted with applications to bare soil, soybean (30 cm crop height with 80% canopy closure), soybean (15 cm crop height with 15% canopy cover), and cotton (50 cm crop height with 40% canopy cover). Soil temperature and soil moisture were not included in the study report. However, since the recommended application method of 2,4-D choline is foliar (i.e., aboveground), temperature and other meteorological parameters will be the drivers of vapor drift. Study results showed a reduction of volatile loss of the choline salt as compared to the ester and DMA salt forms.

Comment: *Most of the information to mitigate against non-target exposures are vague, unrealistic and unenforceable. For instance, for non-target crops the label states, "At the time of application, the wind cannot be blowing toward adjacent commercially grown tomatoes and other fruiting vegetables (EPA crop group 8), cucurbits (EPA crop group 9), grapes and cotton without the Enlist trait." But by the EPA's own admission, volatilization from treated crops does occur for the choline salt, where residues can arguably then move off-site depending on local conditions. Additionally, wind speeds and direction may change throughout the day making it possible that these nearby crops can be impacted. These real-world occurrences go ignored by the agency, as reflected by the language currently approved for the label.*

Response: The EPA's risk assessment considered potential effects from the volatilization of 2,4-D choline salt using several lines of evidence. 2,4-D choline vapor flux data from a field volatility study was used to address exposure from volatilized 2,4-D to plants. First, data from a laboratory plant vapor study (MRID 48911801) indicated that grape was more sensitive to 2,4-D vapor than cotton, tomato, or soybean (this study was only available for qualitative use because of the methodology used to conduct the experiment). Second, data from several field studies related plant damage in grape, cotton, and soybean to growth or yield endpoints (Andersen et al., 2004; Everitt and Keeling, 2009; Kelley et al., 2005; Marple et al., 2008; Ogg et al., 1991; Robinson et al., 2013). Again, grape was the most sensitive crop with 20% damage resulting in decreases in growth and yield (cotton ranged from 58 to

66% damage and soybean from 35 to 52% damage before decreases in yield occurred). The highest 2,4-D choline flux rate from the vapor flux study was used as the input parameter for two models: AERSCREEN and PERFUM. AERSCREEN predicts 2,4-D exposure from wet and dry deposition beyond the 2,4-D choline treated field. The model indicated negligible amounts of 2,4-D would be deposited through this pathway, and thus there were no risk concerns for plants. The PERFUM model predicts the air concentration of 2,4-D that is expected at the edge of the field and various distances beyond. The results showed that the air concentrations of 2,4-D were below the effects threshold interpretable in terms of effects to growth and yield at the edge of the field, thus indicating no risk concerns to plants from vapor exposures. The EPA believes that exposure assessment methods used in the risk assessment and effects determinations are adequate to protect non-target species beyond 2,4-D treated fields. This conclusion is consistent with empirical data from vapor flux exposure for grapes and cotton (sensitive species) that shows the only discernable plant effects occurring within the treated field, and at application rates in excess of the Enlist Duo label (pages 69 and 70 of DP Barcode 428310).

Comment: *In its Environmental Impact Statement, USDA acknowledges that 2,4-D applications are likely to occur over a longer period of the growing season, which, as temperatures rise, increases the likelihood of volatilization. Even with reduced volatility, the availability of older cheaper formulations creates an economic incentive to continue using the latter, regardless of label instructions.*

Response: The EPA has accounted for regionally and seasonally relevant environmental conditions. The review of the field volatility study was completed on November 18, 2013 (USEPA, 2013) and found the study to be adequate for quantitative use in risk assessments. The field volatilization of 2,4-D choline, 2,4-D ethylhexyl ester (EHE), and 2,4-D dimethylamine salt (DMA) was conducted to evaluate vapor phase drift. Trials were conducted at different sites (Indiana, Arkansas, and Georgia) to reflect a range of temperatures and field conditions. A 2,4-D choline-specific flux study was completed using the experimental formulations (both 2,4-D choline alone and 2,4-D choline plus glyphosate end use products). Field studies were performed during the months of July to September and the temperature ranged from 48.6 to 90.6°F in IN, 76.1 to 100°F in AR and 65.6 to 96.7°F in GA. Percent of relative humidity ranged from 26% to 100%.

An evaluation of the legality or risks of other formulations of 2,4-D that are not registered for use on the herbicide resistant crops is external to the regulatory decision for Enlist Duo.

I. Groundwater Assessment

Comment: *The EPA states in the Environmental Fate and Effects Division's Risk Assessment for the Reregistration Eligibility Document for 2.4-Dichlorophenoxyacetic Acid,184 that the EPA SCIGROW groundwater models do not accurately predict maximum concentrations of 2,4-D in groundwater. Also, by its own admission, the EPA's use of the*

maximum monitored National Water Quality Assessment (NAWQA) concentration in the proposal is also likely to be an underestimate because the USGS and the EPA monitoring data come from "non-targeted" sampling areas.

Response: The SCIGROW model is no longer applicable for groundwater assessment. Since the implementation of PRZM-GW for groundwater (USEPA, 2015), revised estimated drinking water concentrations (EDWCs) of 2,4-D in groundwater were calculated in a drinking water exposure assessment, dated April 16, 2016 (USEPA, 2016b), conducted in support of human health risk assessment. Six standard scenarios, each representing a different region known to be vulnerable to groundwater contamination, are available for use with PRZM-GW for risk assessment purposes. The maximum 2,4-D EDWC in groundwater was 2.94 µg ae/L. An updated review of available monitoring data (USEPA, 2016b) showed that 2,4-D is being detected in groundwater at concentrations that are higher than the values predicted by the EPA's PRZM-GW model. Consequently, the EPA is being protective by not using the modeled maximum EDWC of 2.94 µg ae/L versus the maximum monitoring value of 15.0 µg ae/L for groundwater. The EPA has concluded that an approach based on the monitored data is appropriately protective because the available lines of evidence, including PRZM-GW, do not indicate a potential for higher exposures.

III. Other Concerns

Because similar issues were raised in multiple comments, the comments are grouped into major topic areas and representative comments are excerpted and paraphrased for each topic area and addressed below.

A. Label

Comment: *How does the EPA propose to enforce its safety regulations? I do not believe the EPA has the means to enforce its own rules.*

Response: The agency has developed the restrictions on the label to meet the FIFRA standard of no unreasonable adverse effects to humans and the environment and to protect threatened/endangered species. Failure to comply with the label restrictions is a violation of Federal law. The EPA expects that users will comply with the labeling requirements and the agency works with the states to enforce labeling requirements.

Comment: *Robust educational and informational programs must be designed to assist growers with appropriate use of this new technology to reduce the potential for off-target spray drift and to delay the evolution of 2,4-D resistant biotypes.*

Response: The agency has included in the terms of registration for Enlist Duo™ that the registrant must develop education and training programs that will provide growers with the

best available information on herbicide resistance management and proper application methods.

B. Herbicide Resistance

Comment: *Herbicide resistance has significantly changed agriculture forever in the Southeast with several problematic resistant species. Particularly challenging is glyphosate-resistant Palmer amaranth which has a competitive advantage over crops due to rapid growth, large plant stature, and drought tolerance mechanisms. If not controlled, it can dramatically reduce crop yield or destroy a crop. The spread of glyphosate resistance has resulted in an increased need for costlier, less environmentally friendly weed control options such as hand-weeding, mechanical in-crop cultivation, and tillage.*

Response: The development and spread of herbicide resistant weeds is a widespread problem that has the potential to fundamentally change production practices in U.S. agriculture. The agency agrees that Palmer amaranth is an extremely troublesome weed species that presents novel challenges to corn, cotton, and soybean growers in many regions. The agency also recognizes that Palmer amaranth can cause reductions in yield and crop quality. As described in BEAD's benefits analyses (EPA, 2014; EPA, 2016), the agency agrees that 2,4-D in Enlist crops will provide growers with improved weed control, another option to delay the spread of herbicide resistance, and reduce the need for tillage, and consequent soil erosion.

Comment: *Comments asserted that the overuse of any product or technology will rapidly lead to herbicide resistance so the availability of multiple herbicide technologies and mode of action diversity is critical to resistance management. One of the easiest strategies for growers to implement in the fight against herbicide resistance is the use of multiple effective modes of action through tank-mixtures. However, the tank mix instructions of the label state, "Enlist Duo™ may only be tank-mixed with products that have been tested and found not to adversely affect the spray drift properties of Enlist Duo™. A list of those products may be found at EnlistTankmix.com." The list of products currently approved for tank mixes currently only includes adjuvants. Growers must be able to tank mix appropriate products to insure effective and timely pest management in their production fields. In addition, if products must be applied separately, the additional trips may impact worker safety, production costs, soil compaction, fuel use, carbon footprint, and potential for off-target effects due to different environmental conditions with each pass.*

Response: The agency agrees that proper resistance management stewardship is needed to maintain the benefits of the registration of Enlist Duo. In order to adequately manage herbicide resistance and to maintain the longevity of 2,4-D choline on Enlist corn, cotton, and soybean, the agency is requiring a rigorous resistance management plan as a part of this registration. The agency believes that the resistance management plan implemented with this registration will limit the potential of developing resistance in target weeds.

The agency recognizes that tank mixes that use multiple modes of action are one of the simplest ways for growers to apply multiple modes of action to combat the development of herbicide resistance. However, the uncertainties regarding the risk of changes in droplet size due to tank mixes are of concern to the EPA and yet to be fully evaluated. Therefore, Enlist Duo may only be tank-mixed with products that have been tested and found not to adversely affect the spray drift properties of Enlist Duo. As required in the terms of registration, Dow must maintain a website that includes a list of products that have been tested and found to not adversely affect the spray drift properties of Enlist Duo. This list will be continuously updated as more products are found to be acceptable for tank mixing.

Comment: *Comments expressed concern that over dependence on chemical controls has resulted in the overwhelming selection of weeds resistant to the very same chemicals used to control them and notes that scientists have advised against the dependence on herbicides, instead advocating for the use of crop rotations and the rotation to non-GE crops. Comments state that scientists note that the introduction of 2,4-D GE crops and increased use of 2,4-D will inevitably result in 2,4-D resistant weeds.*

Response: The agency agrees that proper resistance management stewardship is needed to maintain the benefits of the registration of Enlist Duo. In order to adequately manage herbicide resistance and to maintain the longevity of 2,4-D choline on Enlist corn, cotton, and soybean, the agency is requiring a rigorous resistance management plan as a part of this registration. The agency believes that the resistance management plan implemented with this registration will limit the potential of developing resistance in target weeds.

C. Five Year Registration

Comment: *The document does not outline the criteria that the EPA will use to evaluate whether to continue or renew the registration beyond the specified five years. Clear criteria should be developed in collaboration with the registrant and taking all factors influencing evolution of resistance into consideration.*

Response: In the terms of registration, the agency has outlined requirements for the registrant and the condition that they must report annually information such as annual sales of Enlist seed and Enlist Duo™, the current grower agreement, the current education program and associated materials, summary of efforts aimed at achieving compliance with the grower agreements, and a summary of their determinations as to whether any reported lack of herbicide efficacy was "likely resistance." The agency plans to use this information to determine if modifications must be made to the terms of registration, or if the registration should be allowed to automatically expire. The automatic expiration of the registration allows the necessary flexibility to address any possible issues or outcomes.

D. Increased Use

Comment: *As evidenced with other GE crops, the use of 2,4-D-tolerant crops will increase 2,4-D use, leading to unreasonable adverse risks that the EPA must consider before allowing an unprecedented increase in 2,4-D use.*

Response: The agency agrees that the registration of Enlist Duo™ will result in an increased usage of 2,4-D because applications will now be allowed on GE cotton, there will be a longer period of time that applications can be made on GE corn, and for the first time, up to two applications can be made over-the-top on GE soybeans. In its human health risk assessment for 2,4-D (***2,4-D.*** *Human Health Risk Assessment for a Proposed Use of 2,4-D Choline on Herbicide-Tolerant Cotton, K. Lowe, 10/27/16*), the agency assumed that 100% of the cotton crop, and 100% of all crops to which 2,4-D may be applied, were treated. All agency worker assessments assume that the crop is treated at the maximum application rate, and further make protective assumptions regarding other exposure parameters such as the number of acres treated to assure that workers are not exposed at unsafe levels. In these ways, any increased usage of 2,4-D was fully accounted for in the risk assessments that the agency has conducted for Enlist Duo™.

E. Conditional Registration

Comment: The *EPA may not conditionally register Enlist Duo as a "me-too" under section 3(c)(7)(A) of FIFRA because Enlist Duo is not "substantially similar to any currently registered pesticide" and it does not "differ only in ways that would not significantly increase the risk of unreasonable adverse effects on the environment."*

Response: As is the case for the Enlist Duo™ registration for use on GE corn and soybean, this proposed new use for use on GE cotton is new only for the 2,4 D component of this product, not for glyphosate. Enlist Duo™ uses on GE corn, soybeans, and cotton are already registered on other glyphosate products and are currently in use on these crops. Since no new use patterns and no new exposures for glyphosate are being considered with this registration action, no new assessment is needed for glyphosate. However, GE corn, soybeans and cotton are new uses for the choline salt of 2,4-D. Therefore, [the Proposed Decision] discusses the results of the EPA's findings specifically to the assessment of the choline salt of 2,4-D on GE corn, soybeans, and cotton.

In general, when the EPA receives an application for a registration action to add a "new use" as defined pursuant to 40 CFR 152.3,[9] the agency assesses the risks and

[9] A "new use" is defined as any proposed use pattern if: (1) it requires a new tolerance action under the Federal Food, Drug, and Cosmetic Act; (2) it is a changed use pattern -- e.g., first outdoor use or first aquatic use; or (3) it may significantly increase exposure or change the route of exposure to humans or the environment. 40 C.F.R. § 152.3.

benefits associated with the new use before making a decision on the application. In situations like Enlist Duo™ where a company submits an application for a new use on a product that contains two or more active ingredients (combination product), and the use being requested for this combination product is currently registered for one or more of the active ingredients, the EPA only assesses the risks and benefits of the active ingredient that does not currently have products registered for that use.

For the other active ingredient(s), in this case glyphosate, the EPA treats the application as if it were a "me-too,"[10] and does not conduct new assessments for the already registered uses. Instead, the EPA determined that the glyphosate in Enlist Duo would not cause unreasonable adverse effects on the environment because the use conditions authorized under the Enlist Duo registration are identical or substantially similar to use conditions already authorized for glyphosate in other existing glyphosate registrations, and the EPA does not expect the registration of Enlist Duo to significantly change the locations, methods, or volume of glyphosate used on corn, soybeans, or cotton. Thus, any decision on the Enlist Duo registration would likely have no effect on whether glyphosate continues to be used on corn, soybeans, and cotton – the decision would only impact which glyphosate product would be used. Reevaluation of registered active ingredients (and all registered uses) generally will occur in registration review pursuant to FIFRA section 3(g). This practice of not conducting a new assessment each time the EPA registers a pesticide product that is already registered for the proposed use is reasonable and consistent with the intent of FIFRA and its implementing regulations.

As stated above, this proposed new use action is specific to the 2,4-D component of Enlist Duo. Here, the EPA is not taking any action as it relates to the glyphosate component of Enlist Duo. Although the EPA considers the glyphosate portion of the product as if it were a "me-too," the EPA is not registering the product as a "me-too" since the application in front of the EPA is for a new use for 2,4-D choline salt. That new use is being conditionally registered under FIFRA section 3(c)(7)(B) because of outstanding data that will be part of the registration review process. This section 3(c)(7)(B) registration adds the cotton use as well as expands the use of the currently registered uses of soybean and cotton to an additional 19 states.

IV. References

[10]The EPA has the authority to issue conditional registrations for pesticide products that are identical or substantially similar in their uses and formulation to one or more products or for a combination of previously approved products that are already registered and marketed in the United States and would not significantly increase the risk of unreasonable adverse effects on the environment. These types of registrations are often referred to as a "me-too" or "follow-on."

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