UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: October 14, 2014
Subject: Response to Public Comments Received Regarding New Uses of Enlist Duo™ on Corn and Soybeans
Product Name: Enlist Duo™
EPA Registration Number: 62719-649
Application Date: November 1, 2011

Response to Comments

The Agency received 417,301 comments in response to the public participation process (Docket ID: EPA-HQ-OPP-2014-0195) regarding the Environmental Protection Agency's (EPA's) proposed decision for the application to register the use of 2,4-D choline salt on (Genetically Engineered) GE 2,4-D and glyphosate tolerant corn and soybeans. Comments received were both in favor of and opposed to the decision to register Enlist Duo™, which will provide growers with additional tools to control a broad spectrum of weeds. 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, EPA strives to document and explain the basis of its regulatory decisions through these and other public documents.

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. Because similar human health issues were raised by many commenters, the comments are grouped into major topic areas and each topic area is addressed below. These topic areas fall under 4 major headings: toxicity, risk, exposure, and epidemiology/incidents.

A. Toxicity

Commenters questioned EPA's assessment of toxic effects including developmental, mutagenic, thyroid, endocrine, cancer, reproductive, immunotoxic, and kidney effects. Commenter's questions focused on how a safety finding could be made when these effects were observed in some toxicity studies, and they expressed concerns about the completeness and adequacy of the toxicity database. In order to address these comments, EPA first presents two important overarching considerations; second, we discuss the Agency's consideration of

the toxic effects regarding each organ system. Following this discussion, EPA identifies and responds to other specific comments regarding toxicity.

1. Overarching Considerations

First, the toxicity database for 2,4-D is complete and robust. This includes a recently completed and reviewed Extended One-Generation Reproductive Toxicity Study (EOGRTS), a study which measures numerous toxic effects in multiple organ systems (endocrine, thyroid, reproductive, developmental, immuno-, and nervous), and across the lifetime of an organism from conception to adulthood. EPA also completed a thorough literature search considering all pertinent toxicity research and found no information which would change the conclusions drawn in the Agency's risk assessment.

A second overarching consideration in responding to commenters' questions is the pharmacokinetic behavior of 2,4-D. 2,4-D is readily absorbed into the blood stream, is removed from the blood by the kidneys unchanged (it is not metabolized), and is rapidly excreted *via* the urine. At high dose levels, renal saturation occurs, which means that the ability of the kidney (renal) to excrete 2,4-D is overwhelmed. As a consequence, 2,4-D builds up in the body. When this occurs, toxic effects are observed. Studies referenced by some commenters utilized dose levels above those causing renal saturation. **However, at doses below those causing renal saturation, toxic effects are not observed.** This is an essential consideration in EPA's 2,4-D assessment: the Agency's assessment establishes a maximum allowable dose which is at least 100-fold below this level, assuring protection of public health, and the levels at which people might be exposed are far below even this level since estimated risks are well below the maximum allowable exposure threshold. Therefore, the Agency's assessment is protective for any effects seen in these studies.

2. Agency Consideration of Toxic Effects regarding Each Organ System

a. Developmental Effects

2,4-D has been thoroughly studied with respect to potential effects on the developing animal. There are two (rat and rabbit) guideline developmental toxicity studies on 2,4-D, which are designed to provide information concerning the effects of exposure of the pregnant test animal on the developing organism (fetal effects including death, structural abnormalities, or altered growth) and an assessment of maternal effects. Functional deficiencies and other postnatal effects have been assessed in the guideline 2-generation reproduction study on 2,4-D and in the 2,4-D extended 1-generation reproduction study, which included a developmental neurotoxicity and immunotoxicity assessment. Developmental toxicity was identified/observed in the rat and rabbit developmental toxicity studies at a maternally toxic dose that exceeded the maternal animal's ability to excrete 2,4-D (i.e., above levels of renal saturation; see *2,4-D. Human Health Risk Assessment for a Proposed Use of 2,4-D Choline on Herbicide-Tolerant Corn and Soybean*, LaMay, August 8, 2013). There are clear no-observed-adverse-effect levels (NOAELs; defined as doses at which no adverse toxic effects are

seen in toxicology studies, and upon which the Agency's estimates are typically quantified) in both studies for the developmental effects observed, and an acute dietary risk assessment point of departure (POD; defined as the NOAEL or other dose level to which safety factors are typically applied when quantifying risks) is based on the rat developmental toxicity study [where fetal skeletal abnormalities (14^{th} rudimentary ribs were observed at a dose level that exceeded the maternal animal's ability to excrete 2,4-D)]. Therefore, the Agency has considered and addressed concerns for developmental toxicity in its risk assessment.

b. Mutagenicity

While the concern for mutagenicity was raised by commenters, no supporting evidence was provided. Similar claims were submitted by the Natural Resources Defense Council (NRDC) in a November 6, 2008 petition requesting that EPA revoke all pesticide tolerances for 2,4-D under section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), and were thoroughly addressed by the Agency in an April 18, 2012 Order denying that petition (*see* 77 FR 23135, 23149-23151 (Apr. 18, 2012)). EPA's current testing requirements focus on tests for mutagenic effects, *i.e.,* heritable changes in DNA that could potentially lead to disease. Based on a full battery of mutagenicity testing, 2,4-D is not considered to be a mutagen.

c. Thyroid Toxicity

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 included thyroid weights, thyroid hormone levels (T3, T4, TSH), and histopathology evaluation of the thyroid. 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 NOAELs were identified, and the endpoints selected for risk assessment are protective of potential thyroid effects. EPA has quantified risk of 2,4-D to assure exposures are at least 100-fold lower than levels where renal saturation occurs.

d. Endocrine Effects

The Agency has comprehensively evaluated the endocrine effects of 2,4-D. As noted in the Order denying the NRDC petition seeking revocation of 2,4-D tolerances under the FFDCA (77 FR 23135 (Apr. 18, 2012)), potential hormonal effects can be detected

through behavioral changes, ability to become pregnant, duration of gestation, signs of difficult or prolonged parturition, apparent sex ratio (ascertained by anogenital distances of the offspring), feminization or masculinization of offspring, number of pups, stillbirths, gross pathology and histopathology of the vagina, uterus, ovaries, testis, epididymis, seminal vesicles, prostate, and any other identified target organs. EPA concluded in its review of the data submitted as part of this petition 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.

In addition to the 1998 test guideline for the mammalian two-generation reproductive toxicity study, EPA has proposed the new OECD test guideline for the extended one-generation reproductive toxicity study (EOGRTS) as an alternate EDSP (Endocrine Disruptor Screening Program) Tier 2 test. The extended one-generation reproductive toxicity study was not only designed to provide the traditional spectrum of information from a reproductive study, but was also enhanced to evaluate reproductive and developmental endpoints associated with the endocrine, nervous, and immune systems in male and female adult rodents and offspring at birth, weaning, and puberty, which may not necessarily be covered in other 40 CFR part 158 test guideline studies.

Both the rat two-generation reproduction study and the EOGRTS are available for 2,4-D and have been evaluated by the Agency and incorporated into the hazard assessment of 2,4-D.

The EOGRT study on 2,4-D examined endocrine related parameters, which included parental (male and female) reproductive function; offspring survival, growth, and development; endocrine and systemic toxicity parameters, including estrous cyclicity (adult and offspring); sperm parameters; anogenital distance; nipple retention; sexual maturation (vaginal opening and balano-preputial separation); organ weights (adrenal, thyroid/parathyroid, pituitary, testes and ovaries/other reproductive organs, liver, kidney); thyroid hormone effects; and histopathology of the thyroid, adrenal, pituitary, liver, pancreas, testes, and ovary/other reproductive organs. 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.

Finally, in response to the 2009 Test Order, EPA determined not to require the *in vivo* mammalian Tier 1 tests for 2,4-D (i.e, Uterotrophic, Hershberger, the Male and Female Pubertal Assays) due to the availability of the extended one generation reproduction

study. EPA has received all required final study reports and data for the five *in vitro* assays from the Tier 1 battery for 2,4-D. Although the submitted Tier 1 *in vitro* studies may inform EPA on mechanistic issues in mammalian systems (e.g., whether 2,4-D can bind to the estrogen or androgen receptor in mammals), the studies will not affect EPA's conclusions on the quantitative endocrine risks posed by 2,4-D for humans given the availability of the extended one-generation reproduction study that comprehensively examined the risks to human health from 2,4-D's interaction with endocrine system endpoints.

e. Cancer

Studies in rats and mice showed no statistically significant tumor response in either species; 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. This is further discussed in the Agency's response to epidemiology comments. In accordance with the Agency's 1986 "Guidelines for Carcinogen Risk Assessment, 2,4-D was classified a "Group D Chemical: Not Classifiable as to Human Carcinogenicity." 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 be 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."

f. Reproductive Effects

For 2,4-D, there are two studies that specifically assess reproductive toxicity. These are the 2-generation reproduction toxicity study and the extended one-generation reproductive toxicity (EOGRT) study. Evidence of possible reproductive effects observed in the 2,4-D database at dose levels that exceeded the rat's ability to excrete 2,4-D led to the requirement of further testing included in the EOGRTS. In the EOGRT study, the following reproductive parameters were assessed: parental male and female reproductive function; offspring growth and development; estrous cyclicity (adult and offspring); sperm parameters; anogenital distance; nipple retention; sexual maturation (vaginal opening and balano-preputial separation); organ weights (testes and ovaries/other reproductive organs); and histopathology (testes, ovary, and other reproductive organs). For all of the parameters assessed, a No-Observed-Adverse-Effect Level (NOAEL) was identified and selected as the point of departure for risk assessment. Since there were no adverse effects observed at this dose, quantifying risks using this dose is protective for any effects occurring at higher dose levels that exceed the body's ability to excrete 2,4-D.

Commenters expressed specific concerns regarding certain reproductive effects. These include estrous cycle changes, increased uterine weights, and effects on male reproductive organ weights. Estrous cycle changes observed were not an adverse effect; differences in the stage of cycling are normal among females. An adverse effect would be the lack of cycling or persistent estrous, which did not occur. Regarding increased uterine weights, the pattern of effects must be considered when determining whether the effects are adverse. For 2,4-D there was no consistent pattern of perturbations in the estrogen pathway as evidenced by the lack of effects in a number of estrogen-dependent parameters including but not limited to pregnancy rate, number corpora lutea, estrous cycling, and sexual maturation. Given that none of these were affected, an isolated finding of increase in uterine weights is not considered adverse. Finally, regarding male reproductive organ weight effects, a pattern of effects is again important when considering whether the effect is adverse. In this case there was no consistent pattern of androgenicity observed, fertility was not affected, mating behavior was normal, sexual maturation was not affected, and sperm motility, count and morphology were unaffected. Therefore, the effect was not considered adverse.

Also, see the response above for endocrine effects for additional information.

g. Immunotoxicity

The standard suite of immunotoxicity effects were measured in the EOGRTS. One measure of the *potential for* immunotoxicity is thymus effects, and decreased thymus weight was observed in the EOGRTS. However, changes in thymus weight alone are not an indication of immunotoxicity. The decreases observed in thymus weight in the EOGRT study showed no dose-response, and there were no histopathological changes in the thymus. Moreover, no evidence of a functional deficit in the immune system was observed in the SRBC AFC (Sheep Red Blood Cell Antibody Forming Cell) response and the Natural Killer Cell Activity assays at dose levels approaching or exceeding renal saturation. In the absence of these additional findings, the decreased thymus weight is not considered an effect of concern.

h. Kidney Effects

The kidney is the major target organ of 2,4-D. 2,4-D is readily absorbed into the blood, removed from the blood by the kidneys unchanged, and excreted *via* the urine. At dose levels in the rat greater than 50 mg/kg/day, the ability of the kidney to excrete 2,4-D is overwhelmed, and 2,4-D builds up in the body resulting in toxic effects. For all of the kidney parameters assessed in the studies on 2,4-D, clear No-Observed-Adverse-Effect Levels (NOAELs) were identified. Points of departure selected for quantifying risk assessment are below levels at which kidney effects were observed and are therefore protective of any potential kidney effects occurring at higher dose levels that exceed the body's ability to excrete 2,4-D.

3. Responses to Other Specific Comments Regarding Toxicity

Comment: *Synergistic effects of 2,4-D and glyphosate and/or formulation inerts must be considered*

Response: The Agency routinely requires submission of acute toxicity data for both individual pesticide active ingredients and formulated pesticide products. 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.

Comment: *Toxicity of the 2,4-D metabolite, 2,4-dichlorophenol (2,4-DCP), must be considered*

Response: There are adequate toxicity data available on 2,4-DCP, which show that 2,4-DCP is less toxic than 2,4-D (i.e., higher dose levels are tolerated; NOAELs/LOAELs are higher). Both the rat National Toxicology Program (NTP) carcinogenicity and mouse NTP carcinogenicity studies (1989) on 2,4-DCP are negative for carcinogenicity. In the 2-generation reproduction study on 2,4-DCP, the NOAEL for effects on offspring is 2,000 ppm (134 mg/kg/day), based on a slight decrease in the number of pups, delayed eye opening in both sexes and generations, and slight (≤1 day) delays in sexual maturation at 543 mg/kg/day. The reproductive toxicity NOAEL is 2,000 ppm (134 mg/kg/day, based on decreased number of implantation sites (F1 parental/F2 offspring) at the LOAEL of 543 mg/kg/day. Developmental toxicity was not observed in the rat.

Although 2,4-DCP is shown to be less toxic than 2,4-D, the Agency assessment assumes 2,4-DCP is as toxic as 2,4-D – thus the risk assessment over-estimates risk and could be refined by considering the reduced toxicity of the metabolite. However, this is not necessary since the assessment assuming equivalent toxicity showed no risks of concern.

Comment: *EPA should use the 2,4-D dose of 100 ppm, not 300 ppm, as the point of departure for human health risk assessment and apply an additional 10-fold safety factor to protect children's health, pursuant to the Food Quality Protection Act.*

Response: The commenter indicated that toxic effects were observed in the EOGRTS below 300 ppm, the dose selected by the Agency as the No Observed Adverse Effect Level (NOAEL). The effects included increased uterine weight, decreased reproductive organ weight in males, thyroid hormone level changes, decreased thymus weight, and kidney effects. Each of these was discussed earlier, but are repeated below to provide in one place a concise response to specific concerns raised regarding the EOGRTS.

Regarding the reproductive effects, the Agency's conclusions were based on the following. Differences in the stage of estrous cycling are normal among females; an adverse effect would be the lack of cycling or persistent estrous, which did not occur in the study. Increased uterine weight was not considered adverse since there was no consistent pattern of estrogenicity, pregnancy rate was not affected, the number corpora lutea was unaffected, estrous cycling was normal, and sexual maturation was not affected. Regarding male reproductive organ weight effects, there was no consistent pattern of androgenicity observed, fertility was not affected, mating behavior was normal, and sexual maturation was not affected.

Regarding thyroid toxicity, 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.

The standard suite of immunotoxicity effects were measured in the EOGRTS. One measure of the *potential for* immunotoxicity is thymus effects, and decreased thymus weight was observed in the EOGRTS. However, changes in thymus weight alone are not an indication of immunotoxicity. The decreases observed in thymus weight in the EOGRT study showed no dose-response, and there were no histopathological changes in the thymus. In the absence of these additional findings, the decreased thymus weight is not considered an effect of concern.

For all of the kidney parameters assessed in the studies on 2,4-D, clear No-Observed-Adverse-Effect Levels (NOAELs) were identified, and the points of departure selected for risk assessment are protective of any potential kidney effects occurring at dose levels that exceed the body's ability to excrete 2,4-D.

The conclusions drawn by the Agency regarding setting of NOAELs and LOAELs for the EOGRTS are consistent with accepted standards for evaluation of toxicology data and determination of whether a toxic effect should or should not be considered adverse. Comments regarding EPA's decision to reduce the FQPA safety factor to 1X are addressed below.

Although the Agency believes its decision to establish the NOAEL from the EOGRTS at 300 ppm and to reduce the FQPA safety factor to 1X is scientifically sound and consistent with established science policy, in order to more fully characterize risk potential, risks were also assessed using the NOAEL = 100 ppm as the risk assessment point of departure and retaining the FQPA safety factor of 10X. Using these inputs, risks were still acceptable for all age groups for all components of the assessment: dietary food and drinking water exposure, volatility, spray drift, residential, and aggregate assessment.

Comment: *The Agency's assessment was largely based on forms of 2,4-D other than the choline salt; the choline salt may exhibit differences in toxicity and absorption relative to other forms of 2,4-D*

Response: The extensive database on 2,4-D was used in the risk assessment on the choline salt of 2,4-D. This is consistent with the use of the 2,4-D database for other 2,4-D salts. There are data that demonstrate similar toxicities among the various salts of 2,4-D, and there are data available to show that 2,4-D salts readily dissociate into 2,4-D acid and the cation. The counter-ion in the Enlist Duo™ formulation, choline, is an essential nutrient, and not of toxicological concern.

Commenters provided no data to substantiate or explain the concern for differences in absorption. As noted above, choline is an essential nutrient, and available toxicity data demonstrate a similar toxicology profile across 2,4-D salts. A similar toxicity profile suggests that any differences in absorption are not of concern.

B. Risk

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

Response: As a result of Section 405 of the Food Quality Protection Act of 1996 (P.L. 104-170), in establishing a "tolerance" under section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA), section 408(b)(2)(C) of the FFDCA states, in part, that:

> "… an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children."

This is commonly referred to as the "FQPA safety factor" or the "10X" safety factor.

Section 2(bb) of FIFRA, in turn, defines "unreasonable adverse effects on the environment" to mean, in part: "… a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under section 408 of the [FFDCA]."

Whether a margin of safety different from the tenfold margin of safety under this provision should be applied was assessed 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 is protective for exposure to infants and children (including fetuses).

As discussed in other comment responses, the Agency has a complete and robust database for 2,4-D for both toxicity and exposure. Please refer to other specific comments for details.

Increased sensitivity was observed in fetuses in the rat developmental study and the rat 2-generation reproduction study. In order to assure that the human health assessment adequately protected children and fetuses for these sensitivities, doses were chosen for regulation which were below the levels at which these effects were seen, i.e., the starting points for determining maximum allowable human exposures (before applying any safety factors) were well below levels at which these more sensitive toxic effects were observed – this assures protection of infants and children for these sensitivities. Additional safety factors of 10X for extrapolation across species and 10X for variability within the human population (total = 100X) were then applied to these doses to assure adequate human health protection.

The Agency assessed all potential 2,4-D exposure pathways for children for all uses of the chemical – dietary exposure through food and drinking water, residential exposures, spray drift, volatilization, and swimming – using protective assumptions which will not underestimate childrens' exposures. These exposure assessments are discussed in detail in the exposure section of this response (pp. 12-17).

Based on these 3 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, and EPA determined that the 10X FQPA safety factor could be reduced to 1X, consistent with the requirements of the Food Quality Protection Act.

Comment: *EPA failed to thoroughly examine all of the significant health and environmental risks of 2,4-D including that of inhalation and aggregate exposure*

Response: EPA thoroughly examined all of the significant environmental and health risks of 2,4-D including inhalation and aggregate exposure. EPA's inhalation assessment evaluated risks using the most sensitive toxic effect – effects in the respiratory tract. Exposure to both residential pesticide users and professional applicators who would be applying the new 2,4-D formulation to herbicide resistant corn and soybeans were well below levels of risk concern.

Regarding inclusion of inhalation exposure in the aggregate assessment, aggregating exposures when toxic effects are different for the different exposure routes (e.g., oral and inhalation) is not scientifically appropriate. Furthermore, EPA calculated the systemic dose corresponding to the inhalation level at which the very sensitive portal of entry inhalation effects occur. These Human Equivalent Doses (HEDs) are well below levels at which effects from oral exposure are regulated; therefore, regulating based on the portal of entry effects will be protective for any contribution from inhalation route to the aggregate exposure.

EPA's aggregate exposure assessment included contributions from food, drinking water, and non-occupational exposure, and was done for both adults and children. High-end, unrefined screening level inputs were used which resulted in exposure estimates well below levels of risk concern. Adult aggregate exposure included contributions from food, drinking water, and incidental oral exposure from swimming in a 2,4-D treated water body; the aggregate MOE was 1,800. Children's aggregate exposure included contributions from food, drinking water, and incidental oral exposure hand to mouth from turf; the aggregate MOE was 340.

Therefore, EPA's risk assessment considered both inhalation and aggregate exposures and concluded that there were no risks of concern.

Comment: *2,4-D is a major source of dioxins presenting risk concerns for use of the chemical; 2,4-D is a component of Agent Orange and therefore of significant risk concern*

Response: 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.

Related to the dioxin comments, some commenters questioned 2,4-D's hazard potential referring to its presence in Agent Orange, a defoliant used during the Vietnam War thought to cause a range of health effects. Although 2,4-D is known as one of the components of Agent Orange, it is not the one responsible for the adverse health effects experienced by those exposed to Agent Orange. Agent Orange was a mixture of two different herbicides—2,4,5-T and 2,4-D—as well as kerosene and diesel fuel. Agent Orange contained high levels of dioxin, a contaminant found in 2,4,5-T that causes cancer and other health concerns in people. EPA cancelled all use of 2,4,5-T in 1985 because of these risks.

Comment: *EPA must consider cumulative risk to 2,4-D and other structurally related compounds*

Response: Chemicals from the same chemical class have been identified and will be further investigated as a possible common mechanism group during the Agency's Registration Review process. However, we note that the compounds with the closest structural similarity to 2,4-D are 2,4-DB (4-(2,4-dichlorophenoxy)butyric acid) and 2,4-DP (2-(2,4-dichlorophenoxy)propanoic acid). The most recent assessments indicate that the dietary risks for these compounds are insignificant. Furthermore, using a highly protective screening-level approach of combining high-end children's risks from the two chemicals results in no risks of concern.

Comment: *2,4-D is linked to Non-Hodgkin's Lymphoma (NHL)*

Response: The FIFRA Scientific Advisory Panel, a Federal Advisory Committee with whom EPA consults regarding novel or contentious scientific issues, evaluated the cause and effect relationship between exposure to 2,4-D and non-Hodgkin's lymphoma in 1994. They concluded that "*data are not sufficient to conclude that there is a cause and effect relationship between exposure to 2,4-D and non-Hodgkin's lymphoma,*" and "*[s]ome case-control studies have shown a risk of non-Hodgkin's lymphoma (NHL) in association with farming but many of these studies did not control for other agents in addition to 2,4-D.*" (US EPA, March, 1994. AN SAB REPORT: ASSESSMENT OF POTENTIAL 2,4-D CARCINOGENICITY. REVIEW OF THE EPIDEMIOLOGICAL AND OTHER DATA ON POTENTIAL CARCINOGENICITY OF 2,4-D BY THE SAB/SAP JOINT COMMITTEE)

In both 1996 and 2004 further reviews were conducted of additional epidemiological studies by Blondell (D311464, 12/8/04) both with similar conclusions.
In 2012, the Agency considered additional information provided by the Natural Resources Defense Council regarding, among other things, 2,4-D's linkage to non-Hodgkin's lymphoma, again resulting in similar conclusions.

Most recently, an abstract was presented at the 23rd Conference on Epidemiology in Occupational Health (EPICOH 2.0.13; Improving the Impact, 18-21 June, 2013, the Netherlands, Freeman, et. al.) considering a prospective cohort of licensed pesticide applicators within the National Agricultural Health Study. The results of this study showed no association between 2,4-D and non-Hodgkins lymphoma.

While there has been much focus on epidemiology data suggesting a linkage between NHL and farm work, there is insufficient scientific evidence supporting a specific linkage with 2,4-D. Furthermore, this linkage is not supported by data on laboratory animals as discussed in the cancer assessment portion of this response.

Based on the available epidemiology data and controlled studies, the Agency therefore concludes that there is not sufficient information to show a cause and effect linkage between 2,4-D exposure and NHL. This conclusion was also reached by Health Canada's Pesticide Management Regulatory Agency.

Comment: *2,4-D is linked to Parkinson's disease (PD)*

Response: The Agency 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). Overall, six key studies explicitly evaluated the putative association of PD with 2,4-D exposure, with four studies documenting elevated risks (Odds Ratios (OR) >1) and two studies finding no increased risk. Of the four studies associating elevated odds for PD with 2,4-D exposure, only one study had statistically significant results (Tanner et al., 2009). Although Tanner et al. (2009) did find a significant association between 2,4-D exposure and PD with OR of 2.59 (95% CI= 1.03, 6.48; *p*-value= 0.04), they did not find a statistically significant evaluated risk associated with 2,4-D in 2011

(OR of 1.2 for men and women, with the CI, 0.57-2.4). Overall, the Agency concludes that the available evidence is not sufficient to conclude that there is a causal link between exposure to 2,4-D and PD.

C. Exposure

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

Response: Field trials were conducted in which 2,4-D tolerant corn and soybean were treated with 2,4-D choline according to label directions, and in the manner likely to lead to highest potential food residues. These field trials were used to determine the residue levels of 2,4-D and 2,4-DCP (2,4-dichlorophenol) in tolerant corn and soybean, which were used in the updated dietary risk assessment and for tolerance setting purposes.

For 2,4-D-tolerant field corn and soybean, the metabolite 2,4-DCP was included as a residue of concern for dietary risk assessment purposes, as there are greater amounts of 2,4-DCP found in resistant crop compared to non-resistant crop. Therefore, the dietary assessment considered the combined residues of 2,4-D and 2,4-DCP in tolerant corn and soybean based on use patterns expected to result in the highest food residues (maximum use rates, maximum number of applications, minimum interval between applications, minimum interval between last treatment and harvest). Furthermore, the Agency assumed tolerance level residues (or higher) in all crops – the tolerance is a statistically-derived upper bound on allowable residues in crops which will not be exceeded with legal use of the pesticide.

Additionally, the dietary risk assessment assumed that 100% of the U.S. corn and soybean crops are treated to account for potential increased use of 2,4-D.

Livestock can also ingest 2,4-D and its metabolites in their diets as a result of eating treated feeds such as corn grain. The Agency's assessment of residues in meat, milk, poultry and eggs will not change as a result of increased usage on any given feed item since the percentage of crop treated is not factored into these assessments; the entire feed crop is assumed to be treated, and livestock are assumed to ingest the corresponding residues. Therefore, the high-end residues and dietary risk estimates assumed to potentially result in livestock commodities will not increase if the usage of 2,4-D expands.

In assessing 2,4-D exposure from breast milk consumption, the Agency considered available data on the ruminant metabolism and magnitude of the residue; a tolerance for residues of 2,4-D in cow's milk is set at 0.05 ppm. As stated above, the tolerance is a statistically-derived upper bound on allowable residues which will not be exceeded with legal use of the pesticide.

The Agency also considered the chemical properties of 2,4-D, specifically the octanol-water partition coefficient (K_{OW}). This is one predictor of the potential for a pesticide or any

chemical to bioaccumulate because high values of K_{OW} indicate a tendency for a chemical to partition into lipids (fat, including milk fat) rather than water. Chemicals that partition into lipids can accumulate in the fatty tissues and milk of an organism, while chemicals that partition into water will be excreted rapidly. 2,4-D has a low log K_{OW} (log K_{OW} = 0.18 at neutral pH). This low value indicates that the chemical prefers to partition into water and would not partition into and accumulate in milk, fat and tissues. The metabolism study in rats confirms this showing that 2,4-D is well absorbed orally, undergoes limited metabolism, and is eliminated quickly from the body primarily unchanged in the urine by active saturable renal transport. Based on this information, EPA does not anticipate that residues in breast milk would be greater than those found in cow's milk. Since tolerance level residues in milk were used in the dietary risk assessment, the human health risk assessment is expected to be protective for breast milk consumption. No data have been submitted, or have been found by the Agency in the literature, refuting this conclusion.

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. Drinking water model descriptions are available on the EPA websites, and the models themselves are available for download. Specific inputs for the 2,4-D assessment are described in the Agency review of this action.

Finally, as discussed in the response to comments section on toxicity, the toxicity endpoint used in the dietary assessment for both 2,4-D and 2,4-DCP was for 2,4-D parent toxicity; since 2,4-DCP is less toxic than 2,4-D, comparing 2,4-DCP residues to 2,4-D endpoints is very protective.

In summary, using the highly protective assumptions described above, the acute and chronic dietary risk estimates for 2,4-D were not of concern for adults, children, pregnant women, or any other population group. Since the Agency assumed that all crops/foods with registered uses for 2,4-D would be treated, and that everyone who ate these foods would consume high-end residues of 2,4-D in all of these foods, any increased usage of 2,4-D will not result in risk estimates higher than those already calculated, which are not of concern.

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: 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 Probabilistic Exposure and Risk model for fumigants (PERFUM). Approaches 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. Although the Agency believes its decision to reduce the FQPA safety factor to 1X is scientifically sound and consistent with established science policy, in order to more fully characterize risk potential, volatility risks were also assessed retaining the FQPA 10X safety factor. It should be noted that even with application of an additional 10X FQPA safety factor, there are no risks of concern at the field edge.

Comment: *Invalid assumptions were used for spray drift (an increased frequency of applications will cause increase in exposure; OPP should evaluate the AgDRIFT and AgDISP models according to CREM recommendations)*

Response: In assessing risks from spray drift, the Agency assumes that spray drifts onto a lawn adjacent to an agricultural field being treated, and children immediately play on that

lawn. This approach has been vetted both through the FIFRA Scientific Advisory Panel and a public comment process. If the pesticide being assessed also has a lawn use, and that lawn use has higher lawn turf residues than those estimated from spray drift, then risks from spray drift will be less than risks from lawn use - if the lawn use shows no risk concern, spray drift will have no risk concern. This is the case for 2,4-D.

The use rate for direct application of 2,4-D to residential turf exceeds the use rate on corn and soybean, thus the residential turf assessment is protective of any potential drift onto nearby lawns. The residential turf uses were assessed using the 2012 Residential Standard Operating Procedures as well as chemical-specific residue data. By using a toxicity value representing 30 days of exposure combined with maximum day-of-treatment turf residues, people on treated lawns were assumed to have the maximum day-of-application exposure every day for 30 consecutive days, a very health protective assumption. There were no risks of concern.

In addition to the lawn use assessment completed to support the aggregate risk assessment for this new use, a quantitative spray drift assessment specific to the new corn and soybean uses was also completed to address several comments brought up during the public comment period. This assessment used the AgDRIFT model to assess spray drift. AgDRIFT has undergone extensive validation including evaluation by a FIFRA Scientific Advisory Panel. This model quantifies residues deposited on a residential lawn that is adjacent to the field being treated. These residues were used in conjunction with the 2012 Residential SOP for turf assessment to determine exposure to children via contact of residues that have deposited on lawns via spray drift. To address specific comments submitted, the Agency conducted this assessment using a risk assessment Point of Departure (PoD) 3-fold lower (more protective) than used in the Agency assessment, and also applied the 10X FQPA safety factor. As with the turf assessment, considering the Agency's use of a toxicity value representing 30 days of exposure combined with maximum day-of-treatment spray drift residue, people on lawns exposed to spray drift were assumed to have the maximum day-of-application exposure every day for 30 consecutive days, a very health protective assumption. There were no risks of concern using even these extremely protective assumptions.

The Agency did not use AgDISP in its assessment, so comments related to use of that model are not pertinent. AgDRIFT was not used in the Agency's initial risk assessment, but was used as described above, to more fully characterize risks from drift in response to comments received on the petition. While AgDRIFT has not gone through the formal CREM (Council for Regulatory Environmental Modeling) evaluation process, it has been evaluated by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) which uses essentially the same criteria in its evaluation and found the model to be scientifically supported and sound. The AgDRIFT model is based on well-established physics, and was developed jointly by the EPA, USDA, and industry, undergoing many quality assurance steps in the process. The model is well supported by data from drift studies. For these reasons, we believe that the study has gone through sufficient review to be used in this context.

Some commenters 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, as described above.

Comment: *The Agency's worker exposure must use maximum application rate*

Response: The worker exposure assessment was completed using the maximum application rate.

Comment: *Residential exposure will increase with this new use (2,4-D is found in carpet dust even though they had not used the pesticide recently; 2,4-D is blowing in or tracked into homes; farmer and farm families' exposures are underestimated)*

Response: EPA believes that the current method of hand-to-mouth exposure assessment for pesticide residues from applications directly to turf is protective of exposure to indoor house dust. The current approach accounts for exposure to residues immediately after a direct application is made at the maximum application rate, residues which will be much higher than those found in house dust from track-in. Furthermore, residues immediately after a direct turf application were used and compared to a toxicity endpoint representing 30 days of exposure. As discussed earlier, this results in very protective estimates of risk.

II. Environment

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

A. Spray Drift

Comment: *Spray drift is a complete exposure pathway for the proposed new uses of 2,4-D. 2,4-D is known to drift and there have been numerous spray drift incidents (mainly crop damage) that have been associated with the use of 2,4-D. Drift will adversely affect sensitive crops in neighboring fields as well as endangered/threatened species or other non-target organisms. In particular, the later timing of 2,4-D applications will increase direct risk to non-target plants (indirect risks to other species that rely on plants) because application events will occur when more plants are more fully leafed out. Spray drift cannot be reasonably restricted to the field to which 2,4-D is being applied and the proposed buffer of 30 ft is too small.*

Response: The Environment Fate and Effects Division (EFED) did identify spray drift as a complete exposure pathway for non-target organisms in the original risk assessment (USEPA 2013a, D400223+). The assessment also acknowledged a large number (~460) of plant incidents as well as incidents to other non-target organisms (reported to the Agency as of

October 31, 2012). Dicotyledonous terrestrial plants were identified as the most sensitive non-target organisms and spray drift buffers of > 1000 ft were calculated to be protective. The 2,4-D choline salt itself has drift/volatility-reducing characteristics. Consequently, the assessment was refined using droplet spectrum data that were specific to the GF2726 formulation (MRID 48844001). As a result, spray drift buffer distances for the most sensitive species (dicotyledonous terrestrial plants) were reduced to 202 ft.

In June 2013, EPA issued an addendum to the original risk assessment (USEPA 2013b, D411614) that revised the terrestrial dicotyledon endpoint that was used in the risk assessment. Originally, an endpoint from a 2,4-D ester had been chosen because it was the most sensitive among all the plant data. EPA reconsidered that endpoint given that 2,4-D choline is not an ester, and changed the endpoint to reflect the most sensitive toxicity value for a 2,4-D salt or amine, consistent with the approach taken in the Registration Eligibility Decision (RED) (USEPA 2005a). Based on the 2,4-D salt/amine endpoint, spray drift buffer distances ranged from < 25 ft to 30 ft to protect the most sensitive plant species. EPA believes this new endpoint is the most appropriate and the buffers are adequate to protect the most sensitive plant species from spray drift.

After determining the appropriate buffer, EPA discussed mitigation measures with Dow AgroSciences, LLC (DAS). To confine spray drift to the field, DAS agreed to implement a 30 ft in-field buffer when the wind is blowing towards a sensitive area that could provide habitat for a non-target species. Non-sensitive areas are considered fields with crops, buildings, or pavement; all other areas constitute potential habitat for non-target species. In cases where the wind is blowing towards a sensitive area, a 30 ft in-field buffer must be implemented. The 30 ft buffer strip may be sprayed at a later time when the wind direction has shifted and is no longer blowing towards the sensitive area. EPA determined that by using this approach, any spray drift from 2,4-D choline salt remains on the corn or soybean field that is being treated.

The proposed use allows for one application pre-plant and up to two applications post-plant. The herbicide resistant traits in the genetically engineered corn and soybean plants allow the timing of the post-applications to be much later in the season (up to 48-in sized corn and flowering soybeans) than conventional corn (up to 8-in sized corn) and soybean (no post-plant applications). Potential risk concerns to non-target species were therefore considered in light of the later timing of applications of 2,4-D choline salt. For those groups of organisms identified in the original screening-level risk assessment (USEPA 2013a) as potentially at risk, the 2014 endangered species assessment (USEPA 2014, D418022) considered how the later 2,4-D application timing could affect non-target species. Using a combination of species-specific biology, diet, habits, migration, and geographic proximity, the assessment (USEPA 2014) determined that no species (terrestrial and aquatic plants, mammals, birds, reptiles, amphibians, terrestrial invertebrates, aquatic invertebrates, or fish) within the 6-state action area (Illinois, Indiana, Iowa, Ohio, South Dakota, Wisconsin) exceeded the level of concern for spray drift as established by the Agency.

B. Synergy of glyphosate and 2,4-D

Comment: *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: Although the Agency does not routinely include a separate evaluation of mixtures of active ingredients, 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.

In the case of a formulation with multiple active ingredients, each active ingredient is subject to an individual risk assessment for a regulatory decision regarding the active ingredient on a particular use site. If effects data are available for a formulated product containing more than one active ingredient, they may be used qualitatively or quantitatively in accordance with the Agency's Overview Document and the Services' Evaluation Memorandum (USEPA 2004; USFWS/NMFS/NOAA 2004).

Synergistic reactions among chemicals are possible, but considered rare. For 2,4-D and glyphosate specifically, the Agency compared the Enlist Duo™ formulation-specific acute oral rat study (OPPTS 870.1100; MRID 48289803) LD_{50} of 623 mg ae/kg-bw (confidence interval of 389 to 4980) with the 2,4-D-only LD_{50} used in the assessment (441 mg ae/kg-bw) (MRID 41413501). The endpoints are similar and do not indicate a synergistic effect of 2,4-D and glyphosate for mammals.

Furthermore, EPA considered an open literature peer-reviewed published study by Abdelghani *et al.* (1997) that specifically looked at the toxicity of glyphosate/2,4-D mixture on channel catfish, bluegill sunfish, and crawfish. The experiment first tested the toxicity of 2,4-D and glyphosate individually. Then the two chemicals were mixed together in a 1:4 ratio (glyphosate:2,4-D); it is recognized that the ratio of glyphosate to 2,4-D choline salt in the Enlist Duo™ formulation (1:1) is higher. After accounting for the inherent differences in toxicity between the individual chemicals, the study concluded that no synergistic effects were observed. EPA agrees with the findings in this study that there is no synergistic interaction of 2,4-D and glyphosate for freshwater fish or freshwater invertebrates.

Given that there is no indication of synergism between 2,4-D and glyphosate for mammals, freshwater fish, and freshwater invertebrates, EPA believes it is reasonable to assume that there are no synergistic interactions for the taxonomic groups that were not tested, including plants.

C. Volatility

Comment: *2,4-D has been known to volatize under certain environmental conditions and cause damage to off-site plants. EPA's volatility assessment relied on questionable laboratory plant data. Furthermore, the volatility study used to derive a vapor flux rate*

specific to 2,4-D choline salt was not fully reviewed. Overall, there are uncertainties regarding EPA's conclusions that the volatilization exposure pathway does not present risk concerns for Enlist Duo.

Response: EFED's risk assessment considered potential effects from the volatilization of 2,4-D choline salt (USEPA 2013a) using several lines of evidence. 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.*, unpublished). Again, grape was the most sensitive 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). Third, a field study (MRID 48862902) placed potted grapes and cotton on and off of a field (5 m and 15 m) that had recently been treated with 2,4-D choline salt. At the end of the 3-day exposure period and 27 day observation period, only plants placed directly on the field showed outward signs of damage (cotton – 40%; grape – 0.6%). From these three lines of evidence, a conservative plant toxicity threshold of 20% physical damage was chosen for the volatility analysis. 2,4-D choline vapor flux data from a field volatility study (MRID 48862902) was used to address exposure from volatilized 2,4-D to plants that were off the field. At the time of the ecological risk assessment, the study was under review, but preliminarily considered to be scientifically sound and appropriate for use in the risk assessment. The review of the field volatility study was completed on November 18, 2013 (USEPA, 2013c) and found acceptable for quantitative use in risk assessments. The highest 2,4-D choline flux rate from the study was used as the input parameter for two models: AERSCREEN and PERFUM. AERSCREEN predicts 2,4-D exposure from wet and dry deposition off of the 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 20% plant damage threshold at the edge of the field, thus indicating no risk concerns to plants from vapor exposures.

D. Data Gaps

Comment: *EPA's ecological risk assessment contained a number of ecological and fate data gaps that are usually required to be filled for outdoor pesticide use patterns.*

Response: The ecological risk assessment (USEPA 2013a) acknowledged a number of ecotoxicological and environmental fate data gaps and explained the assumptions that were made in absence of the data:

- Acute oral toxicity test for passerines: This is a generic data gap and the study has been requested as part of the Registration Review data call-in. In the absence of passerine-

specific data, EPA routinely relies on data from bobwhite quail or mallard duck as surrogate species. Data for both species were available for 2,4-D and scaled to adjust for the smaller passerine bird body size.

- Estuarine/marine invertebrate chronic toxicity test: This is a generic data gap, but the Agency has not requested the data because 2,4-D is not expected to remain in the aquatic environment long enough to result in chronic exposures. For screening-level risk assessment purposes, an acute-to-chronic ratio (commonly used to estimate missing toxicity information when toxicity information is available for similar organisms), based on freshwater invertebrates, was used to estimate the missing chronic toxicity value. Given that chronic exposures are unlikely, the Agency considers this a protective approach.
- Terrestrial plant seedling emergence and vegetative vigor tests for Enlist Duo™: This is a data gap that is specific to Enlist Duo™. Terrestrial plant data for commonly-used formulations are usually required by EPA. In the absence of formulations-specific information, EPA uses the most sensitive data from other formulations. This is a routine practice with 2,4-D and many other pesticides because data are not available for all registered formulations of 2,4-D. In this case, data from 2,4-D salts/amines were used as surrogates for Enlist Duo™. The surrogate approach assumes that although data are not available for every formulation, that the available data capture a range of toxicological responses. For 2,4-D, the Agency has a robust set of plant studies; consequently, we can be reasonably confident that by choosing the most sensitive toxicity values from 2,4-D amine/salt studies, that we are being protective. Consequently, these data are not necessary.
- Terrestrial field dissipation study with 2,4-D choline salt: This is a generic data gap 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 because the salt form is similar to other 2,4-D forms.

Comment: *In addition, data from volatility/spray drift and the Enlist Duo formulation (2,4-D choline salt and glyphosate) were not considered in the risk assessment.*

Response: Risk assessments are usually conducted on a single active ingredient basis. Consequently, mixture data for products with multiple active ingredients (*i.e.,* 2,4-D choline salt and glyphosate) are not usually required. Furthermore 2,4-D choline salt/glyphosate data for the acute oral rat study (MRID 48289803) did not show an increased toxicological response compared with the most sensitive 2,4-D endpoint that was used in the risk assessment (MRID 41413501) (see Synergism comment and response for more discussion).

EFED's assessment incorporated data from several studies into the assessment to account for spray drift and volatility. 2,4-D choline salt-specific deposition curve was developed for the AIXR 11004 nozzle to determine a spray drift buffer distance. 2,4-D choline salt vapor flux data were used in conjunction with terrestrial plant ecotoxicity data to set conservative levels of concern for adverse effects and to model whether off-field plant damage was expected to occur.

Comment: *Effects from low dose exposures may not be captured in the standard suite of ecotoxicity studies listed in Part 158 of the Code of Federal Regulations.*

Response: While studies specifically measuring low-dose effects of a chemical are usually not required by the Agency, the normal suite of toxicity studies captures this same information in the form of sub-lethal effects seen at dosing levels below the LD_{50}/EC_{25} thresholds. Sub-lethal effects are incorporated into the risk characterization section for every taxonomic group.

E. Honeybees

Comment: *Enlist Duo will contribute to the decline of honeybees and other pollinators. In particular, pesticides are a contributor to colony collapse disorder in honeybees. EPA did not follow its own Pollinator Risk Assessment Framework when conducting the risk assessment on Enlist Duo.*

Response: EPA recognizes the importance of pollinators and that colony collapse disorder is a complex phenomenon to which pesticide exposure may contribute. The Agency strives to incorporate the most up-to-date pollinator data and risk assessment practices into its analyses. The Pollinator Risk Assessment Framework was adopted in June of 2014, well after the 2,4-D choline salt risk assessment was developed [the honeybee analysis risk assessment (USEPA 2013a) applied the methodology in the RED (2005)].

Honeybee Assessment Using Pollinator Risk Assessment Framework
Honeybee data for acute contact exposures (LD_{50} > 88 µg ae/bee) and acute oral exposure (LD_{50} > 62.6 µg ae/bee) indicated that 2,4-D choline salt is "practically non-toxic" to honeybees on an acute contact basis. No laboratory data are available for chronic effects to adults or acute or chronic effects to larvae, which are considered generic data gaps for 2,4-D under the Framework (USEPA 2013a).

The environmental exposure concentration (foliar spray) for honeybee via contact exposure is 2.7 µg ae/bee. When compared with the LD_{50} of > 88 µg ae/bee for 2,4-D choline salt or the most sensitive 2,4-D value (from an ester form) of LD_{50} > 66 µg ae/bee, the estimated exposure concentration is lower than the LD_{50} threshold.

For the dietary pathway, the estimated exposure concentration for adult honeybees is 32.12 µg ae/bee/day. When compared with the LD_{50} of > 62.6 µg ae/bee, the estimated exposure concentration is about half of the LD_{50}, if taken at face value. The LD_{50} could be much larger, but this is an uncertainty given the "greater than" value derived from the honeybee acute oral toxicity study.

Considering the results of the acute contact and oral analyses conducted in accordance with the Pollinator Risk Assessment Framework, acute risk concerns to adult honeybees are not expected.

F. Dioxins and Other Chemical Impurities

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: The 2,4-D choline salt risk assessment (USEPA 2013a) evaluated the risk from polychloro dibenzo-*p*-dioxin (PCDD) and polychloro dibenzo-*p*-furans (PCDF) that may be formed during the manufacture of 2,4-D. The Agency reviewed product chemistry data for 2,4-D choline salt (USEPA 2012, D405897; Confidential memo) and found that PCDD and PCDF concentrations were lower than those identified in an earlier assessment with 2,4-D and 2,4-D ethylhexyl. The earlier assessment concluded that there were no risk concerns from these concentrations of PCDD and PCDF; thus those same conclusions hold for 2,4-D choline salt given that dioxin concentrations were even lower (USEPA 2005b, D317729).

G. Glyphosate Specific Comments

Comment: *The population of monarch butterflies is declining. Monarchs rely on milkweed for egg-laying and larval development. The widespread use of glyphosate has drastically decreased the milkweed populations as they are often found within or along the edges of agricultural fields. Enlist, which contains glyphosate as well as 2,4-D choline salt, is anticipated to further the decline of milkweed, and indirectly, the monarch butterfly. EPA's risk assessment for 2,4-D choline salt nor existing risk assessments for glyphosate did not take into account the adverse effects of Enlist on the monarch.*

Response: Glyphosate is currently undergoing Registration Review, and a draft risk assessment is scheduled for completion by December 2014. In this assessment, EPA is considering glyphosate's direct and indirect effects on monarch butterflies (including its obligate plant, milkweed) and other non-target species.

Comment: *No endangered species risk assessment has been performed for glyphosate. EPA has not examined the direct or indirect effects of the glyphosate component of Enlist for the proposed uses on herbicide-tolerant corn and soybean.*

Response: EPA did not conduct an endangered species risk assessment for the glyphosate component of the Enlist Duo™ formulation because the uses on this new formulation were not new to glyphosate. Instead, an endangered species risk assessment will be included in the final registration review decision consistent with the National Academy of Sciences (NAS) recommendations. See the response to the Endangered Species comments below. Given that the agencies are continuing to develop and work toward implementation of the NAS recommendations to assess the potential risks of pesticides to listed species and their designated critical habitat, the draft ecological risk assessment supporting the proposed interim registration review decision for glyphosate will not contain a complete ESA analysis. Once the agencies have fully developed and implemented the scientific methods necessary to

complete risk assessments for endangered and threatened (listed) species and their designated critical habitats, these methods will be applied to subsequent analyses for glyphosate as part of completing the final registration review decision.

H. General Ecotoxicity Concerns

Comment: *EPA's risk assessment states that 2,4-D is toxic to fish, aquatic invertebrates, birds, and mammals. Ecotoxicity data for plants also showed them to be sensitive to 2,4-D. In addition to mortality, many of the ecotoxicological studies documented other signs of toxicity/poisoning.*

Response: EPA requires a suite of toxicological data on mammals, birds, honeybees, freshwater fish and invertebrates, estuarine/marine fish and invertebrates, aquatic plants, and terrestrial plants. The purpose of the data is to determine the toxicity of the pesticide when direct exposures occur. This is known as "hazard" and is one of two components that make up "risk."

The second consideration is "exposure." Exposure constitutes how much of the pesticide will come into contact with an organism. "Risk" is a combination of the hazard of the pesticide and the anticipated exposure of the pesticide. For example, a pesticide that is highly toxic to mammals, but is incorporated in the ground may present low risk to mammals because most mammals would not be exposed to it.

The risk assessment for 2,4-D choline salt incorporates both the hazard and exposure components into its conclusions; thus although it may be toxic to some groups of organisms, the risk varies proportionately with exposure. In particular, the mitigation requirements (in-field buffer, wind direction, rainfastness) and drift reducing properties of the 2,4-D choline salt/glyphosate formulation made it possible to limit the exposure from spray drift to sprayed corn and soybean fields. After toxicity information and Enlist Duo^{TM} exposure were considered (USEPA 2014), EPA determined that there are no risk concerns from spray drift for any threatened or endangered species in the 6 states (IN, IL, IA, OH, SD, WI) that were assessed for this registration. From this information (USEPA 2014), EPA made a "no effect" determination under the Endangered Species Act for threatened and endangered species within these states. Additional assessments will be performed if new states are added to the registration.

See also Comment K. below.

I. Registration Review

Comment: *2,4-D and glyphosate are currently undergoing Registration Review. EPA should delay its decision until the comprehensive Registration Review risk assessments, including endangered species, have been completed for both chemicals.*

Response: The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended by the Food Quality Protection Act (FQPA) of 1996, mandates the continuous review of existing pesticides. The Registration Review program is intended to make sure that, as the ability to assess and reduce risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects. The Agency periodically reevaluates pesticides to make sure that products in the marketplace can continue to be used safely. During this process, label revisions, mitigation measures, and other registration changes are equitably applied to all registrations and registrants.

As noted in an earlier comment (above), EPA is currently reviewing glyphosate within the framework of the Registration Review risk assessment process. This analysis will consider the available data to assess exposures that may cause direct and/or indirect effects to taxa, including non-target organisms such as the monarch butterfly. EPA intends to issue a draft risk assessment by the end of December 2014. Once the agencies have fully developed and implemented the scientific methods necessary to complete risk assessments for endangered and threatened (listed) species and their designated critical habitats, these methods will be applied to subsequent analyses for glyphosate as part of completing this registration review.

2,4-D began the Registration Review process in 2012 and is currently receiving and reviewing data submitted by registrants as a result of the data call-in. Given that Registration Review is a lengthy process that may take many years to complete, the Agency's policy is to continue to make registration determinations for new actions during this process. Proposed new registrations are held to the most current data requirements and up-to-date risk assessment practices and must meet the FIFRA no unreasonable adverse effects standard to be registered.

J. Water Quality

Comment: *2,4-D is likely to leach to aquatic environments because of its low soil-adsorption coefficient. Increased use of 2,4-D will lead to elevated surface water pollution, which will affect the quality of water near agriculture as well as non-target organisms.*

Response: The ecological risk assessment considered 2,4-D exposure to aquatic non-target organisms. The Pesticide Root Zone Model and Exposure Analysis Modeling System (PRZM/EXAMS) was used to estimate conservative environmental exposure concentrations (EECs) based on the environmental fate properties, proposed crops, and application methods and rates of 2,4-D choline salt. These EECs are then compared with ecotoxicity information for fish, aquatic invertebrates, aquatic plants, and terrestrial plants to identify potential risk concerns.

The 2,4-D choline salt assessment also considered real-world monitoring data. Formulated 2,4-D rapidly dissociates into its acid form, so the available monitoring data are not specific to any formulated products. However, 2,4-D acid concentrations in surface water from 2,4-D choline is expected to be lower than other formulated products because of its application restrictions (*i.e.,* ground applications only; nozzle and pressure restrictions).

Monitoring data from the United States Geological Survey's (USGS) National Water Quality Assessment Program (NAWQA), indicate that 2,4-D is present in groundwater (concentrations up to 1.4 µg ae/L) and surface water (concentrations up to 8.7 µg ae/L). These concentrations are much lower than the 58 µg ae/L that was predicted as the exposure value using PRZM/EXAMS and subsequently used in the risk assessment. The monitoring data showed that 2,4-D is being detected at concentrations that are below the values that are being predicted by EPA's computer simulation models. Consequently, EPA is being protective by using the modeled number (58 µg ae/L) versus the monitoring number (8.7 µg ae/L). The Agency recognizes that the NAWQA monitoring data may not capture the highest 2,4-D concentrations in the environment, but they would need to be an order of magnitude higher to approach the modeled concentration. Using the 58 µg ae/L from PRZM/EXAMS, no direct risk concerns were identified for aquatic taxa (USEPA 2013a).

K. Risk Determinations and Endangered Species Assessment

Comment: *EPA's risk conclusions for listed and non-listed species are flawed.*

Response: The Agency will address each item under this comment specifically. The Agency has concluded that it conducted the risk assessment consistent with its policies and guidance in place at the time of the submission of the proposal for registration.

Comment: *The assessment did not consider 2,4-D choline salt degradates, of which 2,4-DCP may be more toxic to some organisms.*

Response: The initial ecological risk assessment considered 2,4-DCP, a major degradate of 2,4-D choline salt, in its analysis. Peer reviewed literature and data presented on the European Footprint Database indicate that 2,4-DCP may be more toxic to freshwater fish and invertebrates than 2,4-D. Table 30 in the assessment compares the 2,4-DCP toxicity endpoints with the predicted environmental concentrations of 2,4-DCP, based on PRZM/EXAMS (USEPA 2013a). The toxicity values are several orders of magnitude higher than the estimated environmental concentrations. Consequently, risks to aquatic organisms are not a concern from 2,4-DCP.

Comment: *Effects to migratory birds were not assessed, as required, under the Migratory Bird Treaty Act.*

Response: Migratory birds are assessed as part of EFED's standard screening-level risk assessment process. Migratory birds are included in the risk conclusions for non-listed birds (for those species that have not been designated as threatened or endangered under the Endangered Species Act), and listed birds (for those species that are threatened or endangered). Acute exposure risk concerns were identified for both listed and non-listed birds in the screening level assessment. The refined endangered species spray drift risk assessment (USEPA 2014) for the six states (IN, IL, IA, OH, SD, WI) made a "no effect" determination for threatened and endangered birds. A memorandum of understanding (MOU) on the Migratory Bird Treaty Act between EPA and the Department of Interior's Fish and

Wildlife Service is in development; the public comment period ended March 7, 2014 (EPA-HQ-OPP-2013-0744 at www.regulations.gov). The 2,4-D choline salt risk assessment is in accord with the process outlined in the MOU.

Comment: *Direct and indirect effect determinations were not made for all species.*

Response: EPA's ecological risk assessment considered both direct and indirect effects to non-target organisms. Indirect effects occur when a species that is not directly affected by the pesticide use rely upon a species that is directly affected. For example, monarch butterfly larvae rely on milkweed for food. If an herbicide kills the milkweed (direct effect on the milkweed), the monarch butterfly may be indirectly affected because its food source has been affected. In the case of the 2,4-D choline salt assessment (USEPA 2014), no indirect effects to endangered or threatened (listed) species were identified based on mitigation measures to limit spray drift exposure to only corn and soybean fields based on species biology and species proximity. Indirect effects to non-listed species would be limited to those species that rely on other non-listed species for food, habitat, or other resources. By requiring pesticide application restrictions that limit off-site exposure to levels below effects thresholds of the most sensitive taxonomic group, the action area (the geographic extent to where effects can reasonably be expected to occur), is limited to the directly treated footprint of the soy or corn field. Consequently, no direct or indirect effects are expected for threatened and endangered species (USEPA 2014) (Addendum to 2,4-D Choline Salt Section 3 Risk Assessment: Refined Terrestrial Plant Exposure Estimates and Effects Determination).

Comment: *EPA did not adequately address risk concerns from runoff.*

Response: EPA acknowledges that these public comments on the risk assessment and effects determination pointed out that the Agency did not explicitly include a consideration of the risk findings for non-target plants as a result of off-field runoff. The Agency considered the spray drift exposure to be the principal risk issue associated with the proposed labeled use of 2,4-D choline, owing to a variety of lines of evidence, including past experience with other 2,4-D formulations and associated spray drift incident reporting. However, in light of these public comments, the Agency reconsidered the runoff risks and the effects of the proposed mitigation to limit off-site runoff in listed species effects determinations.

For this registration action, spray drift and runoff were considered as exposure pathways for 2,4-D choline to terrestrial plants and aquatic organisms. For aquatic organisms, the consideration of both spray drift and runoff loadings to surface waters did not trigger concerns. Risk concerns from spray drift to terrestrial plants were mitigated with an in-field 30-foot buffer that takes into account wind direction during application, and this mitigation yielded no spray drift concerns off field, when incorporated into spray drift modeling.

The in-field spray drift buffer does not mitigate concerns from runoff because 2,4-D choline can be applied up to the edge of the field when the wind is not blowing in that direction; there is no "buffer strip" between the edge of the field and sensitive habitat. The Agency does not currently have a tool to evaluate the effectiveness of buffers in reducing pesticide exposure

via runoff. The Agency has implemented vegetative buffer or filter strips in a few instances to lessen herbicide loading in runoff waters, however in this case there are no risk concerns for aquatic organisms. To assess exposure to terrestrial plants the Agency looked at several lines of evidence to determine potential effects as described below.

2,4-D is absorbed by both shoots and roots and is active at the growing points of the shoot and root. Translocation to the site of action is primarily via the symplastic pathway (with photosynthates in the phloem) and accumulates principally at the growing point of the shoot and root. 2,4-D is not translocated as well in the apoplast (carried with the water and nutrients in the xylem), which would occur with root uptake. Therefore, growth inhibition tends to be more pronounced with foliar uptake than with root uptake (Shaner 2002). Consequently, 2,4-D in runoff waters would not be readily available for mature plant uptake. The Agency is including a statement on the label based on the rainfast period for 2,4-D that prohibits the application of Enlist Duo if rain or irrigation is expected within 24 hours. A rainfast period is the time required for the herbicide to be absorbed into the plant after application and before a rain/irrigation event so as to provide reasonable weed control. The provision of a labeled rainfast period would increase the time available for on-field herbicide adsorption, thereby reducing the amount available for runoff. This, in combination with 2,4-D's limited uptake by roots of terrestrial plants, is anticipated to reduce the amount of 2,4-D choline salt that could adversely affect plants via runoff.

Further, EPA has evaluated the assumptions regarding runoff of 2,4-D from treated fields to adjacent terrestrial habitat. The model TerrPlant assumes, for a chemical with the solubility of 2,4-D in the most mobile acid form, that runoff would amount to 5% of the field applied mass of the herbicide. This modeling approach does not account for pesticide degradation and for pesticide partitioning. These processes that account for loss are important in the mechanistic pesticide runoff models used by EPA (Pesticide Root Zone Model (PRZM)) and in the field. The Agency has compared the TerrPlant assumption of 5% runoff to the runoff predictions for PRZM runs used to characterize pesticide runoff for aquatic exposure. This comparison revealed that runoff predicted by TerrPlant for 2,4-D is grossly overestimated. The total annual runoff is less than a fifth of the amount predicted by TerrPlant for a single runoff event.

In light of these additional lines of evidence, combined with proposed mitigations such as a mandatory rainfast period, the Agency has determined that risks to terrestrial plants from runoff as predicted by TerrPlant modeling are grossly overestimated in the case of 2,4-D choline and a finding of no effects to listed or non-listed species off the treated field is appropriate.

Comment: *The risk assessment analyses did not follow the National Academy of Sciences (NAS) recommendations. The assessment dismissed risks, even when risk quotients were above the level of concern and failed to come to a "may affect" conclusion, when any risk concerns were identified.*

Response: EPA acknowledges that it did not follow the NAS recommendations when evaluating whether the 2,4-D choline salt formulation would affect listed species. However, EPA's determination of "no effect" (USEPA 2014) (Addendum to 2,4-D Choline Salt Section 3 Risk Assessment: Refined Terrestrial Plant Exposure Estimates and Effects Determination)was based on a scientifically valid methodology consisting of an ecological risk assessment conducted in accordance with Agency guidance at the time of drafting the risk assessment and consistent with the methods described in 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," Office of Pesticide Programs 2004 Overview Document. This assessment included a problem formulation describing the nature of the Federal action, an assessment of potential pesticide exposure, an assessment of the toxicological hazards associated with the pesticide, and a risk characterization that integrated all available lines of evidence to support the effects characterization for each taxonomic group and species. Moreover, in situations where there was a potential taxonomic concern, the Agency used available U.S. Fish and Wildlife Service information (i.e., Species Recovery Plans, Species 5-Year Reviews) to conduct focused assessments for individual species.

The National Academy of Sciences' (NAS) report was issued in 2013, after the screening level ecological assessment for 2,4-D choline salt was finalized. EPA and the U.S. Fish and Wildlife Service and the National Marine Fisheries Service have adopted a "day forward" approach for endangered species risk assessments that will begin once consensus is reached on the risk assessment methodology and process. Thus, the analyses used in the 2,4-D choline salt assessments (USEPA 2014) (Addendum to 2,4-D Choline Salt Section 3 Risk Assessment: Refined Terrestrial Plant Exposure Estimates and Effects Determination), use a combination of "old" methods alongside some tools that are being considered for the revised endangered species risk assessment approach.

The assessment process employed in the effects determination is composed of three parts: (1) the original screening-level assessment conducted under the provisions of the Overview Document , (2) a plant endpoint/spray drift addendum that further characterized plant endpoints taking into account all available toxicological information, and (3) an endangered species risk assessment addendum that used the results of the screening risk assessment, drift effects addendum and information on the biology (e.g. food requirements and habitat needs) for each species within the proposed action area to determine if pesticide exposure would have a direct or indirect effect on each species.

The screening level assessment (USEPA 2013a) considered risks to all non-target taxonomic groups of organisms in a manner consistent with the pre-NAS risk assessment process used to support effects determinations. That process uses available environmental fate and effects information to make preliminary determinations of whether conservative estimates of pesticide exposure would raise concerns for one or more taxonomic groups. The screening assessment results suggested that, should actual exposures occur, direct effects may be possible only for mammals, birds, reptiles, land-phase amphibians and terrestrial plants (risk quotients were above the level of concern). However, additional information related to

specific species within these taxonomic groups was needed to ascertain if species biology, geography and timing would lead to a determination that exposures would reasonably occur for these organisms. Additional information included: species specific biology, geographic location, and the ability of spray drift mitigation measures to reduce the geographic extent of exposures of concern to a limit of the boundaries of the treatment site. When these types of information were considered, the endangered species assessment addendum (USEPA 2014) (Addendum to 2,4-D Choline Salt Section 3 Risk Assessment: Refined Terrestrial Plant Exposure Estimates and Effects Determination) concluded that there were no direct risk concerns for mammals, birds, reptiles, land-phase amphibians, and terrestrial plants.

Comment: *Disagreement with the process used to reach a "no effects" determination for threatened and endangered species.*

Response: In conducting the effects determinations, the Agency used the most sensitive taxonomic group effects thresholds to establish the extent to which effects were possible (USEPA 2014). This approach is consistent with both the Overview Document approach and the NAS approach for defining the action areas of the proposed Federal action, when spray drift mitigation measures were taken. Mitigation steps were incorporated into modifications of the proposed Federal action and were incorporated into the risk screening risk assessment that was used as a quantitative input to the effects determinations. Environmental exposures, through the action of proposed mitigation (USEPA 2014), were concluded to be below effects thresholds – the no effect threshold for the most sensitive taxa for areas off the field. This effectively limited this action area of the Federal action to within the bounds of the specific target crop application sites for the pesticide product. Using the process outlined in the Overview Document for the remaining species within the action area, the Agency conducted additional exposure and effects assessment and biological evaluation (USEPA 2014), specific to those species, to determine if effects would occur for those species and to assess whether habitat utilization of the cropped areas was such that herbicide application would result a species relevant effects. See also the comment response on runoff.

Comment: *The number of uncertainties in the risk assessment reduces the confidence in its conclusions.*

Response: The agency believes that despite uncertainties, the conservative nature of the exposure and hazard evaluations as well as the careful consideration of species biology and habitat uses are sufficient to reason that the assessment is reasonable.

III. Other Concerns

A. Labeling

Comment: *The label language regarding the required spray drift buffer was unclear. More specifically, label language concerning the buffer in relation to wind direction needed clarification.*

Response: EPA has worked with the registrant to clarify the intent of this restriction, and to eliminate any confusion that may arise from the buffer label language. The intent of the label is to require a 30 foot in-field buffer at the downwind edge of the field. For example, if the wind is blowing in a southern direction, the buffer would be the 30 foot section of the corn or soybean field to be treated at the southern edge of the field. Therefore the label contains the modified language to read as follows:

You must maintain a 30 foot downwind buffer (in the direction in which the wind is blowing) from any area except:

- Roads, paved or gravel surfaces.
- Planted agricultural fields. (Except those crops listed in the "Susceptible Plants" section)
- Agricultural fields that that have been prepared for planting.
- Areas covered by the footprint of a building, shade house, green house, silo, feed crib, or other man made structure with walls and or roof.

To maintain the required downwind buffer zone:

- Measure wind direction prior to the start of any swath that is within 30 feet of a sensitive area.

- No application swath can be initiated in, or into an area that is within 30 feet of a sensitive area if the wind direction is towards the sensitive area.

EPA also suggested that Dow AgroSciences develop a diagram to clarify this issue which they have added to the label. Please see the buffer diagram on the final approved label in the docket.

Comment: *The restriction of application of Enlist Duo to only one nozzle type and pressure combination does not allow the grower adequate flexibility to other low drift nozzle technologies.*

Response: The registrant has submitted additional data to demonstrate the drift potential of the Enlist Duo™ technology applied with a variety of different nozzles. After careful review of the data, EPA has determined that additional nozzles provide the same or better drift protection as the specific nozzle originally proposed with the registration. As a result, 22 additional nozzles have now been added to the label, providing additional flexibility for the grower. More nozzles can be added to the label, as appropriate, as additional data is submitted that demonstrates at least the same drift reduction properties. See the final approved label for exact nozzle specifications.

Comment: *This product should not be restricted to use in only 6 states when the need for weed resistance management is not limited to these six states alone.*

Response: EPA is currently conducting additional evaluations to assess the use of Enlist Duo™ in the remaining corn and soybean growing states.

B. Registration

Comment: *EPA should not delay the expected timing of this action provided by the Pesticide Registration Improvement Act (PRIA) by the development of endangered species assessments and weed resistance stewardship plans.*

Response: EPA has noted the potential for higher acreage that may result from the amended use of 2,4-D that could lead to increased exposure to non-target species. The increase in acres where this pesticide could be applied could also select for weeds that develop resistance to the herbicide, therefore EPA determined that management of weed resistance in order to prolong the effective use of existing herbicides and allow growers the tools necessary to manage America's food supply must be addressed in this registration decision. Although PRIA does stipulate timeframes deemed necessary to conduct assessments and make regulatory decisions for routine applications of various pesticide actions, it does not supersede the Agency's responsibility to ensure that regulatory decisions meet the standards for registration. There are occasions when an action is more complex than expected by the PRIA timeframes. In these instances, the Agency will typically renegotiate the timeframe with the registrant to describe the additional time that is needed for a complete evaluation and to allow the additional work to be completed. The Agency will only issue a regulatory decision once all assessments deemed necessary are carefully and thoroughly completed, providing a full understanding of the potential risks and benefits of a pesticide use.

Comment: *An increase in glyphosate use could occur with the registration of Enlist Duo. Therefore, glyphosate should be assessed when considering the registration of Enlist Duo.*

Response: The registration of Enlist Duo™ does not represent any new exposures or increase in exposures for glyphosate. Glyphosate is already used on the majority of corn and soybean production acres in the United States today. Glyphosate is presently being applied in the same fields where Enlist Duo™ applications would be expected, using the same application methods as registered for Enlist Duo™. Since the use of Enlist Duo™ would represent an alternative to other registered glyphosate products that already apply glyphosate in the same manner, it would be considered to be a substitute for another equivalent glyphosate application and not an additional one.

Comment: *The use of products containing non-choline 2,4-D on Enlist crops could occur and resulting damage to other crops from drift may occur.*

Response: Enlist Duo™ provides benefit to the grower by allowing the application of the choline salt of 2,4-D at a later growth stage for corn and soybeans, providing control of problem weeds that are present during this application timing. No other 2,4-D product is registered for use on corn and soybeans during this specified time period. EPA notes that it is

a violation of Federal Law to use a pesticide not in accordance with its label. EPA prosecutes illegal use of pesticides to strongly dissuade and correct for any illegal activity.

In addition, although not required by EPA, the Agency is aware of contractual agreements that Dow AgroSciences has developed in a technology use agreement that is legally binding between the grower and the registrant. This contract prohibits the use of 2,4-D products without the choline salt technology on any Enlist seed. If violations to this contract are detected, it is EPA's understanding that DAS reserves the right to discontinue the sale of the seed to any grower who does not comply with this requirement.

Comment: *Enlist Duo may contribute to the weed resistance problem that has been caused by older products labeled for use on GE crops in general, especially those that are known to have aided in widespread weed resistance historically.*

Response: EPA and other stakeholders have studied the resistance problems associated with glyphosate and other pesticides, and EPA has worked with Dow AgroSciences to develop a robust resistance management stewardship plan designed to address this concern. In addition, because the issue of weed resistance is an extremely important issue to keep under control and can be very fast moving, this registration will expire in either 5 years (if there is use of the product on 100,000 or more acres in the first year) or 6 years (if there is use of the product on less than 100,000 acres in the first year) unless this term is removed or modified by EPA. This will ensure that EPA retains the ability to easily modify the registration or allow the registration to terminate if necessary.

C. Benefits of Registration of Enlist Duo™

Comment: *The BEAD benefits memo (April 30, 2014) stated that registration of Enlist Duo would save costs for farmers in controlling glyphosate-resistant weeds. However, if these resistant weeds are in fields, then application of the dual active ingredient product essentially has only one effective herbicide active ingredient. BEAD stated that this scenario would likely require additional herbicide mode(s) of action. This situation would negate the benefit of a dual active ingredient product and would result in more cost to the user.*

Response: The Agency's assessment outlined the general benefits of the Enlist Duo™ technology and identified benefits beyond Enlist Duo™'s ability to manage weeds already resistant to glyphosate. The benefits included increased flexibility to corn and soybean growers, a new tool for broadleaf weed control in herbicide-tolerant soybean, improved ability to manage broadleaf weeds already resistant to glyphosate or other herbicides, and in some cases, extending the viability of glyphosate.

The Agency acknowledges that in cases where resistance to 2,4-D or glyphosate exists, measures must be taken by the herbicide's users to avoid selection for resistance (e.g. add an additional effective mechanism of action). The benefits document states:

"While there are benefits to the proposed use of Enlist Duo™ in the Enlist™ system, it will be important that the system be supported by an active stewardship program as well as a robust program of early intervention and remediation when a lack of herbicide efficacy may be an early sign of resistance developing."

Therefore, the Agency is requiring that DAS have an Herbicide Resistance Management (HRM) Plan in place, which includes education and outreach programs. The HRM Plan, which is detailed in the final decision, will involve DAS working with growers to help identify early signs of weed resistance and to resolve the problem before it spreads. The HRM Plan also requires education and reporting to the Agency.

Comment: *Although the development of resistance to one or more of the active ingredients in Enlist Duo is possible, the potential for resistance development does not eliminate the utility of the product if it is used according to an appropriate management plan.*

Response: The Agency agrees with the comments. As described in its benefits analysis of April 30, 2014, the Agency believes that the registration of Enlist Duo™ would provide weed control benefits to some soybean and corn growers. Also, the registration requires an Herbicide Resistance Management (HRM) Plan that is designed to provide early warning of likely resistance. Moreover, this HRM Plan includes the registrant being proactive in addressing local reports of likely resistance, including investigation, remediation assistance, and reporting. Also, education of users of Enlist Duo™ in resistance management is required.

D. Resistance Management – Enlist Duo™ Use Practices in the Field

Comment: *Certain parts of the use directions described in the proposed decision were overly prescriptive and would not allow growers the flexibility needed to use the herbicide product effectively (e.g., the requirement for growers to scout fields 7-21 days following application). Growers' privacy rights could be at risk due to the requirement for the registrant to investigate reports of lack of herbicide efficacy, or that the Agency could strictly enforce some of the detailed practices described on proposed labels.*

Response: The Agency considered these concerns and determines that these types of labeling requirements are not necessary to ensure that the use of the product not result in resistance to certain weeds. Instead, EPA is placing the burden on the registrant through its stewardship plan and other regulatory measures in the registration. Although the scouting labeling requirement has been removed, the Agency firmly believes that it is a good best management practice to scout fields before and after herbicide application, which is consistent with integrated pest management (IPM) and is essential to early identification of lack of herbicide efficacy that could be an early sign of weed resistance. The critical importance of scouting is widely recognized by research and extension specialists in pest control and should be practiced when using Enlist Duo™ or other pesticides. However, the Agency also recognizes that on-field weed resistance is best managed by the grower who understands his or her specific situation. Therefore, the requirement to scout fields 7-21 days after application will

not be imposed, but the labels will contain recommendations for field scouting. This scouting will be specific to Enlist Duo™ and will be designed to ensure proper use of the herbicide and to detect lack of efficacy quickly so that potential resistance can be managed effectively. The Agency is confident that field scouting programs designed by the registrant will be flexible and will respect the privacy rights of individual growers.

Comment: *The term "eradicate" in the proposed decision, i.e., "DAS [the Enlist Duo registrant] must take immediate action to eradicate likely resistant weeds in the infested area" (emphasis added) is not practical. Also, in many cases, a lack of weed control following an herbicide application is a result of other factors, not a lack of herbicide efficacy.*

Response: The Agency agrees that the term "eradicate" is not appropriate in this context. Moreover, it does not adequately convey the Agency's intent. The Agency believes that areas where there is a lack of herbicide efficacy (not due to other mechanical or environmental causes) must be managed aggressively to minimize the potential for resistance to develop and spread. In areas where the most likely cause of poor weed control is a lack of herbicide efficacy, steps must be taken to destroy likely resistant weeds. Moreover, when weed populations that may be developing resistance are observed, the registrant will become actively involved with growers to ensure that these populations were managed properly. There will also be a requirement for the registrant to report to the Agency and to stakeholders when incidents of unresolved likely resistance are identified.

The Agency recognizes that many incidents of lack of weed control are not related to possible resistance. Rather, lack of weed control may be due to factors such as unexpected rain, a clogged nozzle, a missed spot on the field, or other equipment-related problem. In these cases, the Agency recognizes that on-site investigation and follow up by the registrant are not necessary.

E. Stewardship: Education and Training

Comment: *Stewardship efforts, including education and training programs, are needed to ensure proper use of Enlist Duo, as growers may rely too heavily on Enlist Duo in weed control programs. In these cases, the potential to select for resistant weeds will be greater. Stewardship programs should be flexible and facilitate local management of resistance. Also, the approach to education and training should be generally consistent for pesticides. Responsibility for oversight for education and training requirements was not clear in the proposed decision.*

Response: The Agency agrees that the registration of Enlist Duo™ for use on Enlist seed presents the potential for growers to over-rely on a single product that contains two herbicidal active ingredients. If it happens, the over-dependence can increase the selection pressure on weeds and lead to resistance. Because herbicide use on herbicide-resistant crops presents this increased risk, the Agency is addressing resistance potential in this registration in an unprecedented manner.

The terms of registration for Enlist Duo™ place the responsibility on the registrant for reducing the potential for resistance or to significantly delay the onset of resistance. The Agency is also requiring the registrant to develop education and training programs that will provide growers with the best available information on herbicide resistance management. Although requiring the registrant to provide education and training, the Agency has not imposed label or use restrictions on the grower, enabling him or her to exercise flexibility in weed control practices based on local conditions.

F. Reporting

Comment: *The reporting requirements outlined in the proposed decision were overly strict and could actually deter growers from reporting likely resistance to the registrant. The registrant should report confirmed resistance to the Agency through adverse effects reporting required in section 6(a)(2) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).*

Response: The Agency believes that timely and accurate reporting is needed to fully understand the nature and extent of possible resistance that may develop as a result of Enlist Duo™ use. The Agency believes that growers will be the first ones to recognize the early signs of herbicide resistance. Therefore, the Agency has specified in the terms of registration that it must be easy for growers to report the early signs of resistance to the registrant. The Agency has not mandated specific reporting requirements for growers. Further, the Agency believes it is common practice for growers to readily report the early signs of resistance to the chemical dealer or the registrant.

Instead of placing the burden on the growers, the Agency has determined that the registrant must report to the Agency on a regular basis concerning likely resistance. These reports are needed by the Agency to facilitate its understanding of whether resistance may be developing and, if it is, its severity and geographic distribution. Also, the registrant will be required to report likely resistance to growers who could be affected so they can take appropriate measures to minimize the impact of resistance on their crop production.

The Agency agrees that confirmed resistance must be reported under FIFRA section 6(a)(2). However, it may take several years before resistance is confirmed even though its early signs appeared much sooner. The Agency therefore is requiring the specific reporting described in the final decision. This early warning can help growers understand the potential for resistance to develop and also serve as an early warning system if resistance is found nearby.

G. Other Comments

Comment: *The Agency should consider the Agricultural Biotechnology Stewardship Technical Committee (ABSTC) model for resistance management for Enlist Duo. This model has been adopted for plant-incorporated protectants (PIPs) such as Bt crops. ABSTC is an industry-led structure which is preferable to the proposed registration decision for Enlist Duo which*

appeared to place more responsibility on the grower and makes him or her liable for a lack of compliance.

Response: The Agency agrees that the ABSTC model, if modified for an herbicide registered for use on an herbicide-tolerant crop, is relevant for Enlist Duo™. The ABSTC model was consulted when determining the appropriate terms of the registration for the Enlist Duo™ product. In addition, the Agency is requiring registrants to implement practices intended to facilitate early identification of possible resistance, to remediate lack of herbicide efficacy that could be the start of resistance, follow-up, and reporting. Further, the Agency has not mandated specific practices on labels, thereby allowing maximum flexibility for users of Enlist Duo™.

Comment: *New resistance management requirements for Enlist Duo should also apply for other products and for future registrations as well. Also, the many registrations for 2,4-D and glyphosate make it difficult to address related resistance issues when this proposal applies only to Enlist Duo.*

Response: With the registration of Enlist Duo™, the Agency is establishing a new approach for resistance management for herbicides registered for use on herbicide-tolerant crops. Future registration actions for herbicides used on herbicide-tolerant crops will be patterned after the Enlist Duo™ decision. The Agency will use the registration review process to address resistance managment for the existing registrations of 2,4-D, glyphosate and other herbicides where resistance is an important issue.

Comment: *From 1993 to 2008-2009 there has been approximately a 10-fold increase in the amount and acreage of glyphosate use. In some cases where Enlist Duo may be used, glyphosate-resistant weeds are already present, and resistance to 2,4-D may develop.*

Response: The Agency agrees that glyphosate use has substantially increased since the early 1990s. However, the Agency does not believe there will be an increase in glyphosate use resulting from this action because glyphosate is already used extensively on corn and soybean.

The Agency agrees that Enlist Duo™ may be used on fields where glyphosate resistance is already present. In some of these cases, judicious use of Enlist Duo™ may help manage the glyphosate resistance. However, care must be taken by the herbicide user to carefully manage the potential for these glyphosate-resistant weeds to become resistant to the 2,4-D component of Enlist Duo™. In such cases, the DAS stewardship program will educate the user on the importance of using diverse methods of weed control to reduce the likelihood of 2,4-D resistance developing.

Comment: *Although EPA has recognized that glyphosate-resistance is an important issue, it is not approaching the problem appropriately. Rather than "taking a step back" and reevaluating the GE strategy, the Agency is "rushing" to approve a technology that will continue the "pesticide treadmill" with increased resistance now to 2,4-D.*

Response: The Agency recognizes that the development and spread of herbicide resistant weeds is an important issue for all herbicides, not just for glyphosate and 2,4-D. The presence of herbicide resistant weeds results in increased costs of production to the grower, increases the difficulty of managing crop production, and can require control measures that may have negative effects on the environment (e.g., requiring cultivation that could increase soil erosion).

After extensive analysis and review, the Agency has determined that Enlist Duo™ meets the statutory criteria for registration. Further, the Agency has required as part of the terms and conditions of the Enlist Duo™ registration that the registrant proactively manage the potential development of resistance.

Comment: *While registrants for new auxin-based herbicides claim resistance is unlikely, they leave out that 1) a similar argument was made prior to glyphosate release, 2) it is not the case that "very few" weed species are resistant to 2,4-D—worldwide there are 16 species resistant to 2,4-D, and 3) while the theory that weeds are statistically less likely to develop resistant to two herbicide active ingredients—the fact that the glyphosate-resistant population in some fields is so great that there is a high likelihood that exposure to 2,4-D will result in populations resistant to 2,4-D as well as glyphosate. In addition, these fields are most likely to be planted with stacked tolerant GM crops.*

Response: The Agency agrees with the commenter's concern over the potential for weed resistance development, especially to multiple mechanisms of action. The terms of registration and stewardship requirements are intended to provide early warning and allow for timely intervention when likely resistance is detected. The Agency recognizes that where glyphosate resistance is already present, the 2,4-D component of Enlist Duo™ will only be effective against the broadleaf weeds. In those cases, the Agency will require that the registrant's stewardship plan alert growers to the special problem of glyphosate resistance and provide the grower with education and training to use best management practices that will reduce the probability of resistance to 2,4-D.

Comment: *Traditionally, 2,4-D was registered for use as a single preplant herbicide on cereal fields. The new GM crop will allow higher rates, more applications, in successive crops, over a wider area than currently. Therefore, the potential is high for greater development of resistance to 2,4-D (and other auxin-based herbicides).*

Response: The Agency agrees that there is the potential for resistance to develop as a result of over-use of Enlist Duo™, or using it without best management practices. Therefore, the Agency is requiring the registrant to develop an extensive stewardship program to educate users of this problem. Moreover, through the terms of registration for Enlist Duo™, the Agency is requiring the registrant to undertake several steps that are intended to provide early detection and remediation in cases where a lack of herbicide efficacy may be an early sign of resistance developing.

Comment: *Starlink™ was also regulated but the release failed. What is different about Enlist Duo's possible release?*

Response: The StarLink™ issue related to the release of genetically-modified corn that was not approved for human consumption. That situation, and the circumstances surrounding it, is not comparable to the Agency's action on Enlist Duo™. The USDA Biotechnology Regulatory Services has jurisdiction over the deregulation of the Enlist corn seed. The Agency's action is limited to the registration of Enlist Duo™, the herbicide product that is intended for use on corn and soybean crops grown from Enlist seed.

Comment: 2,4-D usage was estimated to increase 3 to 7 times by 2020 in the USDA 2014 Environmental Impact Statement. As a result of this increased usage the evolution of 2,4-D resistance will be facilitated and will result in changes of conservation tillage practices.

Response: The Agency agrees that there will be increased usage of 2,4-D because of the longer period of time that applications can be made in corn and that for the first time, up to two applications can be made over-the-top in soybeans. Increased usage of 2,4-D was fully accounted for in the risk assessments that the Agency has conducted for Enlist Duo™. Further, because of the likelihood of the development of resistant weeds and their associated impacts, the Agency has established and implemented its new herbicide resistance management approach as described in the Final Registration of Enlist Duo™ Herbicide, dated October 14, 2014.

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