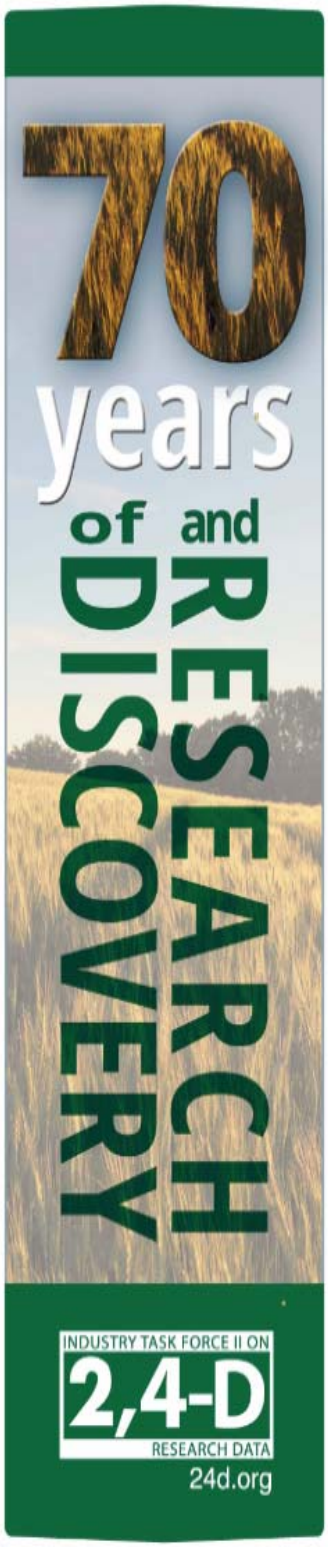

Task Force Comments to the Docket of Registration Review: Draft Human Health and Ecological Risk Assessments of 2,4-D

Synopsis:

The 2,4-D Research Task Force has prepared and submitted comments in response to the EPA's Registration Review Draft Risk Assessments.

The Task Force notes the EPA's overall finding of no human health concerns and supports continued product stewardship to reduce any calculated levels of concern for non-target organisms, in order to preserve 2,4-D's many beneficial uses.

The EPA's draft human health risk assessments states that the following risks are not of concern: dietary, residential, non-occupational, volatilization/residential bystander and aggregate risk estimates. Recent EPA review documents have noted that "2,4-D is not likely to carcinogenic in humans."

There are some points of disagreement. The EPA's draft human assessment identified occupational handler inhalation as a concern for some scenarios; however, there was no concern for occupational handler from dermal exposure. The Task Force will submit comments to demonstrate that occupational handlers enjoy significant margins of safety from inhalation exposure.

Additionally, the EPA's draft ecological risk assessment identified the potential for effects on some non-target organisms. The Task Force's comments will explain that EPA's models are based on very conservative and unrealistic assumptions; moreover, those effects decreased through typical exposure reduction measures, such as limitations on aerial application, boom heights and specification of the spray droplet spectrum.

The full document is available below.

Study Title

Task Force Comments to the docket for Registration Review: Draft Human Health and Ecological Risk Assessments of 2,4-Dichlorophenoxyacetic Acid (2,4-D) Case No. 0073 Docket I.D. EPA-HQ-OPP 2012-0330

Data Requirement

None

Author

Industry Task Force II on 2,4-D Research Data
Technical Committee

Study Completion Date

July 24, 2017

Laboratory Study ID

TFII072417

Total Pages

75

Table of Contents

INTRODUCTION AND SUMMARY

2,4-D was first introduced to American agriculture in 1947 and revolutionized weed control for farmers. Because of its long history, significance to crop protection and widespread use, thousands of regulatory studies and research publications exist for 2,4-dichlorophenoxyacetic acid (2,4-D) and its derivative forms. These included dimethylamine salt (DMA), isopropylamine salt (IPA), triisopropanolamine salt (TIPA), 2-ethylhexyl ester (EHE), butoxyethyl ester (BEE), diethanolamine salt (DEA), isopropyl ester (IPE), sodium salt (Na) and choline salt (Choline). The wealth of information on 2,4-D and its long history of safe use are testament to the quality data and understanding of its use and usage. EPA is urged to review both their exposure assumptions and toxicity data in light of generations of "real world" experience and benefits with 2,4-D.

The Health Effects Division (HED) in its **Human Health Risk Assessment for Registration Review** conducted a hazard assessment to determine that the 2,4-D toxicology database is complete. Using this data, HED then conducted exposure and risk assessments for dietary, residential, non-occupational, and aggregate and concluded no risks of concern. Occupation handler assessments identified inhalation risks that can be mitigated with respirators.

The Environmental Fate and Effects Division (EFED) in the **Preliminary Ecological Risk Assessment for Registration Review of 2,4-D** evaluated environmental fate parameters and toxicity endpoints and prepared its screening-level ecological risk assessment of potential risks to aquatic and terrestrial organisms resulting from the use of 2,4-D and its associated chemical forms. Upon review and synthesis of this information, EFED believes use of 2,4-D presents potential risks to birds, reptiles, amphibians, mammals, terrestrial invertebrates, terrestrial plants, fish, aquatic invertebrates, and aquatic plants.

The Industry Task Force II on 2,4-D Research Data (Task Force) review of the assessment examined the effects endpoints and environmental fate parameters for 2,4-D and the assumptions of HED, EFED, BEAD and others. The Task Force has identified what it respectfully submits are errors and overly conservative assumptions in the assessment documents. Detailed comments and corrections are provided by the Task Force in this response document and will be further supplemented as requested by the Agency.

The Task Force submits that the overall profile of 2,4-D and its forms are acceptable for continued registration and meet the risk standards of the Federal Insecticide, Fungicide and Rodenticide Act.

GENERAL COMMENTS

Comments are presented in the format where the bold face page denotes the page number followed by directions of table, row and column. Narrative directions include paragraph, sentence or line number. A template of this format can be illustrated as:

Guidance for 2,4-D Task Force Comments to 2,4-D Docket for Registration Review

Document		
Page #		
Table #		
Row #		
Column #		

CORRECTION

The statement/ entry should be corrected so that it reads:

Corrections or additions are highlighted in red in this correction block.

For tabular data, the format includes a complete corrected table in most instances. In a few cases where a lengthy table includes minimal revisions, only the row or section containing corrections is shown.

Comments on

2,4-D: Human Health Risk Assessment for Registration Review

EPA-HQ-OPP-2012-0330-0042 / DP Barcode D424052

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "2,4-D is also registered for use on hybrid field corn and soybean containing the inserted aryloxyalkanoate dioxygenase-1 (AAD-1) gene. Expression of the AAD-1 protein encoded by the AAD-1 gene results in a trait that increases the herbicide tolerance of field corn and soybean to 2,4-D via increased metabolism through a pathway involving the metabolite 2,4-dichlorophenol (2,4-DCP). The residue of concern for non-transgenic crop and livestock tolerances is 2,4-D, while for transgenic crops, the residue of concern also includes the metabolite 2,4-DCP."
Page #	4	
Paragraph #	1	
Table #	N/A	

CORRECTION

The statement/entry should be corrected so that it reads:

2,4-D is also registered for use on hybrid field corn containing the aryloxyalkanoate dioxygenase-1 gene (*aad-1*) and soybeans and cotton containing the aryloxyalkanoate dioxygenase-12 gene (*aad-12*). Expression of the AAD-1 or AAD-12 protein encoded by the *aad-1*or *aad-12* gene respectively results in corn, soybeans, and cotton tolerant to 2,4-D via increased metabolism through a pathway involving the metabolite, 2,4-dichlorophenol (2,4-DCP). The residue of concern for non-transgenic crop and livestock tolerances is 2,4-D, while for transgenic crops, the residue of concern for risk assessment also includes the metabolite 2,4-DCP."

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "Residential handler MOEs range from 5,500 to 130,000..."
Page #	5	
Paragraph #	4	
Table #	--	

CORRECTION

The statement should be corrected for consistency with Residential and Occupational Exposure document:

The inhalation MOEs are inconsistent between the Human Health Assessment document and the Residential and Occupational Exposure document due to differences in derivation of the human equivalent dose (HED) values. The HED values in the Residential and Occupational Exposure assessment, which incorporate a factor to account for different breathing rates during different activities are most scientifically justified and should be applied in both documents. Further detail is given in subsequent comments. Corrected MOEs are as follows:

"Residential handler MOEs range from 13,000 to 300,000..."

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "For some scenarios where applicable, the addition of a respirator resulted in risk estimates that were not of concern. However, aerial application of granular formulations to some use sites, assuming enclosed cockpits (i.e., engineering controls), did result in risk estimates of concern."
Page #	6	
Paragraph #	3	

Table #	--	

CORRECTION

The statement should be corrected for consistency with Residential and Occupational Exposure document:

The inhalation MOEs are inconsistent between the Human Health Assessment document and the Residential and Occupational Exposure document due to differences in derivation of the human equivalent dose (HED) values. The HED values in the Residential and Occupational Exposure assessment, which incorporate a factor to account for different breathing rates during different activities are more scientifically justified and should be applied in both documents. This changes the scenarios for which risks of concern are identified. The text here should be adjusted for consistency with the Residential and Occupational Exposure document.

Document #	EPA-HQ-OPP-2012-0330-0042	The review states the following Agency recommendation: On page 7 -"Harmonization of the U.S. tolerance on fruit, citrus, group 10 is acceptable with the Canada as the U.S. citrus residue data do not exceed the Canadian MRL of 2.0 ppm (D221853, D Miller, 07/08/1996)." On pages 8-9 "The recommended harmonization of the U.S. tolerances with the Canadian MRL on citrus fruit crop group 10 and the Codex MRL for berry crop group 13 require revision of 40 CFR §180.142(a) as follows: Berry, group 13 ..... 0.1 ppm Fruit, citrus, group 10..... 2.0 ppm"
Page #	7-9	
Paragraph #	3 and 1	
Table #		

COMMENT

The Task Force disagrees with the Agency recommendation for the following reasons:

The cited D. Miller document recommends a MRL value of 3.0 ppm based on the post-harvest uses on lemons. While the residue values in the trials evaluated in D221853, D. Miller, 07/08/1996 would support the lower MRL, there is also lemon post-harvest data that was reviewed in the 1988 2,4-D Registration Standard that showed residues in lemons up to 2.3 ppm which makes reducing the MRL inadvisable as mentioned in this document. Additionally, as mentioned in DP309450 "Reregistration Eligibility Decision *Revised* Residue Chemistry Considerations" dated October 12, 2004, "The available lemon processing study indicates that 2,4-D residues do not concentrate in citrus oil or juice, but can concentrate by 4.6x in dried pulp derived from treated fruit. Based on HAFT residues of 0.487 ppm from the recent postharvest treatment trials using lemons and oranges, the maximum expected residues in citrus dried pulp would be 2.24 ppm. As this is below the reassessed 3.0 ppm tolerance for citrus fruits, a separate tolerance for dried citrus pulp is not required." Accordingly, if the MRL on group 10 citrus were to be reduced than a separate tolerance for citrus dried pulp would be required.

For these reasons the Task Force thinks that the U.S. tolerance on group 10 citrus should remain at 3.0 ppm.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "The recommended harmonization of the U.S. tolerances with the Canadian MRL on citrus fruit crop group 10 and the Codex MRL for berry crop group 13 require revision of 40 CFR §180.142(a) as follows: Berry, group 13 ..... 0.1 ppm"
Page #	8-9	
Paragraph #	6	
Table #	Appendix F. Tolerance Summary for	

	2,4-D	

OMISSION

The following information/entry was omitted:

The berry group 13 tolerance update mentioned in the text on pages 8-9 is not reflected in the Table in Appendix F under the HED-Recommended Tolerance (ppm). Please clarify the recommendation.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "2,4-D is also registered for use on hybrid field corn and soybean containing the inserted aryloxyalkanoate dioxygenase-1 (AAD-1) gene. Expression of the AAD-1 protein encoded by the AAD-1 gene results in a trait that increases the herbicide tolerance of field corn and soybean to 2,4-D via increased metabolism through a pathway involving the metabolite 2,4-dichlorophenol (2,4-DCP)."
Page #	11	
Paragraph #	4	
Table #	N/A	

CORRECTION

The statement/entry should be corrected so that it reads:

2,4-D is also registered for use on hybrid field corn containing the aryloxyalkanoate dioxygenase-1 gene (*aad-1*) and soybeans and cotton containing the aryloxyalkanoate dioxygenase-12 gene (*aad-12*). Expression of the AAD-1 or AAD-12 protein encoded by the *aad-1*or *aad-12* gene respectively results in corn, soybeans, and cotton tolerant to 2,4-D via increased metabolism through a pathway involving the metabolite, 2,4-dichlorophenol (2,4-DCP)."

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "2,4-D is registered for use on hybrid field corn and soybean containing the inserted aryloxyalkanoate dioxygenase-1 (AAD-1) gene, and expression of the AAD-1 protein encoded by the AAD-1 gene results in a trait that increases the herbicide tolerance of field corn and soybean to 2,4-D via increased metabolism through a pathway involving the metabolite 2,4-dichlorophenol (2,4-DCP)."
Page #	16	
Paragraph #	4	
Table #	N/A	

CORRECTION

The statement/entry should be corrected so that it reads:

2,4-D is also registered for use on hybrid field corn containing the *aad-1* gene and soybeans and cotton containing the a*ad-12* gene. Expression of the AAD-1 or AAD-12 protein encoded by the *aad-1*or *aad-12* gene respectively, results in corn, soybeans, and cotton tolerant to 2,4-D via increased metabolism through a pathway involving the metabolite, 2,4-dichlorophenol (2,4-DCP)."

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042	General comment applicable to several locations in the document: The effect levels determined from the subchronic inhalation study should be referred to as LOAEC and NOAEC, not LOAEL and NOAEL as the study doses are provided as an external air concentration, not mg/kg/day dose levels.
Page #	19, 22	
Paragraph #	3	
Table #	4.5.4.1	

CORRECTION

The statements of effect levels should be corrected so that they read NOAEC/LOAEC ***rather than NOAEL/LOAEL.***

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "At the study LOAEL of 0.05 mg/L/day, squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx, which was not totally resolved following a 4-week recovery period, were observed."
Page #	19	
Paragraph #	3	
Table #	--	

CORRECTION

The statement should be corrected so that it reads:

"At the study LOAEC of 0.05 mg/L/day, squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx~~, which was not totally resolved following a 4-week recovery period,~~ were observed."

In the subchronic inhalation study (MRID 47398701), recovery was only evaluated at the high dose level, so no statements can be made regarding the degree of recovery at the LOAEC. A new inhalation study (MRID 50320801) has recently been submitted characterizing recovery at the lower dose levels from the original study and at shorter intervals. The findings from this study, indicating recovery to non-adverse levels at 0.05 mg/L and 0.1 mg/L within the duration of the study should be included in discussion of the inhalation effects.

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA makes several statements regarding the lack of full recovery in the 28-day inhalation study. In this original study, recovery was evaluated only at the highest concentration. A follow-up study has been conducted and will be submitted that characterizes the kinetics of recovery at the lower doses. The task force respectfully requests that the results of this study be taken into account when evaluating the nature and severity of the portal of entry effects observed in the rat larynx.
Page #		
Paragraph #		
Table #		

SUBMISSION

The Task Force submitted the following focused study to better characterize recovery following inhalation exposure:

Hotchkiss, J.A., Bell, M.P., Hutchinson, K.L., Thomas, J. 2,4-Dichlorophenoxyacetic Acid: 4-Week SubAcute Nose-Only Inhalation Toxicity Study in Crl:CD(SD) Rats with 1-, 2-, and 4-Week Recovery Groups. Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Laboratory Project Study ID 161009, March 14, 2017.(MRID 50320801)

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "A 3X uncertainty factor was applied to account for inter-species variability (to account for the PD differences)"
Page #	19	
Paragraph #	3	
Table #	--	

CORRECTION

The statement should be corrected so that it reads:

"Due to the well-documented heightened sensitivity of the rat to portal-of-entry laryngeal squamous metaplasia in response to inhaled irritant chemicals (Kauffman et al., 2009; Osimitz et al., 2007), the interspecies uncertainty factor is reduced to 1X."

Corrections or additions are highlighted in red in this correction block.

Squamous metaplasia in the larynx is a very commonly observed response to inhaled irritant chemicals in the rat. The occurrence of this effect, the adversity of the changes, and the relative sensitivity and relevance to human risk are described in two separate reviews (Kauffman et al., 2009; Osimitz et al., 2007). Both reviews highlight that the rodent larynx is particularly susceptible to changes due to inhaled irritants when compared to other species. Osimitz et al. (2007) indicate that:

> "*by virtue of their anatomy, the rat is more sensitive to irritation of the tissue in the larynx than is the human. Gopinath et al. (1987) emphasized that "it would appear that the rodent larynx is particularly sensitive to aerosol damage." This would indicate that the same dosage of a xenobiotic delivered to rodent and human larynx would render the rat larynx more likely to develop histopathological alterations based on the aforementioned particular susceptibility.*" (Emphasis added).

Kauffman et al. (2009) elaborate on this sensitivity, indicating differences that would lead to increased susceptibility from both a kinetic standpoint (e.g, differences in anatomy and respiratory patterns that lead to greater aerosol deposition in the rat larynx) and a dynamic standpoint (e.g., differences in normal epithelial types and locations in the larynx leading to a greater potential for development of squamous metaplasia in rodents):

> *"the rat shows a high susceptibility to develop squamous laryngeal metaplasia, due to anatomy, airflow and epithelial pattern. Anatomically, the larynx is the first site of constriction in the rat's respiratory tract and the anterior surface of the larynx is directly targeted by the incoming airflow, as the rat larynx and trachea form a nearly straight line from the nasal turbinates. The constriction combined with the rapid respiratory rate of the obligate nose-breathing rats enhances the impaction of aerosols on the anterior surface of the rat larynx. In contrast, the larynx of humans is more sharply angled (approximately 90 ^{0}) to the oro-nasal cavity, and respiration in humans occurs through both the oral and the nasal cavities. These anatomical and functional differences between rats and humans are responsible for a reduced amount of aerosol impaction on the anterior surface of the larynx in humans compared to rodents. Differences in the direction and intensity of airflow in the larynx (resulting in differences in local aerosol deposition) and differences in the normal epithelial types and locations within the larynx are considered to be key factors contributing to the much lower incidence of squamous metaplasia in humans, primates or dogs compared to rodents (Lewis, 1981; Renne andMiller, 1996; Renne and Gideon, 2006)."* (Emphasis added).

Based on this documented increased species sensitivity of the rat relative to the human, it is considered appropriate to reduce the animal to human uncertainty factor to 1X. The use of an endpoint from a rat is already a conservative approach and no further uncertainty factor should be necessary since it is known that the rat is the more sensitive species and therefore health protective of these types of effects. This approach is consistent with the recommendations of the authors of both reviews that the relative sensitivity of the rat and human should be taken into account when interpreting such effects from a human risk assessment perspective.

References:

Kauffman, W. et al., 2009. *1st International ESTP Expert Workshop: "Larynx squamous metaplasia". A re-consideration of morphology and diagnostic approaches in rodent studies and its relevance for human risk assessment.* Exp. Toxicol. Path. 61: 591-603.

Osimitz, T.G. et al. 2007. *Toxicologic significance of histologic change in the larynx of the rat following inhalation exposure: A critical review.* Toxicol. Appl. Pharmacol. 225: 229-237.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "10X $UF_{LOAEL \rightarrow NOAEL}$ was applied to account for the lack of a NOAEL."

Page #	19	
Paragraph #	3	
Table #	--	

CORRECTION

The statement should be corrected so that it reads:

"3X $UF_{LOAEL \rightarrow NOAEL}$ was applied to account for the lack of a NOAEC."

Corrections or additions are highlighted in red in this correction block.

Use of a 3X uncertainty factor to account for the lack of an NOAEC should be sufficiently protective of human health based on the following:

1) The minimal nature of the effects observed at the LOAEC.
Following a workshop organized by the European Society of Toxicologic Pathology (ESTP), Kauffman et al. (2009) published a review which details the spectrum of effects associated with laryngeal squamous metaplasia in the rat and recommendations on interpretation of those effects as adaptive vs. adverse. Below are the effects occurring in the rat larynx at the LOAEC of 0.05 mg/L in the 28-day inhalation study (Hoffman, 2008) as well as a discussion of their adversity based on the recommendations of Kauffman et al. (2009).
   a) Slight (males) and Minimal to slight (females) squamous metaplasia at the base of the epiglottis observed at 0.05 mg/L would be considered non-adverse according to Kauffman et al. (2009):
      "Treatment-related focal, minimal to slight laryngeal squamous metaplasia limited to the base of epiglottis should be considered as non-adverse, as a dysfunction of the larynx is not to be expected. Treatment-related increase of the incidence of more diffuse, moderate to severe squamous metaplasia at various levels of the larynx should be considered adverse, as dysfunction of the larynx cannot be excluded."
   b) Minimal hyperkeratosis was observed in 8/10 males and 9/10 females. Kauffman et al. (2009) offer little discussion of hyperkeratosis, especially as it relates to the relative adversity of different severities and of focal vs. diffuse hyperkeratosis. They indicate that:
      "Animals may die of airway obstruction due to inhaled keratin. It is considered that the degree of keratinization is closely related to the risk of aspiration."
      Thus, the minimal nature of this effect would reduce the risk of adverse impact. However, conservatively, even minimal hyperkeratosis is interpreted here as an adverse finding.
   c) Mixed inflammatory cells were observed in the laryngeal mucosa of males (9/10 slight inflammation, 1/10 minimal inflammation) and females (1/10 moderate inflammation, 7/10 slight inflammation, 2/10 minimal inflammation). Inflammatory cells were also observed in the control males (4/10 slight inflammation, 5/10 minimal inflammation) and females (4/10 slight inflammation, 6/10 minimal inflammation); however, there was a treatment-related increase in severity of the inflammation present. Again, Kauffman et al. (2009) offer only a superficial discussion of inflammation associated with squamous metaplasia, noting that:
      "Laryngeal epithelial alteration/laryngeal squamous metaplasia may be accompanied by submucosal inflammation, dependent on the irritant effect of the compound. Inflammatory responses due to irritant effects are regarded to be adverse findings."

      Again, the observed inflammation is conservatively interpreted as an adverse finding. However, in all but one animal, the severity of the inflammation is similar to levels observed in control animals indicating the minimal nature of the effect.

      Thus, while adverse hyperkeratosis and inflammation were observed at the LOAEC of 0.05 mg/L, these effects were all of slight or minimal severity.

2) The rapidity with which recovery was observed.
Recovery was not evaluated at the LOAEC of 0.05 mg/L in the initial study by Hoffman (2008). However, a follow-up study has been conducted and will be submitted, which evaluates the kinetics of recovery at lower concentrations, including 0.05 mg/L (Hotchkiss et al., 2017). The effects and recovery observed at this dose level

are presented in the table below, with adverse findings highlighted in red for ease of interpretation.

Effects at 0.05 mg/L		**End of 28-d exposure**			**Recovery**		
					1wk	**2 wk**	**4 wk**
Level I	*Study:*	*Hoffman female*	*Hoffman male*	*Hotchkiss male*	*Hotchkiss male*	*Hotchkiss male*	*Hotchkiss male*
Squamous metaplasia	very slight/ minimal	10% (1/10)	--	--	33% (2/6)	50% (3/6)	50% (3/6)
	slight	90% (9/10)	100% (10/10)	75% (6/8)	17% (1/6)	33% (2/6)	--
	moderate	--	--	25% (2/8)	--	--	--
Hyperkeratosis	very slight/ minimal	90% (9/10)	80% (8/10)	88.5% (7/8)	--	--	--
	slight	--	--	12.5% (1/8)	--	--	--
Inflammation	very slight/ minimal	20% (2/10)	10% (1/10)	50% (4/8)	50% (3/6)	33% (2/6)	50% (3/6)
	slight	70% (7/10)	90% (9/10)	50% (4/8)	17% (1/6)	17% (1/6)	--
	moderate	10% (1/10)	--	--	--	--	--
Level II							
Hyperplasia	very slight/ minimal	--	--	--	--	17% (1/6)	--
	slight	--	--	--	--	--	--

Recovery of the laryngeal effects occurs very rapidly at 0.05 mg/L, with adverse squamous metaplasia and hyperkeratosis recovering completely by the 1 week recovery time point. After 1 and 2 weeks of recovery, the only finding interpreted to be adverse was slight inflammation in a single animal. In the Hotchkiss et al. (2017) study, this was interpreted as an adverse finding as it was an increase over the background level of inflammation; however, in the Hoffman (2008) study, 40% of control animals exhibited slight inflammation, so the impact on the animal is anticipated to be very small. By the end of 4 weeks all effects had recovered to background and/or non-adverse levels. The rapid recovery lends further evidence that 0.05 mg/L is a minimal LOAEC and that a 3X uncertainty factor should be sufficiently protective.

3) The heightened sensitivity of the rat to this effect, suggesting that the NOAEC for humans would be higher. The rat is known to be particularly sensitive to portal-of-entry irritant effects in the larynx such as those observed in these studies. Thus, the dose level required to elicit similar effects in humans to those (minimal) adverse effects observed at 0.05 mg/L in the present rat study would be expected to be higher. As such, application of a 3x factor to account for the absence of an NOAEC should be conservative and health protective for humans.

References:

Hoffman, G.M., 2008. A 28-Day Subchronic Inhalation Toxicity Study of 2,4-Dichlorophenoxyacetic Acid in the Rat via Nose-Only Exposures. Huntingdon Life Sciences Study Number 07-6156. March 26, 2008.

Hotchkiss, J.A., Bell, M.P., Hutchinson, K.L., Thomas, J. 2,4-Dichlorophenoxyacetic Acid: 4-Week SubAcute Nose-Only Inhalation Toxicity Study in Crl:CD(SD) Rats with 1-, 2-, and 4-Week Recovery Groups. Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Laboratory Project Study ID 161009, March 14, 2017.

Kauffman, W. et al., 2009. *1st International ESTP Expert Workshop: "Larynx squamous metaplasia". A re-consideration of morphology and diagnostic approaches in rodent studies and its relevance for human risk assessment.* Exp. Toxicol. Path. 61: 591-603.

Document #	EPA-HQ-OPP-2012-0330-0042	**EPA states:** **"4.5.3 Cancer Classification and Risk Assessment Recommendation** The Cancer Peer Review Committee (CPRC; TXR No. 0050017, dated January 29, 1997) classified 2,4-D as "not classifiable as to human carcinogenicity", based upon bioassays in rats and mice that showed no statistically significant tumor response in either species. 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."
Page #	20	
Table #		
Row #		
Column #		

COMMENT

Epidemiology data support the EPA Guidelines for Carcinogen Risk Assessment descriptor "Not Likely to Be Carcinogenic to Humans"

Beginning in 1988, the EPA initiated a reregistration review of 2,4-D that the Agency completed in 2005 with its publication a Reregistration Evaluation Decision on 2,4-D (USEPA, 2005). The RED concluded that "none of the more recent epidemiological studies definitively linked cancer causes to 2,4-D." The EPA retained the classification from its 1997 cancer review of category D: Not Classifiable as to Human Carcinogenicity. As recently as 2014, the EPA assessed the carcinogenicity of 2,4-D as part of a new product registration: "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" (USEPA, 2014). In 2015, the International Agency for Research on Cancer concluded, "there is inadequate evidence in humans for the carcinogenicity of 2,4-dichlorophenoxyacetic acid (2,4-D)" (IARC 2016). Most of the epidemiology studies published since the 2005 EPA RED show no increased cancer risk. As a result, the growing body of evidence support "Not Likely to Be Carcinogenic to Humans."

Weak associations in early epidemiology studies have not been confirmed

Early case-control studies linked lymphomas to phenoxy herbicide exposure in Australia and Sweden and the U.S. (Kansas) (Hardell et al. 1994; Hoar et al. 1986; Smith and Christophers 1992). Subsequent case-control studies sponsored by the U.S. National Cancer Institute (NCI) collected information specific to 2,4-D and non-Hodgkin lymphoma (NHL). These studies conducted in Nebraska (Zahm et al. 1990) and Iowa and Minnesota (Cantor et al. 1992) reported differing results if the data were self-reported or by proxy. A pooled analysis of the Kansas, Nebraska and Iowa, Minnesota case control studies reported no increased risk of NHL and 2,4-D use (Odds Ratio 0.9, 95% Confidence Interval, CI 0.6 – 1.2) (De Roos et al. 2003). The increasing dose response of 2,4-D exposure and canine malignant lymphoma (Hayes et al. 1991) was not confirmed in an independent reanalysis of the underlying data (Kaneene and Miller 1999). In order to reduce the methodological weaknesses of case control studies, namely recall bias, the NCI launched the prospective Agricultural Health Study in 1993 (Alavanja et al. 1996).

To date, the AHS has more than 100 publications. No significant adverse association has been reported for 2,4-D use among approximately 80,000 participants in studies of children (Flower et al. 2004), breast cancer (Engel et al. 2005), prostate cancer (Alavanja et al. 2003) and melanoma (Dennis et al. 2010). A peer reviewed analysis of 2,4-D and NHL in the AHS has not been published. A poster presented at the 2013 Epidemiology and Occupational Health meeting by Dr. Beane Freeman of the NCI reported "no association with cancer risk overall (p-trend=0.68), NHL overall (p-trend=0.84), or any sub-type of NHL with intensity-weighted lifetime days" (Beane Freeman et al., 2013, and personal communication).

Since the 2005 EPA RED evaluation, several epidemiology studies in addition to the AHS have assessed 2,4-D exposure

and cancer (Hartge, et al. 2005, Mills, et al. 2005, Miligi, et al. 2006, Mills and Yang 2007, Band, et al. 2011, Burns, et al. 2011 (MRID 50285704), Hohenadel, et al. 2011, Pahwa, et al. 2012). The growing body of evidence in epidemiology and recent published reviews and governmental regulatory decisions support the position that 2,4-D is "**Not Likely to Be Carcinogenic to Humans**" (von Stackelberg 2013; Burns and Swaen, 2012 (MRID 48674604); EFSA, 2015; USEPA, 2012; Health Canada PMRA, 2008; USEPA, 2005; New Zealand Environmental Risk Management Authority, 2003).

Meta-analyses of certain cancers show no association

In their recent meta-analysis of 2,4-D exposure and three cancer endpoints, Goodman et al., (2015) (MRID 50285701) systematically reviewed 24 epidemiology studies that specifically evaluated exposure to 2,4-D. In general, study quality was undermined by several methodological limitations, such as exposure measurement error, information bias, and confounding. Results of individual studies were meta-analyzed for NHL (n = 9 studies), prostate cancer (n = 2 studies) and gastric cancer (n = 3 studies). Five of the 9 NHL studies were published since the 2005 RED. Results indicated **no associations** between 2,4-D exposure and any of these cancers. In addition, Goodman et al. (2015) observed evidence of publication bias in epidemiology studies of 2,4-D and NHL indicating small studies presenting positive associations were more likely to be published. Goodman et al., (2017) (MRID 50285702) updated their meta-analysis with raw data from the AHS obtained through the Freedom of Information Act request. The results were attenuated from their 2015 analyses. Another meta-analysis by Schinasi and Leon (2014) observed a slight elevation of NHL risk associated with 2,4-D exposure (RR=1.4, 95% CI: 1.0-1.9). Interpretation of these results is limited by the substantial heterogeneity in the collected results (I-squared = 61.5%). The scope of Schnasi and Leon (2014) was restricted to agricultural exposures to 2,4-D and included only five studies.

Most recently, Smith et al., (2017) conducted a meta-analysis with a focus on the "high exposure groups" of the NHL studies. The rationale of Smith *et al.* (2017) was that "if a true association does exist, higher exposure will usually result in higher relative risks." While this rationale has merit, the approach is flawed. Some limitations include

- The authors did not consider confounders, such as exposure to other pesticides. It appears that they selectively used risk estimates that did not account for other exposures.
- The authors selected risk estimates associated with different exposure metrics across studies. This is inappropriate because these metrics are evaluating different aspects of the exposure that may not be comparable (*e.g.*, duration of exposure *vs.* highest exposure concentration).
- The summary estimate is not meaningful when studies are heterogeneous.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "LOAEL = 0.05 mL/kg/day … HED=1.76 mg/kg/day[B] (residential handler) [B] Residential handler HED (portal of entry endpoint) = rat POD * RDDR * human specific conversion factor * human daily duration = 0.05 mg/L* RDDR (1.49) * 11.8 L/hr/kg * 2 hrs = 1.76 mg/kg/day"
Page #	22	
Paragraph #		
Table #	4.5.4.1	

CORRECTION

The statement should be corrected so that it reads:

"NOAEC$_{(\text{residential handler})}$ = 0.1 mL/kg/day
…
HED=4.22 mg/kg/day[B] (residential handler)

[B] Residential handler HED (portal of entry endpoint) = rat POD * RDDR * human specific conversion factor * human daily duration * relative activity factor = 0.1 mg/L* RDDR (1.49) * 11.8 L/hr/kg * 2 hrs * AF (1.2) = 4.22 mg/kg/day"

Corrections or additions are highlighted in red in this correction block.

The following changes are proposed to the HED for residential handlers:

1) The new Inhalation study (MRID 50320801) showing rapid recovery supports an NOAEC of 0.1 mg/L based on

recovery. For residential handlers, the labeled interval between applications will lead to a recovery period between exposures such that this NOAEC is amply protective for these exposure scenarios.

2) The activity factor accounting for differences in breathing rate for different activities was omitted in the human health assessment document, but included in the residential and occupational risk assessment document. As breathing rates can vary substantially with activity (e.g., flying a plane or driving a tractor vs. carrying a backpack sprayer or pouring from heavy containers) (Ainsworth et al., 2000), it is most appropriate to apply this factor, so the human health assessment document should be updated to include the activity factors used in the residential and occupational assessment.

Reference:

Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS. 2000. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc. Sep;32(9 Suppl):S498-504.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "LOAEL = 0.05 mL/kg/day … HEC= 0.056 mg/L/day[C] (occupational) HED= 5.29 mg/kg/day[D] (occupational handler, depending on scenario) … [C] Occupational HEC (portal of entry endpoint) = rat POD * daily duration adjustment * weekly duration adjustment * RDDR = 0.05 mg/L * (6 hrs/8 hrs) * (5 days/5 days) * Tracheobronchial RDDR (1.49) = 0.056 mg/L [D] Occupational handler HED (portal of entry endpoint) = HEC * human specific conversion factor * daily duration * relative activity factor = HEC (0.056 mg/L) * 11.8 L/hr/kg * 8 hrs = 5.29 mg/kg/day"
Page #	22	
Paragraph #		
Table #	4.5.4.1	

CORRECTION

The statement should be corrected so that it reads:

"LOAEC = 0.05 mL/kg/day
…
HEC= 0.056 mg/L/day[C] (occupational)

HED= 3.18, 6.4, or 11.11 mg/kg/day[D] (occupational handler, depending on scenario)

[C] Occupational HEC (portal of entry endpoint) = rat POD * daily duration adjustment * weekly duration adjustment * RDDR = 0.05 mg/L * (6 hrs/8 hrs) * (5 days/5 days) * Tracheobronchial RDDR (1.49) = 0.056 mg/L
[D] Occupational handler HED (portal of entry endpoint) = HEC * human specific conversion factor * daily duration * relative activity factor = HEC (0.056 mg/L) * 11.8 L/hr/kg * 8 hrs * AF (0.6, 1.2 or 2.1, depending on activity) = 3.18, 6.4, or 11.11 mg/kg/day"

Corrections or additions are highlighted in red in this correction block.

The activity factor accounting for differences in breathing rate for different activities was omitted in the human health assessment document, but included in the residential and occupational risk assessment document. As breathing rates can vary substantially with activity (e.g., flying a plane or driving a tractor vs. carrying a backpack sprayer or pouring from heavy containers) (Ainsworth et al., 2000), it is most appropriate to apply this factor, so the human health assessment document should be updated to include the activity factors used in the residential and occupational assessment.

Reference:

Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH,

Emplaincourt PO, Jacobs DR Jr, Leon AS. 2000. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc. Sep;32(9 Suppl):S498-504.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "2,4-D is on List 1 for which EPA has received all the required Tier 1 assay data. The Agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets (see EPA-HQ-OPP-2012-0330). For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website."
Page #	23	
Paragraph #	4	
Row #		
Column #		

COMMENT

The Task Force proposes adding the conclusions of the June 29, 2015 EDSP Weight of Evidence Conclusions on the Tier 1 Screening Assays for the List 1 Chemicals to the above overview statement.

The statement/entry should be modified so that it reads:

"EPA states: 2,4-D is on List 1 for which EPA has received all the required Tier 1 assay data. The Agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets (see EPA-HQ-OPP-2012-0330). The conclusion of the Agency's WoE evaluation is that 2, 4-D demonstrates no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website."

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "According to the 2005 RED (Memo, T. Dole, 5/12/05, D316597), the major route of degradation is aerobic microbial metabolism, therefore, 2,4-D is non-persistent (t1/2=6.92 days) in terrestrial (aerobic) environments, moderately persistent (t1/2=45 days) in aerobic aquatic environments…" Table 4.1, page 14 of the lists the aerobic aquatic metabolism $t_{1/2=}$15 days, the anaerobic aquatic $t_{1/2}$=333 days and the median terrestrial field dissipation $t_{1/2}$=6.1 days. The Agency should consider maintaining consistency between contemporary documents.
Page #	24	
Paragraph #	3	
Row #		
Column #		

CORRECTION

The text appears to contain an inconsistency from an EPA memo. In the 2016 Preliminary Ecological Risk Assessment DP Barcode 424054, EPA states "2,4-D acid was not stable in aerobic aquatic environments (t1/2=15.0 days)," in the 2nd paragraph, page 13.

As defined in the article Pesticide and Their Behavior in Soil and Water (Rao, et.al., Florida Cooperative Extension Service, Institute of Food and Agricultural Sciences, University of Florida (http://psep.cce.cornell.edu/facts-slides-self/facts/gen-pubre-soil-water.aspx), pesticides with half-lives less than 30 days are classified as **non-persistent**.

The statement/ entry should be corrected so that it reads:

The major route of degradation is aerobic microbial metabolism, therefore, 2,4-D is non-persistent ($t_{1/2}$=6.1 days) in terrestrial (aerobic) environments, non-persistent ($t_{1/2}$=15 days) in aerobic aquatic environments, and highly persistent ($t_{1/2}$=333 days) in anaerobic aquatic environments.

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042
Page #	25
Paragraph #	1
Table #	--

EPA states:
"For 2,4-D-tolerant field corn and soybean, the metabolite 2,4-DCP was also included as a residue of concern for dietary risk assessment purposes as there are greater amounts of 2,4-DCP found in tolerant crops compared to non-tolerant crops."

CORRECTION

The statement/ entry should be corrected so that it reads:

"For 2,4-D-tolerant field corn, soybean, and cotton the metabolite 2,4-DCP was also included as a residue of concern for dietary risk assessment purposes as there are greater amounts of 2,4-DCP found in tolerant crops compared to non-tolerant crops."

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042
Page #	25
Paragraph #	N/A
Table #	5.1.4

EPA states:

Table 5.1.4 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Parent (2,4-D)	Parent (2,4-D)
	Rotational Crop	Parent (2,4-D)	Parent (2,4-D)
	Transgenic Corn and Soybean	2,4-D and 2,4-DCP	Parent (2,4-D)
Livestock	Ruminant	Parent (2,4-D)	Parent (2,4-D)
	Poultry	Parent (2,4-D)	Parent (2,4-D)
Drinking Water		Parent (2,4-D)	Not Applicable

2,4-D is 2,4-Dichlorophenoxyacetic acid, and 2,4-DCP is 2,4-dichlorophenol.

CORRECTION

The statement/ entry should be corrected so that it reads:

In the plant matrix column, it should read, "Transgenic Corn, Soybean, and Cotton"

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042
Page #	27
Paragraph #	1
Table #	

The review states the following Agency recommendation:

"For transgenic cotton, a combined 2,4-D and 2,4-DCP residue value of 0.15 ppm was used in the acute and chronic dietary assessment for cotton seed oil. That value incorporated the empirical processing factors for 2,4-D and 2,4-DCP for cottonseed oil; the 2,4-DCP processing factor is 0.4x and for 2,4-D is assumed to be 1x."

COMMENT

The Task Force disagrees with the Agency recommendation for the following reasons:

The residue value used for the acute and chronic dietary assessment for 2,4-D use on cottonseed oil of 0.15 ppm was overly conservative. In the cotton processing study submitted (Vespestad, 2011) no detectable residues were found at both the 2X and 4X rate in refined cottonseed oil, however it is still possible to calculate a processing factor by using a conservative estimate of ½ of the LOD (0.0015 µg/g) where the residues were non-detectable (in both the refined oil and the cottonseed) and using the values reported between the LOD and LOQ. This resulted in an average processing factor across trials of 0.84 for 2,4-D and 0.08 for 2,4-DCP based on the residue data in the cotton processing study submitted. These processing factors should then be multiplied by the respective undelinted cottonseed STMR values (0.01 for 2,4-D and 0.11 for 2,4-DCP expressed as 2,4-D equivalents) as cottonseed oil is a blended commodity and then summed together to get the cottonseed oil residue value to be used in the dietary risk assessment of 0.02 ppm.

Reference

Vespestad, D., 2011. Magnitude of the residue of 2,4-D in/on transgenic cotton containing the aryloxyalkanoate dioxygenase-12 (aad-12) gene, processing study. S12-02208 Study ID 120431 Dow AgroSciences LLC. Indianapolis, IN. (MRID 49431204)

Document #	EPA-HQ-OPP-2012-0330-0042
Page #	29
Paragraph #	7
Table #	--

EPA states:
"The residential handler margins of exposure (MOEs) range from 5,500 to 130,000 (LOC = 300). All scenarios are not of concern for 2,4-D (MOEs are greater than the LOC of 300 for inhalation)."

CORRECTION

The statement should be corrected so that it reads:

"The residential handler margins of exposure (MOEs) range from 13,000 to 300,000 (LOC = 10). All scenarios are not of concern for 2,4-D (MOEs are greater than the LOC of 300 for inhalation)."

Corrections or additions are highlighted in red in this correction block.

In keeping with the above comments revising the HED for residential handlers, the MOEs should be corrected. Furthermore, the residential LOC should now be 10. There is no need for the LOAEL to NOAEL UF as an NOAEC was established for residential handlers based on recovery of the effect. And as indicated previously, the interspecies UF can be reduced to 1 based on the known increased sensitivity of the rat relative to the human.

Document #	EPA-HQ-OPP-2012-0330-0042
Page #	29
Paragraph #	--
Table #	6.1.1

EPA states:

Exposure Scenario		….	MOE (LOC = 300)
Liquid	Hose-end sprayer		8,500
Ready-to-use or WP in WSP			5,500
Liquid or WP in WSP	Manually-pressurized handwand		130,000
WP in WSP	Backpack		
Liquid			17,000
Granule	Push-type spreader		72,000
	Belly Grinder		110,000

CORRECTION

The table should be corrected so that it reads:

Exposure Scenario		….	MOE (LOC = 10)
Liquid	Hose-end sprayer		20,000
Ready-to-use or WP in WSP			13,000
Liquid or WP in WSP	Manually-pressurized handwand		300,000
WP in WSP	Backpack		
Liquid			38,000
Granule	Push-type spreader		170,000
	Belly Grinder		260,000

Corrections or additions are highlighted in red in this correction block.

In keeping with the above comments revising the HED for residential handlers, the MOEs should be corrected. Furthermore, the residential LOC should now be 10. There is no need for the LOAEL to NOAEL UF as an NOAEC was established for residents based on recovery of the effect. And as indicated previously, the interspecies UF can be reduced to 1 based on the known increased sensitivity of the rat relative to the human.

Document #	EPA-HQ-OPP-2012-0330-0042
Page #	44-45
Paragraph #	5 on
Table #	--

EPA states:
"Risk estimates of concern for the following scenarios were identified with no respirator, but are mitigated with the use of a PF5 respirator (current labels do not require a respirator):

- Mixing/loading granulars for aerial application to the following use sites:
  - Non-cropland @4 lb ae/A
  - Aquatic sites @ 10.8 lb ae/A-ft
  - Field corn/popcorn @ 1.5 lb ae/A
  - Field corn/popcorn, sweet corn, grain or forage sorghum @ 1 lb ae/A
- Mixing/loading granulars for solid spreader application to aquatic sites @ 10.8 lb ae/A-ft
- Applying sprays using mechanically-pressurized handgun to ROW sites @ 0.4 lb ae/gallon
- Mixing/loading/applying WSP using backpack to turf @ 1 lb ae/gallon

Risk estimates of concern for the following scenarios were identified with no respirator, but are mitigated with the use of a PF10 respirator (current labels do not require a respirator):

- Mixing/loading/applying liquids or WSP using mechanically-pressurized handgun to orchard floors @ 1.5 lb ae/gallon

Risk estimates of concern for the following scenarios were identified with engineering controls (i.e., enclosed cockpit):

- Aerial application of granulars to the following use sites:
  - Cranberries and non-cropland areas @ 4 lb ai/A
  - Aquatic areas @ 10.8 lb ae/acre-ft
  - Field corn/popcorn @ 1.5 lb ae/A
  - Field corn/popcorn, sweet corn, grain or forage sorghum @ 1 lb ae/A"

CORRECTION

The statement should be corrected.

As indicated in comments on page 22, the HED values for occupational exposures in this document did not include the activity factors applied in the residential and occupational exposure document. These scenarios need to be updated to be

consistent with that document and the activity-specific HED values. Further comments on specific scenarios are provided in comments on the Residential and Occupational assessment document.

Document #	EPA-HQ-OPP-2012-0330-0042	The Enlist Duo Herbicide label adding use of Enlist cotton was stamped accepted on 1-12-2017. These use directions should be added to Appendix B.
Page #	50	
Paragraph #	Appendix B	
Row #		
Column #		

CORRECTION

The statement/entry should be corrected so that it reads:

ENLIST™ COTTON

CROP STAGE	MAXIMUM APPLICATION RATE / Acre	DIRECTIONS / Timing
Preplant or Preemergence	1.0 lb. acid equivalent	To control emerged broadleaf weed seedlings or existing cover crops, apply before cotton emerges.
Postemergence	1.0 lb. acid equivalent	Apply any time after cotton emergence but no later than full flowering (mid-bloom stage). Make one to two postemergence applications with a minimum of 12 days between applications.

Precautions and Restrictions:

- These use directions are only for cotton identified as containing the Enlist trait.
- **Preharvest Interval:** Do not apply within 30 days of harvest.
- Do not graze treated cotton.
- Do not harvest for forage or hay.
- Do not apply more than one preemergence application and no more than two postemergence applications per use season.
- Do not apply to cotton later than the mid-bloom stage.
- Do not apply more than 3.0 lb. acid equivalent per acre per use season.
- Do not apply more than 1.0 lb. acid equivalent per acre per application
- Do not aerially apply this product.

EPA Chemical Number	Chemical	Formulation	Reentry Interval	Application Method	Application Equipment
51505	Choline	SC/L	48 hr.	Ground spray Broadcast	Ground: boom sprayers

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states:
Page #	51	

Use site	Chemical
Citrus - Lemons	Acid, IPE

Table #	Appendix B	Citrus (Growth Regulator)	Acid, IPE
Row #			
Column #	Chemical		

CORRECTION

2,4-D IPE is the only form of 2,4-D registered for use on citrus. Delete acid from the Chemical column.

The statement/entry should be corrected so that it reads:

Use site	Chemical
Citrus - Lemons	IPE
Citrus (Growth Regulator)	IPE

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042
Page	55
Table #	Appendix B
Row #	
Column #	Application

EPA states :

Use site	Chemical	Application timing	Application type	Application Equipment
Hops	Acid, DMA, TIPA, IPA, DEA	Postemergence; Make application as a directed treatment to the row middles(directed to ground)	Aerial, Ground	Aerial, Ground

CORRECTION

Applications to hops are a directed treatment. Delete aerial application.

The statement/entry should be corrected so that it reads:

Use site	Chemical	Application timing	Application type	Application Equipment
Hops	Acid, DMA, TIPA, IPA, DEA	Postemergence; Make application as a directed treatment to the row middles (directed to ground)	Ground	Ground

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042
Page #	57
Table #	Appendix B

EPA states:

Use Site	Max Number Applications per Season
Sugarcane	1

Row #	
Column #	Max number of applications per season

CORRECTION

2,4-D may be applied once per year in to each crop stage: preemergence and postemergence. Change the number of applications per year to two.

The statement/entry should be corrected so that it reads:

Use Site	Max Number Applications per Season
Sugarcane	2

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042
Page #	58
Table #	Appendix B
Row #	
Column #	Max seasonal application rate

EPA states:

Use Site	Max Seasonal Application Rate
Aquatic weeds in ponds, lakes, reservoirs, etc.	4 ppm; 4 lb ae/A

CORRECTION

The maximum annual rate of application for aquatic weeds in ponds, lakes, etc. is 8 ppm; 8 lb ae/acre.

The statement/entry should be corrected so that it reads:

Use Site	Max Seasonal Application Rate
Aquatic weeds in ponds, lakes, reservoirs, etc.	8 ppm; 8 lb ae/A

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042
Page #	64
Paragraph #	2
Table #	C.2.2

On MRID 47398701, EPA states:
"Systemic NOAEL = 0.30 mg/L/day
Systemic LOAEL = 1.0 mg/L/day based on increased alkaline phosphatase and aspartate aminotransferase levels in females and decreased spleen weights in females.
NOAEL (portal-of-entry effects) = not determined.
LOAEL (portal-of-entry effects) = 0.05 mg/L/day, based on squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx; not totally resolved following a 4-week recovery period."

CORRECTION

The statement should be corrected so that it reads:

"Systemic NOAEL = 0.30 mg/L/day
Systemic LOAEL = 1.0 mg/L/day based on increased alkaline phosphatase and aspartate aminotransferase levels in females and decreased spleen weights in females.
NOAEL (portal-of-entry effects) = not determined.

LOAEL (portal-of-entry effects) = 0.05 mg/L/day, based on squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx; ~~not totally resolved following a 4-week recovery period.~~"

Corrections or additions are highlighted in red in this correction block.

Recovery was not evaluated at the 0.05 mg/L concentration.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "**Dose and Endpoint for Risk Assessment**: No NOAEL for portal of entry effects was determined, and the LOAEL was used as the point of departure. The LOAEL for portal of entry effects is 0.05 mg/L (lowest dose tested), based on squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx, which was not totally resolved following a 4-week recovery period. Excessive salivation, labored breathing, and chromodacryorrhea were observed at the high-dose level following the 12th exposure and continued during the remainder of the exposures."
Page #	72	
Paragraph #	3	
Table #	--	

CORRECTION

The statement should be corrected so that it reads:

"**Dose and Endpoint for Risk Assessment**: No NOAEC for portal of entry effects was determined, and the LOAEC was used as the point of departure. The LOAEC for portal of entry effects is 0.05 mg/L (lowest dose tested), based on squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx, ~~which was not totally resolved following a 4-week recovery period~~. Excessive salivation, labored breathing, and chromodacryorrhea were observed at the high-dose level following the 12th exposure and continued during the remainder of the exposures."

Corrections or additions are highlighted in red in this correction block.

Recovery was not evaluated at the low concentration of 0.05 mg/L.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "The portal of entry effects were squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx. These effects occurred at all dose levels (NOAEL was not identified). The incidence and severity of these effects were increased in a dose-related manner, and the effects persisted following the 4-week recovery period, although the incidence and severity were reduced. A human-equivalent concentration (HEC) was derived from this study based upon the portal of entry effects (residential: 0.013 mg/L; occupational: 0.056 mg/L). A human-equivalent dose (HED) was also calculated (residential: 2.133 mg/kg/day; occupational: 3.18, 6.4, or 11.11 mg/kg/day depending on breathing rate scenario)."
Page #	72	
Paragraph #	4	
Table #	--	

CORRECTION

The statement should be corrected so that it reads:

"The portal of entry effects were squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx. These effects occurred at all dose levels (NOAEC was not identified). The incidence and severity of these effects were increased in a dose-related manner, and the effects at the high concentration persisted following the 4-week recovery period, although the incidence and severity were reduced. A human-equivalent concentration (HEC) was derived from this study based upon the portal of entry effects (residential bystander: 0.013 mg/L; occupational: 0.056 mg/L). A human-equivalent dose (HED) was also calculated (residential handler: 4.22 mg/kg/day; occupational: 3.18, 6.4, or 11.11 mg/kg/day depending on breathing rate scenario)."

Corrections or additions are highlighted in red in this correction block.

Recovery was only evaluated at the highest concentration in the described study. More detailed description of recovery could be added based on the newer recovery study. Endpoints should be updated here in keeping with previous comments.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "Following nose-only inhalation exposure, 2, 4-D was associated with portal-of-entry effects that consisted of squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx. The incidence and severity of the effects were increased in a dose-related manner, and the effects persisted following the 4-week recovery period, although the incidence and severity were reduced."
Page #	77	
Paragraph #	4	
Table #	--	

CORRECTION

The statement should be corrected so that it reads:

"Following nose-only inhalation exposure, 2,4-D was associated with portal-of-entry effects that consisted of squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx. The incidence and severity of the effects were increased in a dose-related manner, and the effects persisted at the high concentration following the 4-week recovery period, although the incidence and severity were reduced."

Corrections or additions are highlighted in red in this correction block.

Unnecessary space in 2,4-D on first line.

Recovery was only evaluated at the highest concentration in the described study. More detailed description of recovery could be added based on the newer recovery study.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "The systemic toxicity LOAEL is 1.0 mg/L/day, based on excessive salivation, labored breathing, and chromodacryorrhea, decreased body weight in females and decreased spleen weights in females. The NOAEL is 0.30 mg/L/day."
Page #	77	
Paragraph #	5	
Table #	--	

CORRECTION

The statement should be corrected so that it reads:

"The systemic toxicity LOAEC is 1.0 mg/L, based on excessive salivation, labored breathing, and chromodacryorrhea, decreased body weight in females and decreased spleen weights in females. The NOAEC is 0.30 mg/L."

Corrections or additions are highlighted in red in this correction block.

These endpoints are concentrations, not doses and the units are mg/L, not mg/L/day.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "**A NOAEL for portal-of-entry effects was not determined. The LOAEL for portal-of-entry effects** (squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx; not totally resolved following a 4-week recovery period) **is 0.05 mg/L, the lowest dose tested.**"
Page #	78	
Paragraph #	1	

Table #	--	

CORRECTION

The statement should be corrected so that it reads:

"**A NOAEC for portal-of-entry effects was not determined. The LOAEC for portal-of-entry effects** (squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx; ~~not totally resolved following a 4-week recovery period~~) **is 0.05 mg/L, the lowest concentration tested.**"

Corrections or additions are highlighted in red in this correction block.

These endpoints are concentrations, not doses and the units are mg/L, not mg/L/day. Recovery was not evaluated at the LOAEC in the described study.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "Occupational Handler HEC = 0.05 mg/L * (6/8) * (5/5) * 1.49 = 0.056 mg/L. Residential Bystander HEC = 0.05 mg/L* (6/24)*(5/7)* 1.49 = 0.013 mg/L. Residential Handler HEC = 0.05 mg/L * 1.49 = 0.075 mg/L."
Page #	104	
Paragraph #	--	
Table #	--	

CORRECTION

The statement should be corrected so that it reads:

"Occupational Handler HEC = 0.05 mg/L * (6/8) * (5/5) * 1.49 = 0.056 mg/L.
Residential Bystander HEC = 0.05 mg/L* (6/24)*(5/7)* 1.49 = 0.013 mg/L.
Residential Handler HEC = 0.1 mg/L * 1.49 = 0.149 mg/L."

Corrections or additions are highlighted in red in this correction block.

The NOAEC of 0.1 mg/L based on recovery in the new Inhalation study (MRID 50320801) should be applicable for residential handlers.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "Human-Equivalent Dose (HED, mg/kg/day) = Dose (HEC value, mg/L) x A x CF (L/hr/kg) x D (hours) = mg/kg Where: A = absorption: ratio of deposition and absorption in respiratory tract compared to absorption by the oral route (1). CF = conversion Factor; a L/hr/kg factor which accounts for respiratory volume and body weight for a given species and strain (11.8). D = duration; duration of daily animal or human exposure (hours). Therefore, the occupational human equivalent dose for 2,4-D is calculated as follows: **Occupational Handler HED:** (0.05 mg/L) x (6/8) x (5/5) x 1.49 x 1 x (11.8 L/hr/kg) x (8 hrs) = 5.29 mg/kg/day **Residential Handler HED**: (0.05 mg/L) x 1.49 x 1 x (11.8 L/hr/kg) x (2 hrs) = 1.76 mg/kg/day"
Page #	104	
Paragraph #	--	
Table #	--	

CORRECTION

The statement should be corrected so that it reads:

"Human-Equivalent Dose (HED, mg/kg/day) = Dose (HEC value, mg/L) x A x CF (L/hr/kg) x D (hours) x AF = mg/kg
Where:
A = absorption: ratio of deposition and absorption in respiratory tract compared to absorption by the oral route (1).
CF = conversion Factor; a L/hr/kg factor which accounts for respiratory volume and body weight for a given species and strain (11.8).
D = duration; duration of daily animal or human exposure (hours).
AF = activity factor accounting for different breathing rates with different activities (0.6, 1.2, or 2.1, depending on activity)
Therefore, the occupational human equivalent dose for 2,4-D is calculated as follows:
Occupational Handler HED:
(0.05 mg/L) x (6/8) x (5/5) x 1.49 x 1 x (11.8 L/hr/kg) x (8 hrs) x (0.6, 1.2, or 2.1, depending on activity) = 3.18, 6.4, or 11.11 mg/kg/day
Residential Handler HED:
(0.1 mg/L) x 1.49 x 1 x (11.8 L/hr/kg) x (2 hrs) x 1.2 = 4.22 mg/kg/day"

Corrections or additions are highlighted in red in this correction block.

The activity factor accounting for differences in breathing rate for different activities was omitted in the human health assessment document, but included in the residential and occupational risk assessment document. As breathing rates can vary substantially with activity (e.g., flying a plane or driving a tractor vs. carrying a backpack sprayer or pouring from heavy containers) (Ainsworth et al., 2000), it is most appropriate to apply this factor, so the human health assessment document should be updated to include the activity factors used in the residential and occupational assessment.

Furthermore, the NOAEC of 0.1 mg/L based on recovery in the new Inhalation study (MRID 50320801) should be applicable for residential handlers.

Reference:
Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS. 2000. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc. Sep;32(9 Suppl):S498-504.

Document #	EPA-HQ-OPP-2012-0330-0042	EPA states: "HEC and HED calculations are summarized in Table D.1. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the calculation of HECs accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X. Since a NOAEL was not attained in the inhalation study, a 10X uncertainty factor is required for LOAEL to NOAEL extrapolation."
Page #	104	
Paragraph #	Last	
Table #	--	

CORRECTION

The statement should be corrected so that it reads:

"HEC and HED calculations are summarized in Table D.1. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 1X due to the documented sensitivity of the rat to these effects from both a pharmacokinetic and pharmacodynamic standpoint. The intraspecies uncertainty factor remains at 10X. Since a NOAEL was not attained in the inhalation study, a 3X uncertainty factor is required for LOAEL to NOAEL extrapolation. For residential handlers, a NOAEC based on rapid recovery of the effect can be applied and this 3X factor is unnecessary."

Corrections or additions are highlighted in red in this correction block.

Consistent with previous comments, the interspecies UF should be reduced to 1X due to the established hypersensitivity of the rat to laryngeal squamous metaplasia following inhalation of irritant chemicals. The use of the rat endpoint without an extra safety factor will be protective of human health.

Based on the minimal nature of the effects at the LOAEC and the already conservative approach of applying the rat

endpoint to the less sensitive human, the LOAEL to NOAEL uncertainty factor should be reduced to 3X. Furthermore, the NOAEC of 0.1 mg/L based on recovery in the new Inhalation study (MRID 50320801) should be applicable for residential handlers. This obviates the need for the LOAEL to NOAEL uncertainty factor for residential handlers.

Document #	EPA-HQ-OPP-2012-0330-0042
Page #	105
Paragraph #	--
Table #	D.1

EPA states:

Table D.1: Inhalation HEC and HED Calculation Summary

Population	Scenario	Tox duration adjustment		HEC		HED
		hr/day	day/wk	mg/L	mg/m3	(mg/kg-day)
Occupational	Handler	8	5	0.056	55.88	5.29
Residential	Handler	NA	NA	0.0745	74.5	1.76
	Bystander	24	7	0.0133	13.3	NA

CORRECTION

The following values should be changed based on comments above:

The HEC for Residential Handlers should be 0.149 mg/L or 149 mg/m^3.
The Occupational HED should be 3.18, 6.4, or 11.1 mg/kg/day, depending on activity.
The Residential Handler HED should be 4.22 mg/kg/day.

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042
Page #	105
Paragraph #	1-2
Table #	--

EPA states:
"The route-specific subchronic inhalation study in rats was selected to evaluate inhalation exposures. The NOAEL was not determined. The LOAEL of 0.05 mg/L is based on histopathological findings in the larynx (squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx). Human equivalent concentrations (HECs) were derived using the LOAEL and the regional deposited dose ratio (RDDR). The RDDR accounts for the particulate diameter [mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD)] and estimates the different dose fractions deposited along the respiratory tract. The RDDR also accounts for interspecies differences in ventilation and respiratory tract surface areas. For the subchronic inhalation toxicity study with 2,4-D, a RDDR was estimated at 1.49 based on portal of entry effects (histopathological findings in the larynx) seen at the LOAEL of 0.05 mg/L, with a MMAD of 1.7 µm and GSD of 1.98.

Human equivalent doses (HEDs) were subsequently calculated from the HECs for residential and occupational handler scenarios. HEC and HED calculations are summarized in Table D.1. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the calculation of HECs accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X. Since a NOAEL was not attained in the inhalation toxicity study, a 10X uncertainty factor is required for LOAEL to NOAEL extrapolation."

CORRECTION

The following changes should be made based on comments on pages 104-105 above:

"The route-specific subchronic inhalation study in rats was selected to evaluate inhalation exposures. The NOAEC was not determined. The LOAEC of 0.05 mg/L is based on histopathological findings in the larynx (squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx). Human equivalent concentrations (HECs) were derived using the LOAEC and the regional deposited dose ratio (RDDR). The RDDR accounts for the particulate diameter [mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD)] and

estimates the different dose fractions deposited along the respiratory tract. The RDDR also accounts for interspecies differences in ventilation and respiratory tract surface areas. For the subchronic inhalation toxicity study with 2,4-D, a RDDR was estimated at 1.49 based on portal of entry effects (histopathological findings in the larynx) seen at the LOAEC of 0.05 mg/L, with a MMAD of 1.7 µm and GSD of 1.98. For residential handlers, an NOAEC of 0.1 mg/L was determined based on the rapid recovery of these portal of entry effects observed in a follow-up study. This value was not considered applicable for occupational handlers who may be exposed for longer durations without opportunity for recovery.

Human equivalent doses (HEDs) were subsequently calculated from the HECs for residential and occupational handler scenarios. HEC and HED calculations are summarized in Table D.1. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 1X due to documented sensitivity of the rat to these effects from both a pharmacokinetic and pharmacodynamic standpoint. The intraspecies uncertainty factor remains at 10X. Since a NOAEC was not attained in the inhalation toxicity study, a 3X uncertainty factor is required for LOAEL to NOAEL extrapolation. For residential handlers, a NOAEC based on rapid recovery of the effect can be applied and this 3X factor is unnecessary."

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0042	The table of MOEs in Appendix H is based on the erroneous endpoints presented in the Human Health document.
Page #	115-128	
Paragraph #	--	
Table #	--	

CORRECTION

It should be updated for consistency with the Residential and Occupational document, including MOEs based on new endpoints as well as other changes detailed in the comments to that document.

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Comments on

2,4-D: Acute and Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for Section 3 Registration on Transgenic Cotton and Registration Review

EPA-HQ-OPP-2012-0330-0045 / DP Barcode D427712

Document #	EPA-HQ-OPP-2012-0330-0045	The review states the following Agency recommendation: "For the proposed new use, the residue value used in the acute and chronic dietary assessment for 2,4-D use on cotton seed oil was a metabolite and parent combined processed conm1odity residue value for refined oil (0.15 ppm). For 2,4-D a processing factor was not calculated for refined oil, so the Health Effects Division's (l-I ED's) Dietary Exposure Science Advisory Council (DESAC) recommended that a processing factor of l.Ox should be multiplied with the HAFT of undelinted cotton seed (0.07 ppm) from the recently submitted magnitude of residue study. The 2,4-DCP processed commodity residue for refined oil (0.08 ppm), was calculated by multiplying the processing factor of 0.4x by the HAFT of undelinted cotton seed for 2,4-DCP (0.206 ppm). The 2,4-D residue product (0.07 ppm) was then added with the 2,4-DCP calculated residue (0.08 ppm) and the sum was 0.15 ppm."
Page #	3	
Paragraph #	5	
Table #		

COMMENT

The Task Force disagrees with the Agency recommendation for the following reasons:

The residue value used for the acute and chronic dietary assessment for 2,4-D use on cottonseed oil of 0.15 ppm was overly conservative. In the cotton processing study submitted (Vespestad, 2011) no detectable residues were found at both the 2X and 4X rate in refined cottonseed oil, however it is still possible to calculate a processing factor by using a conservative estimate of ½ of the LOD (0.0015 µg/g) where the residues were non-detectable (in both the refined oil and the cottonseed) and using the values reported between the LOD and LOQ. This resulted in an average processing factor across trials of 0.84 for 2,4-D and 0.08 for 2,4-DCP based on the residue data in the cotton processing study submitted. These processing factors should then be multiplied by the respective undelinted cottonseed STMR values (0.01 for 2,4-D and 0.11 for 2,4-DCP expressed as 2,4-D equivalents) as cottonseed oil is a blended commodity and then summed together to get the cottonseed oil residue value to be used in the dietary risk assessment of 0.02 ppm.

Reference

Vespestad, D., 2011. Magnitude of the residue of 2,4-d in/on transgenic cotton containing the aryloxyalkanoate dioxygenase-12 (aad-12) gene, processing study. S12-02208 Study ID 120431 Dow AgroSciences LLC. Indianapolis, IN. (MRID 49431204)

Document #	EPA-HQ-OPP-2012-0330-0045	EPA states: "The acute and chronic dietary exposure analyses are based on the parent and metabolite combined processed commodity residue for refined oil, I 00% crop treated assumptions, and default processing factors. Various refinements could be made to the assessments. However, as there are no risk estimates of concern, no refinements were incorporated. The top dietary risk driver for the population with the highest a PAD (Children l -2) is un cooked orange juice with 5 1% of the total exposure for all records."
Page #	7	
Paragraph #	1	
Table #	--	

OMISSION/CORRECTION

The statement should be amended for more transparent risk communication:

The Task Force supports clear and transparent risk communication that allows those without formal training in dietary risk assessment to understand the implications of the exposure and risk estimates being presented. While the Agency does explicitly state the assumptions used in the assessment, a statement on the conservatism in these assumptions would improve transparency and allow for this document to more clearly communicate risk to an audience not trained in risk

assessment. Suggested language below is based on language used by the Agency to describe another unrefined dietary risk assessment (methoxyfenozide):

Example of language with improved transparency regarding exposure assumptions:
"The acute and chronic dietary exposure analyses are highly conservative, largely unrefined dietary exposure assessments based on the parent and metabolite combined processed commodity residue for refined oil, I 00% crop treated assumptions, and default processing factors. Various refinements could be made to the assessments. However, as there are no risk estimates of concern, no refinements were incorporated. The reported risk estimates are likely to be considerably greater than the risks from actual exposure to 2,4-D as a result of registered uses.

The top dietary risk driver for the population with the highest a PAD (Children l -2) is un cooked orange juice with 51% of the total exposure for all records."

Corrections or additions are highlighted in red in this correction block.

Comments on
2,4-D: Revised Drinking Water Assessment in Support of Registration Review
EPA-HQ-OPP-2012-0330-0043 / DP Barcode 432483

Document #	EPA-HQ-OPP-2012-0330-0043	EPA states: "The MCL of 70 µg/L is lower than the Tier II surface water 1-in-10-year mean and 30-year mean values but higher than the 1-in-10-year peak concentration."
Page #3	3	
Paragraph #	1	
Row #		
Column #		

CORRECTION

The statement/entry should be corrected so that it reads:

The MCL of 70 µg/L is higher than the Tier II surface water 1-in-10-year mean and 30-year mean values but lower than the 1-in-10-year peak concentration.

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0043	EPA states: "The detection frequencies in both surface water and groundwater are higher than the previously reported frequencies for monitoring data (USEPA, 2004). In 2012, BEAD provided a 2,4-D usage data for 2000-2010 (USEPA 2012). The 2,4-D usage averaged approximately 29 million pounds active ingredient for 55 million treated acres. Data also suggest that since 2005 there is an upward trend of 2,4-D usage of pound active ingredient as well as total treated acres. The increasing trend of 2,4-D usage and treated acres may have contributed to higher detection frequencies in surface water and ground water."
Page #	7	
Paragraph #	1	
Row #		
Column #		

COMMENT

The increase in detection frequency from pre-2004 to post-2004 monitoring could be due to a number of factors independent of the amount of 2,4-D used, or the proximity of that use to vulnerable aquifers. The detection limits for analytical methods tend to decrease over time as analytical technology improves. This will have the effect of increasing the detection rate since a compound will likely be detected in more samples when the detection limit is lower. The Task Force recommends that the applicable detection limit be included for each monitoring program listed in Table 2. This will enable more informed interpretation of the monitoring data. Also, EPA should reference a source for its statement "[d]ata also suggest…". The Task Force suggests that, at minimum, the EPA include a sentence at the end of this paragraph that acknowledges the potential impact of lowering detection limits on detection frequencies.

Document #	EPA-HQ-OPP-2012-0330-0043
Page #	5
Table #	2
Row #	
Column #	

EPA states:

Table 2. Descriptive Statistics of 2,4-D Concentrations in Surface Water and Groundwater Monitoring Programs

Monitoring Program	Sampling Medium	Sampling Period (Year)	Number of samples	Percent of Detection Frequency Across All Site-Years	Maximum Conc.	Range and (Median) Conc.
					µg/L	
Pesticide Regulation						(1.53)
Washington Department of Agriculture	Surface Water	2003-2012	3208	42.0	42.0	0.0047- 42.0

^Data received via email from Craig Nordmark, California Dept. of Pesticide Regulation (March 7, 2016)

COMMENT:

Table 2 shows “42.0” as both the ‘Percent Detection Frequency’, and for the ‘Max. Conc’

Please check these numbers.

Comments on
2,4-D: Occupational and Residential Exposure Assessment for Registration Review
EPA-HQ-OPP-2012-0330-0044 / DP Barcode D433386

Document #	EPA-HQ-OPP-2012-0330-0044	EPA states: "A 3X uncertainty factor was applied to account for interspecies variability (to account for the pharmacodynamic differences), a 10X uncertainty factor was applied to account for intra-species variability, and a 10X $UF_{LOAEL \rightarrow NOAEL}$ was applied to account for the lack of a NOAEL."
Page #	4	
Paragraph #	3	
Table #	--	

CORRECTION

The statement should be corrected based on comments to Human Health Assessment document:

As indicated in comments provided to the Human Health Assessment document, application of a 300X uncertainty factor to the portal of entry inhalation effects is overly conservative given the known increased sensitivity of the rat to these effects and the rapid recovery observed at the LOAEL in a recently submitted follow-up study. Please correct this document accordingly (details provided in comments to Human Health Assessment document).

Document #	EPA-HQ-OPP-2012-0330-0044	EPA states: "The residential handler risk estimates range from 6,700 to 160,000 (LOC = 300). All scenarios are not of concern for 2,4-D (MOEs are greater than the LOC of 300 for inhalation)."
Page #	6	
Paragraph #	2	
Table #	--	

CORRECTION

The statement should be corrected based on comments to Human Health Assessment document:

"The residential handler risk estimates range from 13,000 to 300,000 (LOC = 10). All scenarios are not of concern for 2,4-D (MOEs are greater than the LOC of 10 for inhalation)."

Corrections or additions are highlighted in red in this correction block.

In keeping with the above comments revising the HED for residential handlers, the MOEs should be corrected. Furthermore, the residential LOC should now be 10. There is no need for the LOAEL to NOAEL UF as an NOAEC was established for residents based on recovery of the effect. And as indicated previously, the interspecies UF can be reduced to 1 based on the known increased sensitivity of the rat relative to the human.

Document #	EPA-HQ-OPP-2012-0330-0044	EPA states: "A 3X uncertainty factor was applied to account for inter-species variability (to account for the PD differences), a 10X uncertainty factor was applied to account for intra-species variability, and a 10X $UF_{LOAEL \rightarrow NOAEL}$ was applied to account for the lack of a NOAEL."
Page #	8	
Paragraph #	1	
Table #	--	

CORRECTION

The statement should be corrected based on comments to Human Health Assessment document:

"A 1X uncertainty factor was applied to account for inter-species variability due to the known greater sensitivity of the rat to these effects, a 10X uncertainty factor was applied to account for intra-species variability, and a 3X $UF_{LOAEL \rightarrow NOAEL}$ was applied to account for the lack of a NOAEL. For residential handlers, an NOAEC of 0.1 mg/L was applied based on rapid recovery of the portal-of-entry effects in a follow-up Inhalation study (MRID 50320801). Based on this, no $UF_{LOAEL \rightarrow NOAEL}$ was applied."

Corrections or additions are highlighted in red in this correction block.

As indicated in comments provided to the Human Health Assessment document, application of a 300X uncertainty factor to the portal of entry inhalation effects is overly conservative given the known increased sensitivity of the rat to these effects and the rapid recovery observed at the LOAEL in a recently submitted follow-up study. Furthermore, the follow-up Inhalation study (MRID 50320801) supports a NOAEC of 0.1 mg/L based on rapid recovery of the effects which should be applied for residential handlers where the label requires an interval between applications that would allow time for recovery.

Document #	EPA-HQ-OPP-2012-0330-0044	EPA indicates a residential handler HED value of 2.133 mg/kg/day.
Page #	9	
Paragraph #	--	
Table #	3.0.2	

CORRECTION

The statement should be corrected based on comments to Human Health Assessment document:

As indicated in comments provided to the Human Health Assessment document, the follow-up Inhalation study (MRID 50320801) supports a NOAEC of 0.1 mg/L based on rapid recovery of the effects which should be applied for residential handlers where the label requires an interval between applications that would allow time for recovery. The HED, calculated based on this endpoint is 4.22 mg/kg/day.

Document #	EPA-HQ-OPP-2012-0330-0044	EPA indicates an LOC of 300.
Page #	9	
Paragraph #	--	
Table #	3.0.2	

CORRECTION

The statement should be corrected based on comments to Human Health Assessment document:

As indicated in comments provided to the Human Health Assessment document, application of a 300X uncertainty factor to the portal of entry inhalation effects is overly conservative given the known increased sensitivity of the rat to these effects and the rapid recovery observed at the LOAEL in a recently submitted follow-up study. Please correct as follows:

$UF_A = 1$
$UF_H = 10$
$UF_{LOAEL \rightarrow NOAEL}$ = 3X or 1X (for residential handler)

Residential Handler LOC for MOE = 10

Residential Bystander and Occupational LOC for MOE = 30

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0044	EPA states: "The residential handler risk estimates range from 6,700 to 160,000 (LOC = 300). All scenarios are not of concern for 2,4-D (MOEs are greater than the LOC of 300 for inhalation)."
Page #	11	
Paragraph #	last	
Table #	--	

CORRECTION

The statement should be corrected so that it reads:

"The residential handler risk estimates range from 13,000 to 300,000 (LOC = 10). All scenarios are not of concern for 2,4-D (MOEs are greater than the LOC of 10 for inhalation)."

Corrections or additions are highlighted in red in this correction block.

In keeping with the above comments revising the HED for residential handlers, the MOEs should be corrected. Furthermore, the residential LOC should now be 10. There is no need for the LOAEL to NOAEL UF as an NOAEC was established for residents based on recovery of the effect. And as indicated previously, the interspecies UF can be reduced to 1 based on the known increased sensitivity of the rat relative to the human.

Document #	EPA-HQ-OPP-2012-0330-0044
Page #	12
Paragraph #	--
Table #	5.1.1

EPA states:

Exposure Scenario		….	MOE (LOC = 300)
Liquid	Hose-end sprayer		10,000
Ready-to-use or WP in WSP			6,700
Liquid or WP in WSP	Manually-pressurized handwand		160,000
WP in WSP	Backpack		
Liquid			20,000
Granule	Push-type spreader		88,000
	Belly Grinder		130,000

CORRECTION

The statement should be corrected so that it reads:

Exposure Scenario		….	MOE (LOC = 10)
Liquid	Hose-end sprayer		20,000
Ready-to-use or WP in WSP			13,000
Liquid or WP in WSP	Manually-pressurized handwand		300,000
WP in WSP	Backpack		
Liquid			38,000
Granule	Push-type spreader		170,000
	Belly Grinder		260,000

Corrections or additions are highlighted in red in this correction block.

In keeping with the above comments revising the HED for residential handlers, the MOEs should be corrected. Furthermore, the residential LOC should now be 10. There is no need for the LOAEL to NOAEL UF as an NOAEC was established for residents based on recovery of the effect. And as indicated previously, the interspecies UF should be reduced to 1 based on the known increased sensitivity of the rat relative to the human.

Document #	EPA-HQ-OPP-2012-0330-0044	EPA identifies the following scenarios of concern: • "Mixing/loading granulars for aerial application to the following use sites: o Aquatic sites @ 10.8 lb ae/A-ft o Field corn/popcorn @ 1.5 lb ae/A • Mixing/loading granulars for solid spreader application to aquatic sites @ 10.8 lb ae/A-ft
Page #	25	
Paragraph #	5	
Table #	--	

CORRECTION

These scenarios should be removed from the scenarios of concern.

MOEs for these scenario are ≥230. Based on the revised LOC of 30, these scenarios are not of concern.

Document #	EPA-HQ-OPP-2012-0330-0044	EPA identifies the following scenarios of concern: • "Applying sprays using mechanically-pressurized handgun to ROW sites @ 0.4 lb ae/gallon • Mixing/loading/applying liquids or WSP using mechanically-pressurized handgun to orchard floors @ 1.5 lb ae/gallon"
Page #	25	
Paragraph #	5	
Table #	--	

CORRECTION

These scenarios should be removed from the scenarios of concern based on lack of target tissue exposure, and calculated MOEs that do not exceed the revised LOC of 30.

The exposure to the larynx required to elicit the portal of entry effects observed in the inhalation study requires exposure to particles in the inhalable range (<100 µm in diameter). Aerosol particle size distribution has been determined for mechanically-pressurized handgun applications and the spray consists of <1% inhalable particles. Triplicate samples from a handgun sprayer applying water showed 0, 0, and 0.85% of particles in the inhalable range; triplicate samples from the same handgun spraying a pesticide formulation showed 0.1, 0.12, and 0.69% inhalable particles (DAS report). In a second study, a mechanical handgun sprayer operated at 3 different nozzle pressures generated a spray with 0.6, 0.7, and 0.78% of particles below 250 µm (http://www.newss.org/proceedings/proceedings_1988_vol42.pdf page 164). In a guidance for waiving acute studies (USEPA, 2012), EPA indicates that "*An aerosol for a product formulation or application method may be considered essentially non-inhalable provided >99% of the particles by mass are >100 µm in diameter at the point where humans are exposed*." Therefore, sprays from mechanically-pressurized handguns are considered non-inhalable and scenarios for application via this method should not be evaluated against an inhalation toxicity endpoint.

References:

http://www.newss.org/proceedings/proceedings_1988_vol42.pdf page 164
USEPA. March 1, 2012. Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides and Pesticide Products (Acute Oral, Acute Dermal, Acute Inhalation, Primary Eye, Primary Dermal, and Dermal Sensitization).

Document #	EPA-HQ-OPP-2012-0330-0044	EPA indicates an amount handled of 1000 gallons/day for backpack sprayers.
Page #	53, 56	

Paragraph #	--	
Table #	--	

CORRECTION

These scenarios should be recalculated.

It is not realistic that someone applies liquids with a backpack sprayer with an amount handled of 1000 gallons/day. These calculations should be revised using the standard 40 gallons/day for backpack sprayers.

Document #	EPA-HQ-OPP-2012-0330-0044	EPA indicates inhalation MOEs for scenarios involving application or mixing/loading applying liquids or WSP via mechanically-pressurized handguns.
Page #	60, 63, 65	
Paragraph #	--	
Table #	--	

CORRECTION

These scenarios should be removed from the scenarios evaluated against the portal-of-entry inhalation endpoint.

As indicated above, inhalable aerosol particles are not anticipated from mechanically-pressurized handgun applications based on spray particle size distribution data. Therefore, inhalation exposures via this route are not relevant. These scenarios should be evaluated for potential inhalation exposure during mixing and loading, but not during application.

Comments on
2,4-D: Tier II Incident Report
EPA-HQ-OPP-2012-0330-0046 / DP Barcode D431743

Document #	EPA-HQ-OPP-2012-0330-0046	In the last sentence of the paragraph, EPA states: "Utilization of these data will aid HED in better defining and characterizing the potential risk of diazinon pesticide products to the U.S. population….."
Page #	2	
Paragraph #	1	
Table #	--	

CORRECTION

The statement should be corrected so that it reads:

"Utilization of these data will aid HED in better defining and characterizing the potential risk of 2,4-D pesticide products to the U.S. population….."

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0046	The incident report includes case reports from a wide span of time including many reports from incidents prior to 1980. Such reports are intermingled with more recent reports based on exposures to current products. Similarly, it is not always clearly indicated whether the reported exposure was to a product containing multiple active ingredients, 2,4-D only, or even in some cases, unspecified phenoxy herbicides.
Page #		
Paragraph #		
Table #	--	

CORRECTION

The incident report should be revised for clarity and utility:

This incident report would be of greater utility if it allowed for a clearer picture of the information known about the exposures related to reported effects. Specifically, in all cases, what is known about the pesticide exposure should be clearly stated, including whether other active ingredients were present as well. Furthermore, it would be helpful if incidents were stratified by date, especially separating those that have occurred since the RED, when the most recent significant changes to 2,4-D labels and use patterns were made. Also, the very old reports (e.g., pre-1980) will often be to products containing toxic coformulants that would not be used today. Having the reports separated into groups by similar date may help with interpretation and teasing out effects from 2,4-D vs. other components of the formulations (which will have changed over time).

Document #	EPA-HQ-OPP-2012-0330-0046	EPA states: "There is fairly efficient dermal and inhalation absorption of 2,4-D."
Page #	8	
Paragraph #	2	
Table #	--	

CORRECTION

The statement should be corrected for consistency with other human health documents:

This statement is based on poisoning case reports from 1961 and 1974. Dermal and inhalation absorption are not quantitated in these cases. Furthermore, co-formulants popular at the time (e.g., kerosene) can increase dermal penetration and are not applicable to current exposure scenarios.

Dermal absorption of 2,4-D has been measured in empirical studies and is consistently below 10%. Claims made based on case studies should be placed into context with the larger (and we submit more scientific) mammalian toxicity database for 2,4-D. More generally, it would aid in interpretation of the information in this report if an effort were made to relate information from these incident reports to what is known from animal studies.

Comments on

Preliminary Ecological Risk Assessment for Registration Review of 2,4-D

EPA-HQ-OPP-2012-0330-0047 / DP Barcode D424054

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "A number of 2,4-D products are formulated with other herbicides. Data are not available to quantify the extent to which combinations of herbicides in formulated products influence the toxicological endpoints used in this risk assessment, especially with regard to terrestrial plants."
Page #	5	
Table #		
Row #		
Column #		

COMMENT

Studies have been conducted in accordance with USEPA requirements to test a TEP containing the active ingredient of interest. Where studies have been conducted with combinations of herbicides (e.g. Enlist Duo) the lowest endpoint, as used in the RA, has not differed significantly from the lowest endpoint for the respective TEP containing the individual a.i.s.

As stated in the Overview Document (USEPA, 2004), ". . . the Agency does not routinely include, in its screening risk assessments, an evaluation of mixtures of active ingredients . . ." This is consistent with the registration review process that is intended to reevaluate individual a.i.s. This is also consistent with the provisional position of the Agency as outlined at the CLA Regulatory Conference in 2017 as only applying to new chemical registrations. In the case of 2,4-D, it is impractical and unnecessary to assess the risk posed by all possible mixture products, impractical because of the large numbers, and unnecessary because usually one mixing partner accounts for most of the toxicity to nontarget species.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Acute estuarine/marine invertebrate data for 2,4-D esters were non-definitive; test concentrations were very low, which resulted in uncertainties surrounding the risk conclusions for 2,4-D ester uses."
Page #	5	
Table #		
Row #		
Column #		

COMMENT

It is not possible to test higher concentrations of esters due to water solubility limits. Therefore, the non-definitive data actually are reliable in the context of actual environmental concentrations of ester forms and suggest toxicity will not occur.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Adult (chronic) and larval (acute/chronic) honeybee data were not available • Transient sub-lethal effects were observed in the adult dietary and contact studies, which signals the potential for adverse 2,4-D effects on terrestrial invertebrates. • An acute larval honeybee study is being initiated in Spring 2016. • Risk to terrestrial invertebrates (adult chronic exposure; larval acute and chronic exposure) could not be assessed in the absence of data."
Page #	5	
Table #		
Row #		
Column #		

COMMENT

See comments below in relation to honeybees.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Problem Formulation Update In addition, an acute passerine dietary study (MRID 49472501 – acceptable classification), and acute larval honeybee study (MRID 49270401 – invalid classification) were submitted in response to the Registration Review data call-in."
Page #	6-7	
Paragraph #	5	
Row #		
Column #		

CLARIFICATION

The acute larval honeybee study (MRID 49270401) was classified as "Supplemental" in the DER dated 3-11-2015, DP Barcode D419872. ***Note that the Task Force has now submitted a Tier 1 larval acute/chronic study (MRID 50181701), and that the 'invalid' study was a Tier 2 study.***

The statement/entry should be corrected so that it reads:
…acute larval honeybee study (MRID 49270401 – supplemental classification) were submitted in…

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "In particular, fish and aquatic invertebrate data for major degradate 2,4-DCP were used in the Assessment."
Page #	7	
Paragraph #	3	
Row #		
Column #		

COMMENT

See comment below for pages 56-57 regarding deficiencies in following data quality guidance for these 2,4-DCP toxicity data.

Document #	EPA-HQ-OPP-2012-0330-0047	The Enlist Duo Herbicide label adding use of Enlist cotton was stamped accepted on 1-12-2017. These use directions should be added to Table 3.1.
Page #	8	
Table#	3.1	
Row #		
Column #		

CORRECTION

The statement/ entry should be corrected so that it reads:

ENLIST™ COTTON

CROP STAGE	MAXIMUM APPLICATION RATE / Acre	DIRECTIONS / Timing

Preplant or Preemergence	1.0 lb. acid equivalent	To control emerged broadleaf weed seedlings or existing cover crops, apply before cotton emerges.
Postemergence	1.0 lb. acid equivalent	Apply any time after cotton emergence but no later than full flowering (mid-bloom stage). Make one to two postemergence applications with a minimum of 12 days between applications.

Precautions and Restrictions:

- These use directions are only for cotton identified as containing the Enlist trait.
- **Preharvest Interval:** Do not apply within 30 days of harvest.
- Do not graze treated cotton.
- Do not harvest for forage or hay.
- Do not apply more than one preemergence application and no more than two postemergence applications per use season.
- Do not apply to cotton later than the mid-bloom stage.
- Do not apply more than 3.0 lb. acid equivalent per acre per use season.
- Do not apply more than 1.0 lb. acid equivalent per acre per application
- Do not aerially apply this product.

EPA Chemical Number	Chemical	Formulation	Reentry Interval	Application Method	Application Equipment
51505	Choline	SC/L	48 hr.	Ground spray Broadcast	Ground: boom sprayers

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Cereal grains (wheat, barley, millet, oat, rye, and tiff)"
Page #	8	
Table #	3.1	
Row #		
Column #		

CORRECTION

The statement/ entry should be corrected so that it reads:

Cereal grains (wheat, barley, millet, oat, rye, and teff)

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0047	Table 3.1 indicates that applications can be made to hops by ground or aerial broadcast spray.
Page #	10	
Table #	3.1	
Row #		
Column #		

CORRECTION

Applications can be made to hops by directed treatment to the row middles (directed to ground).

The statement/entry should be corrected so that it reads:

Ground (directed)

Corrections or additions are highlighted in red in this correction block.

COMMENT

Please account for the reduction in potential exposure from spray drift resulting from this correction in the final version of the risk assessment.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Although 2,4-DCP is a minor degradate in the terrestrial environment, it is a major degradate (≤32.6%) under anaerobic aquatic conditions. There are some toxicity data for 2-DCP available in the ECOTOX database[1] and the European Footprint database[2] that suggest it is more toxic than 2,4-D for selected aquatic organisms (freshwater fish and invertebrates). Therefore, 2,4-D, as well as its degradate, 2,4-DCP, will be considered as independent residues of concern in the ecological risk assessment."
Page #	17-18	
Table #		
Row #		
Column #		

COMMENT

See comment for pages 56-57 below.

Document #	EPA-HQ-OPP-2012-0330-0047	**COMMENT** Section 4.3: EPA has employed modified version of the Tier I Rice and Cranberry models to calculate EEC values for these uses. However, EPA is now using the Pesticides in Flooded Applications Model (PFAM) for these types of uses that more realistically simulates water management and can more fully represent degradation and sorption in the benthic compartment. In addition, the PFAM (or PWC) model can also be applied to the aquatic weed control uses with some minor modifications to the input parameterization as a potential refinement of the "First Order Degradation Kinetics" formulation used in the assessment. For example, PWC was used to model aquatic weed control use EECs in a recent proposed approval decision for the herbicide florpyrauxifen-methyl (docket reference EPA-HQ-OPP-2016-0560-0011). It is suggested that the Agency explore these more rigorous models for these uses, as exceedances of LOC were calculated in some cases.
Page #	18	
Paragraph #		
Table #		

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "The AgDRIFT model was used to estimate a peak concentration of 7.03 µg/L for the aquatic environment by using the default scenario for an aerial application (Appendix B). The resulting concentration represents the maximum instantaneous concentration predicted by direct drift from the application to the pond. Runoff of 2,4-D esters to aquatic
Page #	19	
Paragraph #	3	

Table #		systems was not considered here given the assumption of rapid conversion of the esters to the acid in terrestrial systems."

INCONSISTENCY and ERROR

The Task Force agrees that this a proper treatment of the fate of 2,4-D esters. However, in table 6.1 (pg 40), 6.3 (p 43), 6.5 (p 45), RQ values for runoff of esters are calculated and show exceedances for a level of concern for several terrestrial applications. Upon back-calculation, these "runoff RQ" values were calculated from the EEC values in Table 4.2, compared to the ester LC50 values. The EEC's that were modelled (with SWCC) using inputs derived from the properties of 2,4-D acid. This drastically overestimate the potential aquatic exposure of 2,4-D esters and the corresponding RQ. For example, in Table 6.1 (p 40), the RQ listed for corn is 0.15. Back-calculating, the exposure assumed was:

0.15 * 428 µg ae/L = 64.2 µg ae/L

This EEC apparently corresponds to the corn value of 62.3 µg ae/L in table 4.2 (p 20 row 2), calculated with SWCC. However, SWCC was parameterized with the properties of 2,4-D acid (i.e., a low soil sorption value) and thus the EEC does not apply to 2,4-D esters and is over nine times higher than the maximum spray drift value for esters of 7.03 µg ae/L (pg 19, paragraph 3). The proper RQ for this use is thus:

7.03 µg ae/L/428 µg ae/L = 0.02

This RQ is below the lowest aquatic LOC of 0.05 (acute listed species). This is the RQ listed in the "spray drift" column of the table. Therefore, for terrestrial uses of 2,4-D esters, the "Runoff" column of RQ values in the above listed tables does not apply and should be eliminated.

This serious error was propagated throughout the aquatic risk assessment and the final risk conclusions (detailed below). This led to incorrect conclusions of risk concerns to aquatic organisms for use of the 2,4-D esters in terrestrial applications.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states [referring to ester forms]: "A 21-day or 60-day EEC for spray drift was not provided because the hydrolysis soil slurry data indicate that dissipation in a non-sterile water body will occur at all pHs and therefore longterm exposures are unlikely."
Page #	19	
Paragraph #	3	
Table #	6.1, 6.3,.6.5	

CORRECTION

The Task Force agrees that this is a proper approach to the fate of 2,4-D esters. However, the tables 6.1 (pg 40), 6.3 (p 43), 6.5 (p 45) are all titled "Acute and Chronic … Risk Quotients". No chronic assessment was performed (correctly). The table titles should be corrected for consistency.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Maximum concentrations of 2,4-D detected in surface source water and ambient groundwater are 58 µg/L and 14.8 ug/L, respectively."
Page #	23	
Paragraph #	last	
Table #		

COMMENT

The values cited above do not match the values reported in Table 2 of the Drinking Water document, which reports values from the same databases cited in this document. Table 4.3 shows the maximum as 59.0 ug/L

Document #	EPA-HQ-OPP-2012-0330-0047	Detection frequency is presented as a percent across all site-years. The descriptive statistics for the distributions provided in the table are the maximum, range, and median. The median (and range) exclude non-detects.
Page #	24-25	
Paragraph #		
Table #	Table 4,3	

COMMENT

It is unclear how these presumably non-targeted collections of monitoring data were analyzed as site-years, a term which typically has a precise statistical meaning. Should the table heading actually read merely "Detection Frequency (Percent)?" The Task Force believes that more apt terminology is needed.

A reasonable uncensoring approach for values less than the analytical method detection quantification and detection limits should be applied so that most or all of the samples are considered in the distributions. Then, additional percentiles of the distributions should be provided such as 75^{th}, 90^{th}, 95^{th}, 99^{th}, and 99.9^{th} and all, including the corrected median and the maximum should be compared to the same percentiles in the model predicted distributions to determine whether the actual measurement data corroborate the model estimates.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "The detection frequencies in both surface water and groundwater are higher than the previously reported frequencies for monitoring data (USEPA, 2004). In 2012, BEAD provided 2,4-D usage data for 2000-2010 (USEPA 2012). The 2,4-D usage averaged approximately 29 million pounds active ingredient for 55 million treated acres. Data also suggest that since 2005, there has been an upward trend of 2,4-D usage as well as total number of treated acres. The increasing trend of 2,4-D usage and treated acres may have contributed higher detection frequencies in surface water and groundwater."
Page #	25	
Paragraph #	3	
Table #		

COMMENT

The increase in detection frequency from pre-2004 to post-2004 monitoring could be due to a number of factors independent of the amount of 2,4-D used, or the proximity of that use to vulnerable aquifers. The detection limits for analytical methods tend to decrease over time as analytical technology improves. This will have the effect of increasing the detection rate since a compound will likely be detected in more samples if the detection limit is lower. The Task Force recommends that the applicable detection limit be included for each monitoring program listed in Table 2. This will enable more informed interpretation of the monitoring data. Also, if EPA is citing an increase in 24D use in the paragraph above, they should include a citation, or include the supporting data.
The Task Force suggests that, at minimum, the EPA include a sentence at the end of this paragraph that acknowledges the potential impact of detection limits on detection frequencies.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "There is no detection recorded above the maximum detection level of 0.041 µg/L in 26 surface water samples from the USGS- NAWQA-Pacific NWSQA site."
Page #	26	
Paragraph #	2	
Table #		

CORRECTION

Should 'maximum' in the sentence above be 'minimum'? Please review.

Document #	EPA-HQ-OPP-2012-0330-	EPA states: "The Enlist Duo corn and soybean assessment indicated that there were risk concerns for

	0047	mammals (acute and chronic) and birds, reptiles, and land-phase amphibians (acute) (USEPA 2013b, 2015a). There are higher application rates, but these were not modeled because risk concerns are expected to be similar or greater and would not change the risk picture."
Page #	28	
Paragraph #		
Row #		
Column #		

COMMENT

The Task Force notes that the Enlist Duo corn and soybean assessment used a default foliar dissipation rate [half-life] of 35 days ("this may be an over-estimate"), not the more realistic value used in the PRA of 8.8 days. Therefore, the chronic risk concerns for mammals stated in the Enlist Duo assessment are not directly comparable. The Task Force believes that 8.8 days should be used.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "The analysis is presented in Section 6.1."
Page #	31	
Paragraph #	4.7	
Table #		

CORRECTION

The statement/entry should be corrected so that it reads:

"The analysis is presented in Section 6.3"

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "The analysis is presented in Section 6.1."
Page #	31	
Paragraph #	4.8	
Table #		

CORRECTION

The statement/entry should be corrected so that it reads:

"The analysis is presented in Section 6.3"

Corrections or additions are highlighted in red in this correction block.

Document#	EPA-HQ-OPP-2012-0330-0047	EPA states: "Since the Problem Formulation, 2,4-D choline salt data were submitted for freshwater fish (acute), freshwater invertebrates (acute), and non-vascular aquatic plants (green algae). The data confirmed that the bridging scenario developed for 2,4-D salts was applicable to the choline salt as well. The choline salt freshwater fish limit test (no mortalities or effects) established a new most sensitive endpoint. For the acid/salts/and amine forms, 2,4-D is "slightly toxic" to fish and aquatic invertebrates on an acute basis."
Page #	32	
Paragraph #	1	
Row #		
Column #		

CORRECTION

Non-definitive endpoints cannot be used for acute risk assessment, as it is contrary to established science to calculate a definitive mortality-based risk quotient using a NOEC. The sole utility of a "greater than" endpoint in a screening level assessment is to roughly estimate a "less than" RQ. The Task Force points out that on page 41, EPA declined to calculate RQs using the 48 mg/L endpoint because it was non-definitive. However, for the 4 lb/ac use in aquatic weed control, EPA concluded, "4 ppm is lower than 48 ppm, but is not 20X lower than the EEC, risk concerns are probably low (some uncertainty)". This implies that if an RQ had been calculated, it would have exceeded the endangered species LOC of 0.05. The two examples are inconsistent in approach. The Task Force recommends using the previous definitive endpoints of 101 mg/L for freshwater fish and 80.2 mg/L for saltwater fish.

Document #	EPA-HQ-OPP-2012-0330-0047	EC_{50} for *Navicula* is quoted as 3.88 mg/L (based on growth inhibition conducted with DMA). On page 46, Table 6.6, a value of 0.388 mg/L is used.
Page #	33 and 46	
Table #		
Row #		
Column #		

CORRECTION

The statement/entry should be corrected so that it reads:

For Freshwater diatom (*Navicula pelliculosa*), Conducted with DMA: EC_{50} = 4.39 mg ae/L. The study (MRID 41505903) reported the EC_{50} = 5.28 mg/L, accounting for the percent a.i. of 66.7%. The reported EC_{50} converts from 5.28 mg ai/L to 4.39 mg ae/L (e.g., 5.28 x 0.8305).

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: For Freshwater diatom (*Navicula pelliculosa*), Conducted with DMA: EC_{50} = 3.88 mg ae/L
Page #	33	
Paragraph #		
Table #	5.1	

CORRECTION

The statement/ entry should be corrected so that it reads:

For Freshwater diatom (*Navicula pelliculosa*), Conducted with DMA: EC_{50} = 4.39 mg ae/L. The study (MRID 41505903) reported the EC_{50} = 5.28 mg/L, accounting for the percent a.i. of 66.7%. The reported EC_{50} converts from 5.28 mg ai/L to 4.39 mg ae/L (e.g., 5.28 x 0.8305)

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0047	The review states the following Agency recommendation: For Duckweed (*Lemna gibba*), Conducted with EHE: IC_{05} = 0.03 mg ae/L[2] Footnote: [2]The NOAEC was non-definitive; consequently, the IC_{05} will be used for the "no effect" concentration.
Page #	34	
Paragraph #		
Table #	5.2	

COMMENT

The Task Force disagrees with the Agency recommendation for the following reasons:

Derivation of an IC_{05} in place of a NOAEC is not likely to be meaningful, as these studies were designed to include statistical power to accurately predict an IC_{50} and not down to the level of an IC_{05}. (The confidence interval for this IC_{05} is likely to be extremely wide.) It is likely that use of the IC_{05} in place of a NOAEC would overestimate risk and fall within the variability of the control data. Instead, the definitive NOAEC for 2,4-D butoxyethyl ester (BEE) for duckweed can be used to represent the esters for vascular plants. The NOAEC for *Lemna gibba* for BEE is 0.204 mg a.i./L (0.141 mg a.e/L) (MRID 420688402). The EC_{50} from this study is 0.576 mg a.i./L (0.397 mg a.e./L) which corresponds well to the EC_{50} for EHE for *Lemna gibba* (MRID 41735303) of 0.5 mg a.i./L (0.33 mg a.e./L), indicating the esters have similar toxicity to aquatic vascular plants.

Document #	EPA-HQ-OPP-2012-0330-0047	Table 5.3. Honeybee Chronic (larval) toxicity value is estimated by ACR.
Page #	35/36	
Table #		
Row #		
Column #		

COMMENT

A larval chronic study has been submitted (MRID 50181701) but was not available at the time of this assessment.

Document #	EPA-HQ-OPP-2012-0330-0047	The review states the following Agency recommendation: For Terrestrial Plant Seedling Emergence; Salt/Amine/ Acid; Monocot; Sorghum (*Sorghum bicolor*): EC_{25} = 0.026 lb ae/A and NOAEC = 0.015 lb ae/A (based on fresh weight Conducted with DMA)
Page #	36	
Paragraph #		
Table #	5.3	

COMMENT

The Task Force disagrees with the Agency recommendation for the following reasons:

Fresh weight, as a growth response, is recognized to be more variable than the dry weight response required according to both the draft (OPPTS 850.4100, 1996) and final (OCSPP 850.4100, 2012) EPA test guidelines. Guideline-compliant studies that measure dry weight should be used in place of older studies that measure fresh weight, when possible. Therefore, the following substitution is recommended, based on data available for Onion from MRID 47106001:

For Terrestrial Plant Seedling Emergence; Salt/Amine/
Acid; Monocot; Onion (*Allium cepa*): EC_{25} = 0.097 lb ae/A and NOAEC = 0.091 lb ae/A (based on dry weight Conducted with DMA)

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: For Terrestrial Plant Seedling Emergence; Ester; Monocot; Onion (*Allium cepa*): NOAEC = 0.0019 lb ae/A (Based on shoot height Conducted with EHE)
Page #	36	
Paragraph #		

Table #	5.3	

CORRECTION

The statement/entry should be corrected so that it reads:

For Terrestrial Plant Seedling Emergence; Ester; Monocot; Onion (*Allium cepa*): NOAEC = 0.019 lb ae/A (Based on shoot height Conducted with EHE).

Corrections or additions are highlighted in red in this correction block.

0.019 is the correct value for the NOAEC for this study per page 1/133 in the DER for this study (MRID 47106003) and in the data analysis shown on page 45/133 of the DER (Barcode D345223).

Document #	EPA-HQ-OPP-2012-0330-0047	The review states the following Agency recommendation: For Terrestrial Plant Vegetative Vigor; Salt/Amine/Acid; Monocot; Onion (*Allium cepa*): EC_{25} = 0.0075 lb ae/A and NOAEC < 0.0075 lb ae/A (Based on fresh weight Conducted with Acid)
Page #	36	
Paragraph #		
Table #	5.3	

COMMENT

The Task Force disagrees with the Agency recommendation for the following reasons:

Fresh weight, as a growth response, is recognized to be more variable than the dry weight response required according to both the draft (OPPTS 850.4100, 1996) and final (OCSPP 850.4100, 2012) EPA guidelines. Guideline-compliant studies that measure dry weight should be used in place of older studies that measure fresh weight, when possible. Therefore, the following substitution is recommended, based on data available for Onion from MRID 47106002:

For Terrestrial Plant Vegetative Vigor; Salt/Amine/Acid; Monocot; Onion (*Allium cepa*): EC_{25} = 0.14 lb ae/A and NOAEC 0.135 lb ae/A (Based on dry weight Conducted with DMA)

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Since the Problem Formulation, 6828 incidents have been attributed to 2,4-D (Table 5.5). Approximately 99% of the incidents affected plants. As with the EIIS database, a lack of incidents to other taxa does not indicate that incidents are not occurring; rather, the incidents may have gone unreported."
Page #	38	
Paragraph #	1	
Row #		
Column #		

COMMENT

Approximately 99% of the incidents affected plants; although lack of incidents with other taxa does not indicate that incidents are not occurring, it is likely that, for example, bee kills/colony collapse and vertebrate mortalities would be reported if significant, thus adding weight to conclusions that the risk assessment in the following pages for these taxa are conservative.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "2,4-D is on List 1 for which EPA has received all the required Tier 1 assay data. The Agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets
Page #	39	

Paragraph #	2	(see EPA-HQ-OPP-2012-0330). For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website."
Row #		
Column #		

COMMENT

The Task Force proposes adding the conclusions of the June 29, 2015 EDSP Weight of Evidence Conclusions on the Tier 1 Screening Assays for the List 1 Chemicals to the above overview statement.

The statement/ entry should be modified so that it reads:

"2,4-D is on List 1 for which EPA has received all the required Tier 1 assay data. The Agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets (see EPA-HQ-OPP-2012-0330). The conclusion of the Agency's WoE evaluation is that 2, 4-D demonstrates no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website."

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "In addition, acute direct risk concerns for listed freshwater fish were identified for corn, noncroplands, pastures/rangelands/perennial grasslands, forestry, soybean, cranberry, and cereal crops from ester runoff; . . ."
Page #	40	
Paragraph #	1	
Row #		
Column #		

CORRECTION

The updated problem formulation in this risk assessment assumes runoff from application of ester forms is unlikely due to rapid hydrolysis to the acid. EPA therefore concluded that runoff modeling for ester forms was not necessary. The risk concern expressed here must be based on runoff modelling for non-ester forms and is an error.

Document #	EPA-HQ-OPP-2012-0330-0047	Table 6.1. Acute and Chronic Fish Risk Quotients for Ester Forms of 2,4-D.
Page #	40	
Table #	6.1	
Row #		
Column #		

CORRECTION

The title of Table 6.1 should be corrected to read as follows:

Table 6.1. Acute Fish Risk Quotients for Ester Forms of 2,4-D.

Also, the columns headed "Runoff" should be deleted (see previous comment).

Document #	EPA-HQ-OPP-2012-0330-0047	Table 6.1.

Page #	40	
Table #		
Row #		
Column #		

CORRECTION

Table 6.1. Why is there a run-off scenario for direct applications to water for aquatic weed control? Why is there a scenario for estuarine/marine for direct applications to water for aquatic weed control – does this apply to rivers and/or e.g. Florida brackish water weed control? These scenarios seem inappropriate and should be reconsidered.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states in Table 6.1: "Footnote '[1]RQs were not calculated because the endpoint was non-definitive'"
Page #	40/41	
Table #	6.1	
Row #		
Column #		

CORRECTION

EPA declined to calculate RQ's using the ester endpoint because it was non-definitive. They should therefore apply the same logic to the freshwater fish endpoint of >48 mg ae/L.

Document #	EPA-HQ-OPP-2012-0330-0047	Table 6.2. Fresh water and estuarine/marine fish LC_{50} values.
Page #	41	
Table #		
Row #		
Column #		

CORRECTION

EFED used non-definitive values for fish – see earlier approach by EFED re: ester and present all non-definitive values for acid/amines/salts and use the highest non-definitive value or lowest definitive value for RQ calculations (see comments in Table 6.3, page 43 'but no sub-lethal effects observed and the lowest definitive EC50 = 121.4 mg ae/L' for ester scenarios – why not do same for amines/salts/acid? Please review and reconsider.

Document #	EPA-HQ-OPPEPA-HQ-OPP-2012-0330-0047	Table 6.3. Acute and Chronic Aquatic Water Column Invertebrate Risk Quotients for Ester Forms of 2,4-D
Page #	42	
Table #		
Row #		
Column #		

CORRECTION

The title of Table 6.3 should be corrected to read as follows:

Table 6.3. Acute Aquatic Water Column Invertebrate Risk Quotients for Ester Forms of 2,4-D

Document #	EPA-HQ-OPP-2012-0330-0047	Table 6.3
Page #	42-43	
Table #		
Row #		
Column #		

CORRECTION

Same comments as for fish with respect to run-off scenarios and estuarine/marine species exposure via direct application to water.

Document #	EPA-HQ-OPP-2012-0330-0047	The 2,4-D water monitoring data (Table 4.3) show a peak concentration above the NOAEC for listed aquatic vascular plants. However, given that there was only one observed value out of ~25,000 samples that exceeded the NOAEC (42 ppb observed; NOAEC = 30 ppb), it is not appropriate to generalize that this translates into risk concerns for aquatic plant communities.
Page #	45	
Paragraph #	3	
Table #		

COMMENT

This is the type of probability statement that should be used throughout, particularly for exposure estimated by monitoring data. It would be appropriate to express this as a probability of ~4 x 10^{-5}. See also comment above for Table 4.3 concerning proper analysis of distributions of measured values.

Document #	EPA-HQ-OPP-2012-0330-0047	The review states the following Agency recommendation: For Vascular, Listed: IC_{05} = 0.03 mg ae/L
Page #	45	
Paragraph #		
Table #	6.5	

COMMENT

The Task Force disagrees with the Agency recommendation for the following reasons:

See previous discussion regarding the use of the definitive NOAEC for BEE for vascular plants in place of this value.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "For Non-vascular, Non-listed: IC_{50} = 0.388 mg ae/L"
Page #	46	
Paragraph #		
Table #	6.6	

CORRECTION

The statement/ entry should be corrected so that it reads:

The value does not match that used in Table 5.1 which is 3.88 mg ae/L. However, we propose the following: For Non-vascular, Non-listed: IC_{50} = 4.39 mg ae/L

Corrections or additions are highlighted in red in this correction block.

The study (MRID 41505903) reported the EC_{50} = 5.28 mg/L, accounting for the percent a.i. of 66.7%. The reported EC_{50} of 5.28 mg ai/L converts to 4.39 mg ae/L (e.g., 5.28 x 0.8305)

Document #	EPA-HQ-OPP-2012-0330-0047	Table 6.6 Run-off scenario.
Page #	46	
Table #		
Row #		
Column #		

CORRECTION

Run-off scenario not included in Table 6.6, but was included in Table 6.5 for ester (and in fish and invertebrate scenarios).

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Given that acute (short grass, tall grass, broadleaf plants, fruits/pods, and arthropods for small and medium size classes; short grass, tall grass, broadleaf plants, and arthropods for large birds) risk concerns for birds (surrogates species for reptiles and terrestrial-phase amphibians) were recently identified at rates of 1 lb ae/A (USEPA 2013b), . . .".
Page #	47	
Paragraph #	1	
Row #		
Column #		

CORRECTION

The passerine study which showed regurgitation (MRID 49357902, 49357903, 49357904, 49357905) was followed up with a dietary study (MRID 49472501) showing low toxicity (study classified by EPA as acceptable). An acute dietary study with bobwhite (MRID 45336401) was previously conducted. Together, all indicate that dietary exposure is less hazardous than gavage exposure, and so demonstrate RQs are highly conservative.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Chronic RQs were calculated for the highest 2,4-D application rate (4 lb ae/A). Only the short grass dietary item was equal to the LOC of 1, indicating potential chronic risk concerns for birds with exclusive short-grass diets. However, the confidence that there is actual risk is low because there were no effects reported in the study (*i.e.*, the toxicity value was the highest dose tested). In addition, chronic effects would only be expected for a species that consumed short grass as 100% of its diet, which is unlikely for this food source. Consequently, chronic risk concerns are not expected for any registered uses of 2,4-D (Table 6.7)."
Page #	47	
Paragraph #	2	
Row #		
Column #		

CORRECTION

The Task Force supports these statements.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "…..potential concerns were flagged for drinking water exposures for IPE, DMA, DEA, acid, Na, IPA, and TIPA."
Page #	48	
Paragraph #	1	
Row #		
Column #		

COMMENT

The exposure estimate for each source of drinking water is an overestimate, since 100% of the daily drinking water intake is assumed to come from a single source. The Task Force also notes that the potential concerns come from a Tier 0 screening exposure model that fails to take into account actual initial concentration, washoff, degradation, and other real-world processes. Refinement in the exposure estimates based on these factors is suggested.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Given that acute (short grass, tall grass, broadleaf plants and arthropods for all size classes) and chronic (short grass, tall grass, broadleaf plants and arthropods for small and medium size classes; short grass and broadleaf plants for large mammals) risk concerns for mammals were recently identified at rates of 1 lb ae/A (USEPA 2013b), only application rates below this rate were assessed here."
Page #	48	
Paragraph #	2	
Row #		
Column #		

COMMENT

A previously conducted mouse dietary study showed low toxicity. This indicates that dietary exposure is less hazardous than gavage exposure, and so demonstrates that all RQs are conservative. Also, the risk assessment reported in USEPA (2013b) used a chronic endpoint of 5 mg ae/kg bw and assumed a foliar dissipation half-life of 35 days; therefore the data used to reach the conclusions of risk concerns for mammals at a rate of 1 lb ae/A are not consistent with what was used in this more recent assessment, a chronic endpoint of 55 mg ae/kg bw and a foliar dissipation half-life of 8.8 days. Risk potential at the 1 lb ae/A application rate is actually much lower for long-term effects.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "At an application rate of 0.5 lb ae/A acute RQs are above only the LOC (0.1) for listed species for the two smallest size classes and for one dietary item(short grass). Chronic risk concerns (LOC = 1) are only identified in small mammals consuming short grass at this rate but no concerns at lower rates."
Page #	48-49	
Paragraph #	Last - First	
Row #		
Column #		

COMMENT

No refinements were considered concerning percent of time feeding on the treated field on short grass or other factors (such as interception by target broadleaf weeds) contributing to more realistic exposure estimates. It is likely that the slight LOC exceedances would be eliminated by such refinements.

Document #	EPA-HQ-OPP-2012-0330-0047	**EPA states:** **"6.2.3. Terrestrial Invertebrates** Risk quotients could not be calculated for acute adult exposures because the available toxicity data were non-definitive (i.e., "greater than" values). Instead, the EECs were compared directly to the toxicity value."
Page #	50	
Paragraph #	2	

Row #		
Column #		

COMMENT

The type of comparison made here to assess risk is not definitive in that there is no means to determine whether or not the EECs are actually toxic.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Risk concerns are possible for adults (dietary acute exposures) at application rates higher than 2 lb ae/A and (Table 6.9)."
Page #	50	
Paragraph #	2	
Row #		
Column #		

CORRECTION

Typo – seems to be some text missing as sentence is incomplete.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Although the toxicity data are non-definitive, sub-lethal effects (reduced coordination) were noted in the dietary toxicity study. Effects occurred at the three highest treatment levels, but appeared to be transient with only one individual affected in the two highest treatment groups at the end of the study (48 hours). Given that application rates about 2 lb ae/A could yield EECs higher than the 62.2 µg ae/bee that was tested, direct risk concerns are possible. Note that there is uncertainty associated with this conclusion because data are not available."
Page #	50	
Paragraph #	2	
Row #		
Column #		

COMMENT

The direct risk concerns are highly speculative, considering they are based primarily on transient sub-lethal effects observed in a single individual. The non-definitive endpoint most likely suggests effects are not observed at higher doses than those tested, not that this herbicide is toxic to colonies of honeybees or populations of other non-target invertebrates.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Additionally, adult chronic and larval acute/chronic data are not available and risk to these life-stages/exposure durations was not assessed. Further data on pollinators are recommended to fully characterize the risk associated with 2,4-D use to all developmental stages of honeybees, as sensitivity may vary according to life-stage and length of exposure (adult vs. larval and acute vs. chronic, respectively)."
Page #	50	
Paragraph #	2	
Row #		
Column #		

COMMENT

An acute/chronic larval honeybee study (MRID 50181701) has been submitted.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Table 6.9. Adult contact. 10.8 µg ae/bee is more than 2.5x lower than the contact LD50 of > 66 µg ae/bee, thus risk concerns are unlikely."
Page #	50	
Table #	6.9	
Row #		

Column #		

COMMENT

The Task Force agrees that risk concerns are unlikely.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Table 6.9. Adult dietary. 128 µg ae/bee may be higher than the oral LD50 of > 62.6 µg ae/bee. **Risk concerns cannot be precluded, based on presence of sub-lethal effects."**
Page #	51	
Table #	6.9	
Row #		
Column #		

COMMENT

See earlier comment on page 50, paragraph 2 concerning sub-lethal effects..

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "In general, amine/salt/acid formulations of 2,4-D appear to be more toxic to terrestrial plants than ester formulations, based on the toxicity data, in contrast with aquatic plants."
Page #	51	
Paragraph #	1	
Row #		
Column #		

COMMENT

It is difficult to understand this conclusion, considering the data presented for vegetative vigor in Table 5.3. (The seedling emergence endpoint is not reliable for such a comparison, as the ester form hydrolyses rapidly in moist soil.) Confidence bounds on the EC25 endpoints are not given, but regardless, for vegetative vigor the acid forms are more active on monocots, while the reverse is true for dicots, the main target for weed control.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA has calculated Terrestrial Plant Risk Quotients (RQ) using the following value for Seedling Emergence; Ester; Monocot; Onion (*Allium cepa*): NOAEC = 0.0019 lb ae/A. RQ values for listed monocots for esters are as high as 316 (for forest sites, non-cropland at 4 lb ae/A, using aerial spray application in semi-aquatic areas)
Page #	51-55	
Paragraph #		
Table #	6.10	

CORRECTION

The statement/entry should be corrected so that it reads:

As mentioned previously, the NOAEC of 0.0019 lb ae/A is a typographical error. The correct NOAEC for seedling emergence, monocots, ester is 0.019 lb ae/A. Using the correct value, the highest RQ value for listed monocots for esters is an order of magnitude lower, at 31.6 (for forest sites, non-cropland at 4 lb ae/A, using aerial spray application in semi-aquatic areas). Overall there are five fewer exceedances of LOC in the modeled scenarios than with the incorrect value. Corrected RQ are shown in Attachment 1 in red.

Document #	EPA-HQ-OPP-2012-0330-	EPA has calculated Terrestrial Plant Risk Quotients (RQ) using the following values for Salt/Amine/Acid; Monocot; Seedling Emergence: EC_{25} = 0.026 lb ae/A, NOAEC = 0.015

	0047	lb ae/A, and Vegetative Vigor: EC_{25} = 0.0075 lb ae/A, NOAEC <0.0075 lb ae/A. RQ values for salt/amine/acid forms are as high as 85 for non-listed monocots and 147 for listed monocots (for forest sites, non-cropland at 4 lb ae/A, using aerial spray application in semi-aquatic areas).
Page #	51-55	
Paragraph #		
Table #	6.10	

COMMENT

The Task Force disagrees with the Agency recommendation for the following reasons:

As mentioned previously, studies reporting endpoints based on fresh weight should not be used when there are available data based on dry weight in compliance with current guidelines. Using the proposed dry weight values for Salt/Amine/Acid; Monocot; Seedling Emergence: EC_{25} = 0.097 lb ae/A, NOAEC = 0.091 lb ae/A and Vegetative Vigor: EC_{25} = 0.14 lb ae/A and NOAEC = 0.135 lb ae/A, the highest RQ for salt/amine/acid forms esters 22.68 for non-listed monocots and 24.18 for listed monocots (for forest sites, non cropland at 4 lb ae/A, using aerial spray application in semi-aquatic areas). Overall there are 34 fewer exceedances of LOC in the modeled scenarios than with the fresh weight-based endpoints. Proposed revised RQs are shown in Attachment 2 in red.

Document #	EPA-HQ-OPP-2012-0330-0047	**EPA states:** **6.3. Additional Analyses** ***Drinking Water Exposure Pathway (Birds and Mammals)*** 2,4-D exposure concentrations in puddles and dew on foliage were calculated using equations from TIM and then inserted in the "solubility" field in the SIP model (Appendix E)……. Given that the lowest application rate yielded risk concerns from dew for birds and mammals, risk concerns are expected for all application rates of 2,4-D for acid, Na, choline, IPE, IPA, DEA, DMA, and TIPA.
Page #	55-56	
Table #		
Row #		
Column #		

CORRECTION

See comment for page 48 above.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "Data from the European Footprint database and ECOTOX database indicate that 2,4-DCP, a major degradate of 2,4-D, is more toxic to fish and invertebrates than 2,4-D; aquatic plant data were not available. Footprint database toxicity values could not be evaluated because the Agency did not have access to the actual studies. Likewise, formal reviews of the open literature studies from the ECOTOX database were not conducted." "These risk concerns may not be equally observed throughout the water column unless mixing occurs since 2,4-DCP is only formed as a major degradate in the anaerobic aquatic study. Therefore, some taxa could be affected more than others depending on where they spend time in the water column."
Page #	56-57	
Paragraph #	Last / First	
Row #		
Column #		

CORRECTION

It is clear that EPA has not followed its own data quality guidance for literature searches related to publicly available data in this instance. Specifically, EPA did not state that procedures described in the Overview Document (2004), the 2011 Data Evaluation guidelines, the more recent ESA interim process for the OP insecticides, or the existing Agency-wide data quality guidelines were followed to insure that the 2,4-DCP data found in the ECOTOX database and the European Footprint database were suitable for use in risk assessment with respect to data quality and data relevance. This information should be made available in the final version of the risk assessment, and those data not passing the data quality and data relevance screen should be removed from the assessment.

Consistent with EPA guidance[3], we recommend that a systematic review of the reliability and relevance of the available

data, including data submitted by registrants be conducted to select the most appropriate results for use in the risk assessment. The approach used for review, as well as the reasoning for selection of results should be presented in a clear, transparent manner.

[3] Evaluation Guidelines for Ecological Toxicity Data in the Open Literature, U.S. EPA Office of Pesticide Programs, May 9, 2011

Document #	EPA-HQ-OPP-2012-0330-0047	The review states the following Agency recommendation: Reported acute value for Freshwater fish = 70 µg/L
Page #	57	
Paragraph #		
Table #	6.11	

COMMENT

The Task Force disagrees with the Agency recommendation for the following reasons:

No details about the study were provided.

The Task Force has previously conducted a review of the aquatic toxicity data available for 2,4-DCP. This review included:

- Locating all relevant records in the ECOTOX database.
- Sorting for same/similar species as 2,4-D aquatic data (e.g., uncommon and non-US species excluded)
- Removing studies with duration, measures of effect, or endpoints that were atypical
- Prioritization of studies done under flow-through conditions and with analytical confirmation of test concentrations
- Obtaining original articles and reviewing to assess quality

Buccafusco et al. (1981)[1] reported an LC_{50} = 2000 µg/L for bluegill in a flow-through study with analytical confirmation of test material. This result was determined to be the most reliable acute result available for freshwater fish species. This value should be used in the risk assessment unless evidence is available demonstrating that the result selected by the Agency is from a more relevant and reliable study, or from an equally relevant and reliable study for a more sensitive species.

1. Buccafusco RJ, Ells SJ, and LeBlanc GA. 1981. Acute Toxicity of Priority Pollutants to Bluegill (*Lepomis macrochirus*). *Bull. Environm. Contam. Toxicol*. 26, 446-452

Document #	EPA-HQ-OPP-2012-0330-0047	The review states the following Agency recommendation: Reported chronic value for Freshwater fish = 10 µg/L
Page #	57	
Paragraph #		
Table #	6.11	

COMMENT

The Task Force disagrees with the Agency recommendation for the following reasons:

No details about the study were provided.

The Task Force has previously conducted a review of the aquatic toxicity data available for 2,4-DCP. This review included:

- Locating all relevant records in the ECOTOX database.
- Sorting for same/similar species as 2,4-D aquatic data (e.g., uncommon and non-US species excluded)

- Removing studies with duration, measures of effect, or endpoints that were atypical
- Prioritization of studies done under flow-through conditions and with analytical confirmation of test concentrations
- Obtaining original articles and reviewing to assess quality

Hodson et al. (1991) reported a chronic value of 181 µg/L for rainbow trout in an 85-day, flow-through study with analytical confirmation of test material. Growth inhibition was the most sensitive response observed in the study, as it occurred at exposure levels equal to or lower than those that increased mortality rates. The chronic effect level of 181 µg/L is based on the 0.44 µM EC_{25} result from the Bootstrap estimate, wet weight response, 4 week fry post swim-up (85 day measurement), with appropriate unit conversion. This endpoint is relevant and is more conservative than the reported 35-day LOEC reported. The chronic value of 181 µg/L was determined to be the most reliable chronic result available for freshwater fish species. This value should be used in the risk assessment unless evidence is available demonstrating that the result selected by the Agency is from a more relevant and reliable study, or from an equally relevant and reliable study for a more sensitive species.

1. Hodson, P.V., R. Parisella, B. Blunt, B. Gray, and K.L.E. Kaiser. 1991. Quantitative Structure-Activity Relationships For Chronic Toxlclty of Phenol, P-Chlorophenol, 2,4-Dichlorophenol, Pentachlorophenol, P-Nitrophenol And 1,2,4=Trichlorobenzene To Early Llfe Stages Of Rainbow Trout (*Oncorhynchus mykiss*). Canadian Technical Report of Fisheries and Aquatic Sciences 1784

Document #	EPA-HQ-OPP-2012-0330-0047	The review states the following Agency recommendation: Reported chronic value for Freshwater invertebrates = 210 µg/L
Page #	57	
Paragraph #		
Table #	6.11	

COMMENT

The Task Force disagrees with the Agency recommendation for the following reasons:

No details about the study were provided.

The Task Force has previously conducted a review of the aquatic toxicity data available for 2,4-DCP. This review included:

- Locating all relevant records in the ECOTOX database.
- Sorting for same/similar species as 2,4-D aquatic data (e.g., uncommon and non-US species excluded)
- Removing studies with duration, measures of effect, or endpoints that were atypical
- Prioritization of studies done under flow-through conditions and with analytical confirmation of test concentrations
- Obtaining original articles and reviewing to assess quality

Gersich and Milazzo (1988) reported a NOEC of 740 µg/L (based on survival and reproduction) for *Daphnia magna* in a 21-day, static renewal study with analytical confirmation of test material. This result was determined to be the most reliable chronic result available for freshwater invertebrate species. This value should be used in the risk assessment unless evidence is available demonstrating that the result selected by the Agency is from a more relevant and reliable study, or from an equally relevant and reliable study for a more sensitive species.

1. Gersich FM and Milazzo DP. Chronic Toxicity of Aniline and 2,4-Dichlorophenol to *Daphnia magna* Straus. *Bull. Environ. Contain. Toxicol.* 40:1-7.

	EPA-HQ-OPP-2012-0330-	Table 6.11. 2,4-DCP Toxicity Values and Toxicity Thresholds for Freshwater Fish and Invertebrates

Document #	0047	
Page #	57	
Table #	6.11	
Row #		
Column #		

CORRECTION

See comment above for pages 56-57.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "After granting the registration for Enlist Duo, the EPA discovered that claims of "synergistic herbicidal weed control" had been made in its Provisional and Non-provisional patent applications to the U.S. Patent and Trademark Office for Enlist Duo. In response, the Agency requested a new study with non-target plants that will demonstrate the potential toxic effects, including any evidence of synergism, for the two active ingredients (2,4-D and glyphosate) when used together in combination so that the Agency can adequately assess the safety of the combination herbicide for non-target plants (USEPA 2016c). These data were and are currently under review. These data will only be applicable to 2,4-D/glyphosate formulations and do not address the potential for synergy from other registered herbicide combinations."
Page #	58	
Paragraph #	2	
Row #		
Column #		

CORRECTION

The data for 2,4-D/glyphosate formulations have been accepted and the details of the EPA's review of this data can be found in the document entitled, 2,4-D Choline: Review of Seedling Emergence and Vegetative Vigor.
Studies have been conducted in accordance with USEPA requirements to test a TEP containing the active ingredient of interest. Where studies have been conducted with combinations of herbicides (e.g. Enlist Duo) the lowest endpoint, as used in the RA, has not differed significantly from the lowest endpoint for the respective TEP containing the individual a.i.s.

As stated in the Overview Document (USEPA, 2004), ". . . the Agency does not routinely include, in its screening risk assessments, an evaluation of mixtures of active ingredients . . ." This is consistent with the registration review process that is intended to reevaluate individual a.i.s. This is also consistent with the provisional position of the Agency as outlined at the CLA Regulatory Conference in 2017 as only applying to new chemical registrations. In the case of 2,4-D, it is impractical and unnecessary to assess the risk posed by all possible mixture products, impractical because of the large numbers, and unnecessary because usually one mixing partner accounts for most of the toxicity to nontarget species.

Terrestrial Plant Studies for the Formulated Product Enlist Duo, found in docket EPA-HQ-OPP-2016-0594. See also comment for page 5 above.

Document #	EPA-HQ-OPP-2012-0330-0047	Vapor Exposure pathway
Page #	61-63	
Paragraph #		
Table #		

COMMENT

Vapor/Volatilization Exposure Pathway
Although the calculations of potential exposures from vapor employs well-understood modeling methodology, it should be noted that applying these models to materials with limited volatility is relatively new – PERFUM has been successfully applied in the management of highly volatile materials like fumigants, for example, but using it for materials like 2,4-D may create some uncertainties that require further research and discussion.

In addition, the definition of a biologically-relevant hazard endpoint for the vapor route of exposure is difficult and is likely extremely variable depending upon not only the plant species but even uncontrollable factors like plant water or thermal stress. The endpoint determined here, as was pointed out in the cited reference, was in actuality was based upon a visual injury rating from a single experiment and it is unclear if the level of visual injury used would indeed lead to agronomically-relevant effects.

In summary, if such analyses are to be used in a quantitative risk assessment/management structure, further examination of the underlying data and methodologies is needed.

Document #	EPA-HQ-OPP-2012-0330-0047	In the line for the 4 hours exposure duration, the air concentrations at a 2 lb ae/acre rate are shown as: DMA -0.48 EHE – 0.77
Page #	63	
Paragraph #		
Table #	6.13	

CORRECTION

Examining plots on the previous page, the DMA and EHE values are reversed in the table.
The values should be reflected as:
DMA: 0.77
EHE: 0.48

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0047	***Spray Drift Distances (Non-Listed Terrestrial Plants)*** Terrestrial plants are the most sensitive group of organisms to 2,4-D. This section explores spray drift distances for non-listed terrestrial plants in combination with variables such as application type (aerial versus ground), boom height, wind speed (15 versus 10 mph), and droplet size. 2,4-D has a robust collection of terrestrial plant data (seedling emergence and vegetative vigor).
Page #	64	
Table #		
Row #		
Column #		

COMMENT

The Task Force applauds EFED's use of SSDs to take into account effects on a range of species sensitivity in terrestrial plant communities. It is unclear, however, how the 53rd percentile is considered in the risk conclusions for plant populations and communities. Also, if the most sensitive EC25 was selected for each species, it may be difficult to differentiate between effects resulting from spray drift and soil exposures.

The examination of drift mitigation options (by examining the effects of some of the AgDRIFT input parameters) should be expanded to encompass more recent developments in application technology, such as low-drift nozzles. Such representations are available, by employing, for example, the RegDISP tool, which expands the options available for groundboom applications beyond the Spray Drift Task Force data described by AgDRIFT. For aerial applications, further options, beyond the simple examination of wind speed shown in the assessment, should be examined further.

In addition, the possible application of further Drift Reduction Technology (DRT) options, under the implemented DRT program[1], could also be examined.

https://www.epa.gov/reducing-pesticide-drift/about-drift-reduction-technology-program

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: The percentile for each selected endpoint was determined using a simple equation (i.e., 100-((Ranking/N[# of samples]*100) and rounded to the nearest whole number.
Page #	64	
Paragraph #	3	
Table #		

CORRECTION

The statement/ entry should be corrected so that it reads:

The percentile for each selected endpoint was determined using a simple equation (i.e., 100-((Ranking/N[# of samples])*100)) and rounded to the nearest whole number.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: Percentile for ranking 1 = 100
Page #	65	
Paragraph #	6.14	
Table #		

CORRECTION

The statement/ entry should be corrected so that it reads:

Percentile for ranking 1 = 93

According to the equation presented for calculating percentiles represented by each rank: “The percentile for each selected endpoint was determined using a simple equation (i.e., 100-((Ranking/N[# of samples])*100)) and rounded to the nearest whole number.”

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: Percentile for ranking 1 = 100
Page #	66	
Paragraph #	6.14	
Table #		

CORRECTION

The statement/ entry should be corrected so that it reads:

Percentile for ranking 1 = 94

According to the equation presented for calculating percentiles represented by each rank: “The percentile for each selected endpoint was determined using a simple equation (i.e., 100-((Ranking/N[# of samples])*100)) and rounded to the nearest whole number.”

Document #	EPA-HQ-OPP-2012-0330-	EPA states: “Table 6.16 provides distances at the 50th percentile using the selected AgDRIFT input

	0047	parameters, below (detailed results are presented in Tables G-1-G3, Appendix G).”
Page #	66	
Paragraph #	1	
Table #		

CORRECTION

Detailed results are presented in Tables **H1-H3**, **Appendix H**.

Corrections or additions are highlighted in red in this correction block.

Document #	EPA-HQ-OPP-2012-0330-0047	Risk Conclusions
Page #	67	
Table #		
Row #		
Column #		

CORRECTION

The Task Force points out that the risk conclusions are based on a screening assessment that is designed primarily to identify which uses pose potential (not actual) risks for specific taxa, with the understanding that more refined assessments will occur to quantify the probability of actual risk and the need for possible risk mitigation (USEPA, 1998). The final version of the risk assessment should therefore, after correcting the errors identified in these comments and taking into account the new data now available, include more refined estimates of risk to allow the Agency to arrive at appropriate regulatory decisions. There is a wealth of information available to make these refinements, since the 2,4-D molecule has been used for more than 60 years and has been studied in great detail.

Specific examples of necessary refinements include those related to more realistic assumptions, data, and information, as well as probabilistic modeling approaches to better characterize risk. Suggestions follow.

Birds, reptiles, and terrestrial-phase amphibians: use a probabilistic avian risk model such as TIM, or preferably, LiquidPARAM.

Mammals: use probabilistic total daily intake modeling to estimate daily doses.

Terrestrial invertebrates: the Task Force notes that the preliminary risk assessment was completed more than a year ago and therefore does not include the most recent science related to honeybee (terrestrial invertebrate) risk assessment. New developments should be included in the final version, especially those related to herbicides that are not expected to have an Adverse Outcome Pathway relevant to insects.

Terrestrial plants: compare TerrPlant runoff estimates to the distribution of values from modeling of runoff leaving the field; differentiate between spray drift effects on vegetative vigor and runoff effects on seedling emergence; account for lower soil activity under field conditions compared to foliar (contact) activity; account for the limited length of overland sheet flow when evaluating exposure to plants in dry areas; account for recovery from minor levels of non-lethal effects; account for the differing sensitivity of annuals, biennial and perennial broadleaves, and woody plants as indicated on 2,4-D product labels, where varying application rates are necessary to achieve control.

Aquatic plants: use SSDs with appropriate HCx for aquatic plant communities; apply more realistic exposure modeling.

In the risk/benefit analysis for both non-listed and listed aquatic taxa (plants and animals), account for the benefit of habitat restoration resulting from the aquatic weed control use. The Task Force also notes that partial treatment of water bodies greatly reduces potential adverse effects due to recolonization from nearby refugia.

Reference
USEPA. 1998. Guidelines for Ecological Risk Assessment. EPA/630/R-95/002F.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA conclusion: **Fish and Aquatic-Phase Amphibians** • Direct acute risk concerns for listed freshwater fish for ester forms of 2,4-D for the corn,non-croplands, pastures/rangelands/perennial grasslands, forestry, soybean, cranberry, and cereal crops. EPA Conclusion: **Aquatic plants** • Direct risk concerns for the ester forms of 2,4-D for listed vascular plants from corn, noncroplands, pasture/rangelands/perennial grasslands, forestry, and cranberry uses.
Page #	68	
Paragraph #		
Table #		
COMMENT		
Risk Conclusions: the Task Force does not agree with several conclusions of risk concerns resulting from the uses of 2,4-D ester on terrestrial crops. Specifics are outlined below. **Response: The acute risk assessment for these uses is incorrect, as the SWCC-modeled exposures of 2,4-D acid were improperly compared with hazard endpoints for 2,4-D esters (described in detail above). There are no exceedance of LOC for these uses.** **Response: The acute risk assessment for these uses is incorrect (except cranberry), as the SWCC-modeled exposures of 2,4-D acid were improperly compared with hazard endpoints for 2,4-D esters (described in detail above). There are no exceedance of LOC for these used.**		

Document #	EPA-HQ-OPP-2012-0330-0047	**EPA states:** **7. Listed Species of Concern** "Given that the agencies are continuing to develop and work toward implementation of the Interim Approaches to assess the potential risks of pesticides to listed species and their designated critical habitat, this preliminary risk assessment for 2,4-D does not contain a complete ESA analysis that includes effects determinations for specific listed species or designated critical habitat. Although EPA has not yet completed effects determinations for specific species or habitats, for this preliminary assessment EPA conducted an assessment for all taxa of non-target wildlife and plants that assumes for the sake of the assessment that listed species and designated critical habitats may be present in the vicinity of the application of 2,4-D. This assessment will allow EPA to focus its future evaluations on the types of species where the potential for effects exists once the scientific methods being developed by the agencies have been fully vetted."
Page #	69	
Paragraph #	3	
Row #		
Column #		
COMMENT		
The Task Force agrees that a complete ESA analysis is premature and should only be conducted in future after adequate scientific methods and data have been developed. The preliminary risk assessment points only to a potential for possible harm to listed species or adverse modification of habitat and is not a reliable predictor of actual harm.		

Document #	EPA-HQ-OPP-2012-0330-	EPA states:

	0047	"This risk assessment for 2,4-D indicates potential risks of direct effects to listed terrestrial plants, birds, reptiles, terrestrial-phase amphibians, mammals, terrestrial invertebrates, fish, aquatic invertebrates, and aquatic plants on some of its registered use sites. Listed species of all taxa may also be affected through indirect effects because of the potential for direct effects on listed and non-listed species upon which such species may rely. Potential direct effects on listed terrestrial plants, birds, reptiles, terrestrial-phase amphibians, mammals, terrestrial invertebrates, fish, aquatic invertebrates, and aquatic plants from the use of 2,4-D may be associated with modification of Primary Constituent Elements (PCEs) of designated critical habitats, where such designations have been made. 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 2,4-D as part of completing this Registration Review."
Page #	69-70	
Table #		
Row #		
Column #		

COMMENT

See the previous comment.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: "An endangered species assessment has been performed for Enlist Duo (Registration Number 62719-649) registration on corn and soybean for the following states: Arkansas, Iowa, Illinois, Indiana, Kansas, Louisiana, Minnesota, Mississippi, Missouri, Nebraska, North Dakota, Ohio, Oklahoma, South Dakota, and Wisconsin. After implementing in-field spray drift buffer and wind direction mitigations, a determination of "No Effect" was reached for direct and indirect listed species in those states; however the analysis is being revisited at this time. This analysis only applies to Enlist Duo in the 15 aforementioned states (USEPA 2013c, 2014a, 2014b, and 2014d)."
Page #	70	
Table #		
Row #		
Column #		

COMMENT

This registration decision has been finalized as reflected in EPA-HQ-OPP-2016-0594-0660.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA modelled the soil and aquatic degradate of 2,4-D, DCP with the SWCC model for an example terrestrial use (LA sugarcane) by estimating an "application rate" of the degradate, assuming the maximum fractional formation of the degradate in soil and anaerobic aquatic systems.
Page #	78	
Paragraph #		
Table #	B-3	

COMMENT

This is a worst-case representation of the potential aquatic exposure to DCP. However, since the degradation pathway of 2,4-D to the DCP is known and kinetically characterized, it is possible to use the "daughter product" functionality of SWCC (now PWC) to more realistically model the rise and decline of DCP in aquatic systems.

A similar functionality is available in PFAM to allow examination of the time-course of the parent and degradate formation and decline for the aquatic uses.

Document #	EPA-HQ-OPP-2012-0330-0047	EPA states: For Seedling Emergence; Monocot NOAEC = 0.0019 lb ae/A
Page #	87	
Paragraph #		

Table #	4	

CORRECTION

The statement/ entry should be corrected so that it reads:

For Seedling Emergence; Monocot NOAEC = 0.019 lb ae/A

0.019 is the correct value for the NOAEC for this study per page 1/133 in the DER for this study (MRID 47106003) and in the data analysis shown on page 45/133 of the DER.

Corrections or additions are highlighted in red in this correction block.

ATTACHMENT 1
Table of original and revised RQ values from TerrPlant for Ester forms of 2,4-D

Based on Table 6.10. Terrestrial Plant Risk Quotients (ester)

Type of Plant		Ground Spray			Aerial Spray		
		Dry Areas	**Semi-Aquatic Areas**	**Spray Drift Only**	**Dry Areas**	**Semi-Aquatic Areas**	**Spray Drift Only**
Citrus at 0.1 lb ae/A (ester)							
Monocot	Non-listed	<0.1	<0.1	<0.1	N/A	N/A	N/A
	Listed	**1.05*** ** 0.11	**5.79*** ** 0.58	<0.1	N/A	N/A	N/A
Dicot	Non-listed	0.17	0.92	0.48	N/A	N/A	N/A
	Listed	0.34	**1.90*** **	0.60	N/A	N/A	N/A
Potato at 0.07 lb ae/A (ester)							
Monocot	Non-listed	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
	Listed	0.74 <0.1	**4.05*** ** 0.41	<0.1 <0.1	**2.21*** ** 0.22	**5.53*** ** 0.55	0.14 0.14
Dicot	Non-listed	0.12	0.64	0.33	0.35	0.88	**1.67*** **
	Listed	0.24	**1.33*** **	0.42	0.72	**1.81*** **	**2.10*** **
Many Uses (See Table 3.1) at 1 lb ae/A (ester)							
Monocot	Non-listed	0.12	0.65	0.11	0.35	0.88	0.57
	Listed	**11*** ** **1.05**	**58*** ** **5.79**	0.41 0.41	**32*** ** **3.16**	**79*** ** **7.89**	**2.04*** ** **2.04**
Dicot	Non-listed	**1.67*** **	**9.17*** **	**4.76*** **	**5.00*** **	**13*** **	**24*** **
	Listed	**3.45*** **	**19*** **	**5.99*** **	**10*** **	**26*** **	**30*** **
Cereal Grains at 1.25 lb ae/A (ester)							
Monocot	Non-listed	0.15	0.81	0.14	0.44	**1.10*** **	0.71
	Listed	**13*** ** **1.32**	**72*** ** **7.24**	0.51 0.51	**39*** ** **3.95**	**99*** ** **9.87**	**2.55*** ** **2.55**
Dicot	Non-listed	**2.08*** **	**11*** **	**5.95*** **	**6.25*** **	**16*** **	**30*** **
	Listed	**4.31*** **	**24*** **	**7.49*** **	**13*** **	**32*** **	**37*** **

Type of Plant		Ground Spray			Aerial Spray		
		Dry Areas	Semi-Aquatic Areas	Spray Drift Only	Dry Areas	Semi-Aquatic Areas	Spray Drift Only
Ornamental Turf at 1.5 lb ae/A (ester)							
Monocot	Non-listed	0.18	0.97	0.17	N/A	N/A	N/A
	Listed	**16*** **1.58**	**87*** **8.68**	0.61 **0.61**	N/A	N/A	N/A
Dicot	Non-listed	**2.50***	**14***	**7.14***	N/A	N/A	N/A
	Listed	**5.17***	**28***	**8.98***	N/A	N/A	N/A
Many Uses (see Table 3.1) at 2 lb ae/A (ester)							
Monocot	Non-listed	0.24	**1.29***	0.23	0.71	**1.76***	**1.14***
	Listed	**21*** **2.11**	**116*** **11.58**	0.82 0.82	**63*** **6.32**	**158*** **15.79**	**4.08*** **4.08**
Dicot	Non-listed	**3.33***	**18***	**9.52***	**10***	**25***	**48***
	Listed	**6.90***	**37.93***	**11.98***	**20.69***	**51.72***	**59.88***
Cranberries at 4 lb ae/A (granular ester)							
Monocot	Non-listed	0.24	**2.35***	N/A	N/A	N/A	N/A
	Listed	**21*** **2.11**	**211*** **21.05**	N/A	N/A	N/A	N/A
Dicot	Non-listed	**3.33***	**33***	N/A	N/A	N/A	N/A
	Listed	**6.90***	**69***	N/A	N/A	N/A	N/A
Forest Sites, Non-Cropland at 4 lb ae/A (ester)							
Monocot	Non-listed	0.47	**2.59***	0.45	**1.41***	**3.53***	**2.27***
	Listed	**42*** **4.21**	**232*** **23.2**	**1.63*** **1.63**	**126*** **12.6**	**316*** **31.6**	**8.16*** **8.16**
Dicot	Non-listed	**6.67***	**37***	**19***	**20***	**50***	**95***
	Listed	**14***	**76***	**24***	**41***	**103***	**120***

Starred and bolded values indicate that an LOC was exceeded.
***Exceeds the chronic listed and non-listed species LOC of 1
N/A – not applicable (use is not registered for this type of application)
Not Calculated - data not available (NOAEC was non-definitive and an RQ could not be calculated)
Red = revised values. Revised values exceeding LOC are in bold.

Input values used were as follows:

	Ground spray	Aerial	Granular
Application rate	Varied, as per Table 6.10		
Incorporation	1	1	1
Runoff Fraction	0.01	0.01	0.01
Drift Fraction	0.01	0.05	0

ATTACHMENT 2
Table of original and revised RQ values from TerrPlant for Amine/Salt/Acid forms of 2,4-D

Based on Table 6.10. Terrestrial Plant Risk Quotients (amine/salt/acid)

Type of Plant		Ground Spray			Aerial Spray		
		Dry Areas	**Semi-Aquatic Areas**	**Spray Drift Only**	**Dry Areas**	**Semi-Aquatic Areas**	**Spray Drift Only**
Citrus at 0.1 lb ae/A (amine/salt/acid)							
Monocot	Non-listed	0.23 <0.1	**1.96***** 0.53	0.13 <0.1	N/A	N/A	N/A
	Listed	0.40 <0.1	**3.40***** 0.56	Not Calculated	N/A	N/A	N/A
Dicot	Non-listed	0.23	**1.96*****	0.26	N/A	N/A	N/A
	Listed	0.30	**2.55*****	0.59	N/A	N/A	N/A
Potato at 0.07 lb ae/A (amine/salt/acid)							
Monocot	Non-listed	0.16 <.01	**1.37***** 0.37	<0.1 <0.1	0.27 <0.1	**1.48***** 0.40	0.47 <0.1
	Listed	0.28 <0.1	**2.38***** 0.39	Not Calculated	0.47 <0.1	**2.57***** 0.42	Not Calculated
Dicot	Non-listed	0.16	**1.37*****	0.18	0.27	**1.48*****	0.92
	Listed	0.21	**1.79*****	0.41	0.35	**1.93*****	**2.06*****
Wild Rice at 0.25 lb ae/A (amine/salt/acid)							
Monocot	Non-listed	0.58 0.15	**4.90***** **1.31**	0.33 <0.1	0.96 0.27	**5.29***** **1.51**	**1.67***** 0.14
	Listed	**1.00***** 0.16	**8.50***** **1.4**	Not Calculated	**1.67***** 0.27	**9.17***** **1.51**	Not Calculated
Dicot	Non-listed	0.58	**4.90*****	0.66	0.96	**5.29*****	**3.29*****
	Listed	0.75	**6.38*****	**1.47*****	**1.25*****	**6.88*****	**7.35*****
Hops at 0.5 lb ae/A (amine/salt/acid)							
Monocot	Non-listed	**1.15*** 0.31	**9.81*** **2.63**	0.67 <0.1	**1.92*** 0.52	**11*** **2.84**	**3.33*** 0.26
	Listed	**2.00*** 0.33	**17*** **2.80**	Not Calculated	**3.33*** 0.55	**18*** **3.02**	Not Calculated
Dicot	Non-listed	**1.15***	**9.81***	**1.32***	**1.92***	**11***	**6.58***
	Listed	**1.50***	**13***	**2.94***	**2.50***	**14***	**15***
		Ground Spray			**Aerial Spray**		

Type of Plant		Dry Areas	Semi-Aquatic Areas	Spray Drift Only	Dry Areas	Semi-Aquatic Areas	Spray Drift Only
Many Uses (see Table 3.1) at 1 lb ae/A (amine/salt/acid)							
Monocot	Non-listed	**2.31*** 0.62	**20*** **5.26**	**1.33*** 0.10	**3.85*** **1.03**	**21*** **5.67**	**6.67*** 0.52
	Listed	**4.00*** 0.66	**34*** **5.6**	Not Calculated	**6.67*** **1.10**	**37*** **6.04**	Not Calculated
Dicot	Non-listed	**2.31***	**20***	**2.63***	**3.85***	**21***	**13***
	Listed	**3.00***	**26***	**5.88***	**5.00***	**28***	**29***
Cereal Grains at 1.25 lb ae/A (amine/salt/acid)							
Monocot	Non-listed	**2.88*** 0.77	**25*** **6.57**	**1.67*** 0.13	**4.81*** **1.29**	**26*** **7.09**	**8.33*** 0.64
	Listed	**5.00*** 0.82	**43*** **7.01**	Not Calculated	**8.33*** **1.37**	**46*** **7.55**	Not Calculated
Dicot	Non-listed	**2.88***	**25***	**3.29***	**4.81***	**26***	**16***
	Listed	**3.75***	**32***	**7.35***	**6.25***	**34***	**37***
Grapes at 1.36 lb ae/A (amine/salt/acid)							
Monocot	Non-listed	**3.14*** 0.84	**27*** **7.15**	**1.81*** 0.14	N/A	N/A	N/A
	Listed	**5.44*** 0.90	**46*** **7.62**	Not Calculated	N/A	N/A	N/A
Dicot	Non-listed	**3.14***	**27***	**3.58***	N/A	N/A	N/A
	Listed	**4.08***	**35***	**8.00***	N/A	N/A	N/A
Blueberries at 1.4 lb ae/A (amine/salt/acid)							
Monocot	Non-listed	**3.23*** 0.87	**27*** **7.36**	**1.87*** 0.14	N/A	N/A	N/A
	Listed	**5.60*** 0.92	**48*** **7.85**	Not Calculated	N/A	N/A	N/A
Dicot	Non-listed	**3.23***	**27***	**3.68***	N/A	N/A	N/A
	Listed	**4.20***	**36***	**8.24***	N/A	N/A	N/A
		Ground Spray			**Aerial Spray**		

Type of Plant		Dry Areas	Semi-Aquatic Areas	Spray Drift Only	Dry Areas	Semi-Aquatic Areas	Spray Drift Only
Ornamental Turf (ground only) and Strawberries at 1.5 lb ae/A (amine/salt/acid)							
Monocot	Non-listed	**3.46*** 0.93**	**29*** 7.89**	**2.00*** 0.15**	**5.77*** 1.55**	**32*** 8.51**	**10.00*** 0.77**
	Listed	**6.00*** 0.99**	**51*** 8.41**	Not Calculated	**10*** 1.65**	**55*** 9.07**	Not Calculated
Dicot	Non-listed	**3.46***	**29***	**3.95***	**5.77***	**32***	**20***
	Listed	**4.50***	**38***	**8.82***	**7.50***	**41***	**44***
Many Uses (see Table 3.1) at 2 lb ae/A (amine/salt/acid)							
Monocot	Non-listed	**4.62*** 1.24**	**39*** 10.52**	**2.67*** 0.21**	**7.69*** 2.06**	**42*** 11.34**	**13*** 1.03**
	Listed	**8.00*** 1.32**	**68*** 11.21**	Not Calculated	**13*** 2.20**	**73*** 12.09**	Not Calculated
Dicot	Non-listed	**4.62***	**39***	**5.26***	**7.69***	**42***	**26***
	Listed	**6.00***	**51***	**12***	**10***	**55***	**59***
Forest Sites, Non-Cropland at 4 lb ae/A (amine/salt/acid)							
Monocot	Non-listed	**9.23*** 2.47**	**78*** 21.03**	**5.33*** 0.41**	**15*** 4.12**	**85*** 22.68**	**27*** 2.06**
	Listed	**16*** 2.64**	**136*** 22.42**	Not Calculated	**27*** 4.40**	**147*** 24.18**	Not Calculated
Dicot	Non-listed	**9.23***	**78***	**11***	**15***	**85***	**53***
	Listed	**12***	**102***	**24***	**20***	**110***	**118***

Starred and bolded values indicate that an LOC was exceeded.
***Exceeds the chronic listed and non-listed species LOC of 1
N/A – not applicable (use is not registered for this type of application)
Not Calculated - data not available (NOAEC was non-definitive and an RQ could not be calculated)
Red = revised values. Revised values exceeding LOC are in BOLD

Input values used were as follows:

	Ground spray	Aerial
Application rate	Varied, as per Table 6.10	
Incorporation	1	1
Runoff Fraction	0.05	0.05
Drift Fraction	0.01	0.05