UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: **12/09/2015**

SUBJECT: **Endothall: Human Health Risk Assessment in Support of Registration Review, and the Petition to Re-evaluate Tolerances for Livestock, and Remove the Restriction that Prohibits Livestock from Drinking Treated Water.**

PC Code: 038901 (Acid), 038904 (Dipotassium), and 038905 (Monoalkylamine)
Decision No.: 492480 and 502452

Petition No.: 4F8293

Risk Assessment Type: Single chemical/aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D422204 and D426245

Registration No.: 70506-174, 70506-175, 70506-176, 70506-191,70506-190, 70506- 180, 70506-302
Regulatory Action: Reg Review and Tolerance Petition
Case No.: 2245
CAS No.: 145-73-3; 2164-07-0; and 66330-88-9
40 CFR: 180.293

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As part of Registration Review, the Pesticide Re-Evaluation Division (PRD) of the Office of Pesticide Programs (OPP) has requested that the Health Effects Division (HED) evaluate the hazard and exposure data and conduct occupational and residential exposure assessments, as needed, to estimate the risk to human health that will result from the currently registered uses of pesticides. This memorandum serves as HED's scoping document and draft human health risk assessment for endothall. In addition, the Registration Division (RD) has requested the evaluation of United Phosphorous Inc. tolerance petition for endothall on meat, milk, poultry and eggs to support the removal of the restriction on consumption of water treated with endothall by livestock. The most recent quantitative human health risk assessment was conducted in 2013 to support the proposed use of the dipotassium form of endothall on apples (D403274, S. Tadayon, 3/18/2013).

1.0 Executive Summary

Endothall is a dicarboxylic acid that is a selective contact herbicide, defoliant, desiccant, growth regulator, and aquatic algaecide. The free acid of endothall (PC Code 038901) is the active ingredient that forms from the breakdown of the endothall salts, and is not applied directly to use sites. Endothall dipotassium (PC Code 038904) and monoalkylamine (PC Code 038905) salts are registered primarily as aquatic herbicides for the control of a variety of plants in water bodies, including irrigation canals. Tolerances are established in the 40 CFR § 180.293 for endothall and its monomethyl ester on food and feed items as a result of direct and inadvertent (aquatic) residues resulting from endothall products. An interim tolerance for negligible residues of endothall in sugar beets is established in 40 CFR § 180.319. In addition to exposure through dietary pathways, exposure may result from residential and occupational uses of endothall. This risk assessment is prepared in support of registration review (scoping and draft risk assessment actions) and the petition to remove the restriction that prohibits livestock from drinking water treated with endothall.

Hazard/Toxicity

The toxicology database for endothall is complete. The Hazard and Science Policy Committee waived the need for acute and subchronic neurotoxicity studies (HASPOC, TXT # 0056545, 12/19/2012) in rats and the need for an immunotoxicity study (HASPOC, TXT # 0056794, 09/26/2013).

Endothall is a caustic chemical with toxicity being the result of a direct degenerative effect on tissue. The dog is particularly sensitive to endothall toxicity. Orally, it damages the canine digestive tract at relatively low doses, and then the liver and kidneys at lethal doses. Dermally, it destroys the stratum corneum and then the underlying viable epidermis in rabbits and rats. The rabbit is extremely sensitive to ocular instillation of endothall. In the eye irritation study, endothall technical was extremely irritating to the eye, and was also lethal. In a dermal irritation study, endothall was an extreme irritant. Although it was classified as a category III in an acute dermal toxicity study, endothall has been shown to be a severe irritant in a dermal absorption study and in a 21-day dermal toxicity study after one application. Based on all available data, endothall is classified as a severe dermal irritant. Endothall is also an extreme irritant by the acute oral and acute ocular routes of administration, and is a skin sensitizer. In the acute inhalation study, it was classified as slightly irritating, however, there was irritation and other respiratory effects observed in 5-day and 28-day inhalation toxicity studies supporting the conclusion of the irritant effects of endothall.

Endothall does not cause pre-natal toxicity following *in utero* exposure to rats nor pre-and post-natal toxicity following exposures to rats for two generations. In the developmental mouse study, there was severe maternal toxicity (i.e., greater than 30% mortality) at the highest dose tested; at this dose level, a slight increase in vertebral and rib malformations was observed in the offspring indicating that these effects were most likely secondary to severe maternal toxicity. The hazard data for endothall indicate no evidence of quantitative or qualitative increased susceptibility of rat fetuses exposed *in utero* to endothall in the developmental toxicity studies. In addition, no evidence of quantitative or qualitative increased susceptibility of rat fetuses or neonates was observed in the 2-generation reproduction study.

Appropriate endpoints were identified for the chronic dietary risk assessment based on proliferative lesions of the gastric epithelium in both sexes; for the short-term occupational and residential, and the intermediate-term occupational inhalation risk assessments based on indications of lung toxicity in a subchronic inhalation toxicity study in the rat; and for the short-term incidental oral risk assessment based on decreased pup body weight in a 2-generation rat reproduction oral study. An acute dietary endpoint attributable to a single dose was not identified from any study. No dermal endpoint was selected for endothall because the dermal irritation observed in a repeated-dose study is considered self-limiting. Endothall is classified as "not likely to be carcinogenic to humans" based on lack of evidence of carcinogenicity in mice or rats. It has no mutagenic potential.

Residue Chemistry

The residues of concern in plant and livestock commodities for risk assessment are endothall and its monomethyl ester. The residue of concern in drinking water is the free acid of endothall. Methods are available for enforcement of tolerances for endothall on food and feed commodities as a result of direct and inadvertent (aquatic) residues resulting from the use of endothall products. An independent laboratory validation (ILV) for a livestock enforcement method and a storage stability study have been submitted and evaluated in support of the removal of the label restriction that prohibits livestock from drinking water treated with endothall. The chemistry database of endothall is adequate to support the proposed updated tolerances for livestock commodities, the removal of the label restriction, and registration review of endothall provided that data needs and tolerance recommendations described in Section 2.0 are addressed.

Dietary Exposure and Risk

A refined, chronic dietary exposure and risk assessment was conducted incorporating average percent crop treated data, average field trial residues for all crops, DEEM 7.81 default and crop specific processing factors for all commodities. The drinking water inputs were based on modeled surface water values from the scenario which is likely to provide the highest estimated environmental concentration. The estimated exposure (food and water) to the U.S. population from the existing uses of endothall resulted in an estimated risk equivalent to 32% of the chronic population adjusted dose (cPAD). The most highly exposed population subgroup is children 1-2 years of age with an exposure equivalent to an estimated risk of 90% of the cPAD. Exposures to endothall for all food and water uses are below HED's level of concern (LOC; < 100% of the cPAD).

Residential Exposure and Risk Estimates

Endothall products are intended for use on residential sites, but labels require certain PPE to be worn (long sleeve shirt, pants, gloves, and, a dust /mist respirator). Standard HED assumptions for residential/consumer applicator specific assessments, such as wearing shorts and a t-shirt without PPE like chemical-resistant gloves or respirators, would represent non-compliance with current endothall products; therefore, a residential handler assessment has not conducted. An exposure assessment for occupational handlers/applicators assuming compliance with label requirements for work clothing and/or PPE was conducted. If products containing endothall are meant to be marketed towards and performed by consumers/homeowners in on residential sites, HED recommends that label requirements for PPE be reevaluated or separate consumer-specific labels be developed and a separate residential handler assessment be conducted to evaluate such products.

Based on the aquatic application scenarios, HED assessed inhalation and incidental oral (water ingestion) post-application exposures from the aquatic use (adult and children). Post-application dermal risk assessments were not conducted because no hazard was identified via the dermal route for the relevant exposure durations. The resulting margins of exposure (MOEs) for short-term post-application inhalation and incidental oral exposures are not of concern to HED (i.e., MOEs > 30 for inhalation exposures and MOEs ≥100 for incidental oral exposures).

Aggregate Exposure and Risk

A short-term aggregate assessment considering exposures from food and water with those from residential exposure (i.e., incidental ingestion of treated water (swimmers)) was conducted. Post-application oral exposure for adults and children were combined with the chronic dietary exposure from the mostly highly exposed subpopulations. The short-term risk is not of concern as the MOEs are above the level of concern (LOC) of 100.

Occupational Exposure and Risk Estimates

The registered labels require occupational handlers to wear the following personal protective equipment (PPE): long-sleeved shirts, long pants, chemical resistant gloves, protective eyewear and dust mist respirator (TC-21C). The occupational handler exposure and risk estimates for some aquatic scenarios indicate that short- and intermediate-term non-cancer inhalation MOEs are of concern to HED (i.e., MOEs < 30) with label recommended PPE, and even with a closed system (i.e., engineering control). The MOEs for aquatic scenarios range from 1 to 873. The occupational handler exposure and risk estimates for agricultural scenarios indicate that short- and intermediate-term non-cancer inhalation MOEs are not of concern to HED (i.e., MOEs > 30) with label recommended PPE (i.e., dust/mist respirator). The MOE's for agricultural scenarios range from 31 to 2,900. The acute toxicity classification for primary eye irritation of endothall is category I which requires a 48-hour restricted entry interval (REI). The 48-hour REI listed on the agricultural labels is appropriate.

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. Additional information on how these studies are considered can be found in Appendix C.

2.0 HED Recommendations

The hazard database for endothall is complete and adequate to support registration review.

The residue chemistry database of endothall is adequate to support the removal of the restriction that prohibits livestock from drinking water treated with endothall; provided that data deficiencies, recommended tolerance levels, and tolerance expression described in Section 2.1 and 2.2.2 are addressed.

HED concludes the following regarding the occupational and residential exposure database:

- There are occupational inhalation risk estimates of concern associated with the currently registered uses of one of the two granular formulations of endothall, the dimethyl alkyl amine salt (Hydrothol 191 Granular; EPA Reg. No. 70506-174). The dipotassium granular formulation (Aquathol Super K; EPA Reg. No. 70506-191) is not likely to result

in an inhalation risk of concern based on the following: it is coated with polymer minimizing formation of respirable/inhalable dust; tests performed by the registrant showed that granules can be ground to very small particles only by vigorous attrition measures, and an attrition type study with dipotassium salt of endothall demonstrated that small respirable particles are not formed. However, studies addressing the formation of respirable particles by other granular formulations, e.g. Hydrothol 191 Granular, are not available. As such, risks of concern are associated with these end-use products.

2.1 Data Deficiencies

The following data deficiencies were identified in the endothall residue chemistry chapter:

- 860.1340: Existing data collection methods are adequate, assuming confirmatory data are submitted which shows that recoveries of monomethyl ester of endothall are acceptable for the irrigated crops studies (D356315) and the apple blossom study (D384206).
- 860.1500: Two additional trials in Region 11 are required to support the use of endothall on alfalfa grown for seed (D426753 and D321179). Alternatively, enforceability of the label restriction to use the seed for food, feed or oil needs to be demonstrated, and that residues are not likely to be present in the crop grown from the harvested seed to classify this use as non-food, see Section 3.3.
- 860.1340: The proposed enforcement method for livestock incorporating the recommendations of the ILV laboratory needs to be submitted to the Agency.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Plants: An enforcement method (GC with microcoulometric nitrogen detection) is listed as Method I in the Pesticide Analytical Manual (PAM, Volume II) for the determination of endothall residues (total common moiety) in plant commodities. Using this method, residues in crop commodities are extracted using acetone acidified with HCl. Any endothall present is converted to the N-methoxyimide derivative by reaction with methoxyamine hydrochloride. The imide derivative is partitioned into chloroform, concentrated and analyzed. The method limit of quantitation (LOQ) is 0.1 ppm. HED modified the residue of concern definition for tolerance enforcement in plants to parent endothall only. Therefore, is no longer necessary that the recovery of the monomethyl ester is tested by the enforcement methods for plants. See section 5.1 for further information.

Livestock: The ILV to support Method KP-245R0 as an enforcement method for livestock commodities was submitted and evaluated. The method consists of extraction, followed by derivatization of the residues of endothall and endothall monomethyl ester via a common-moiety approach. The samples are analyzed by LC/MS/MS. Adequate recoveries of endothall and its monomethyl ester were obtained using cow and poultry commodities. The method LOQ is 0.01 ppm for each analyte. The method is a suitable for enforcement purposes; however, some clarifications in the procedure as suggested by the ILV laboratory need to be incorporated, refer to the residue chemistry chapter (D426753).

Confirmatory method for plants and fish: An LC/MS method (Method No. KP-218R0) is available for determining residues of endothall and its monomethyl ester in fish and in plant commodities. For this method, residues are extracted with water, acidified and, if necessary, purified using a C_{18} solid phase extraction (SPE) column. Residues are then derivatized with heptafluoro-*p*-tolylhydrazine (HFTH) and partitioned into dichloromethane (DCM). Derivatized residue are concentrated, redissolved in toluene, and cleaned up using a silica gel cartridge. Residues are determined by liquid chromatography with a mass selective detector (LC/MSD) using the 397 amu ion for detection and quantitation. The LOQ is 0.05 ppm for fish, and range from 0.01-0.10 ppm for plant commodities. This method has undergone a successful independent laboratory validation using fish samples.

Multiresidue Methods: Endothall is not recovered through the FDA multiresidue methods.

2.2.2 Recommended Tolerances

The residue of concern definition for endothall was reevaluated as part of registration review based on a proposal from the registrant to establish parent endothall only as the residue of concern in plants. HED understands that parent endothall is an adequate marker of misuse in plants as it is the only or main residue observed in metabolism studies. Although the tolerances established in the 40 CFR § 180.293 for plant commodities may have contribution from the monomethyl ester, the metabolism studies suggest that the main residue is parent endothall and an appropriate marker of misuse as well. The tolerances are not likely to underestimate the residue levels and are considered adequate for enforcement purposes as they are not likely to be significantly overestimated. Parent endothall and the monomethyl ester are still considered the residues of concern for risk assessment, refer to section 5.1.

In support of registration review and the tolerance petition to update the current tolerances for milk, meat, poultry and eggs (MMPE), a new tolerance expression for inadvertent residues and updated/new tolerances are recommended. Table 2.2.3 summarizes the established, proposed and recommended tolerances for MMPE. The registrant proposes updated tolerances for all livestock commodities at the LOQ of the enforcement method (0.01 ppm for milk, 0.05 ppm for the remaining commodities) with the exception of ruminant kidney for which a tolerance of 0.06 ppm is proposed based on residues of 0.051 ppm observed in the cow feeding study. Following calculations of anticipated residues, HED recommends tolerances at the LOQ level for all MMPE commodities. In addition, tolerances recommended for shellfish (1 ppm for crustaceans, and 4 ppm for mollusc) need to be included in the 40 CFR § 180.293 as previously recommended (D. Soderberg, D324426, 02/27/2006), and the tolerance for fish should be moved to section *(d) Indirect or Inadvertent residues*.

Further review of the magnitude of residue study on potato shows that proportionality can be applied to the residue data generated at 2x and a reassessed tolerance can be established at 0.2 ppm. Upon personal communication with RD and PRD (G. Waleko and D. Sunderland, 02/11/2015), it was determined that uses of endothall on rice are no longer on the labels. Based on this, HED understands that tolerances for rice grain and rice straw can be moved from section *(a) General (1)* to section *(d) Indirect or Inadvertent residues* to cover residues resulting from irrigation with water treated with endothall. Moreover, the interim tolerance under section *(a) General (2)* to cover residues of endothall in drinking water is not needed as OPP no longer

establishes tolerances in drinking water. EPA's Office of Water has established a maximum contaminant level (MCL) for endothall at 0.10 ppm. Finally, HED recommends the establishment of tolerances of 2.0 ppm for alfalfa, seed and clover, seed, 0.2 ppm for cotton, undelinted seed, and 8.0 ppm for cotton gin byproducts to section *(a) General (1)* to cover residues of endothall resulting from harvest aid uses on alfalfa and clover.

An interim tolerance for negligible residues of endothall in sugar beets is established in 40 CFR § 180.319. This tolerance is not needed as residues of endothall in/on sugar beets are covered under the tolerance for Vegetable, root and tuber, group 1 established under 40 CFR § 180.293 (d).

The tolerance expression included under the 40 CFR § 180.293 *(a) General (1)* and *(d)* needs to be modified in accordance with the Interim Guidance on Tolerance Expressions (S. Knizner; 05/27/2009). A new section and tolerance expression, e.g. (e), needs to be added for tolerances in livestock commodities. The recommended tolerance expression is:

(a) General. Tolerances are established for the residues of endothall, including its metabolites and degradates, in or on the commodities in the table, below. Compliance with the tolerance levels specified, below, is to be determined by measuring only endothall (7-oxabicylco [2.2.1] heptanes-2,3-dicarboxylic acid).

(d) Indirect or inadvertent residues in plant commodities. Tolerances are established for the indirect or inadvertent combined residues of the herbicide endothall in potable water resulting from uses to control aquatic plants in canals, lakes, ponds, and other potable water sources. Tolerances are established for the residues of endothall, including its metabolites and degradates, in or on the commodities in the table, below. Compliance with the tolerance levels specified, below, is to be determined by measuring only endothall (7-oxabicylco [2.2.1] heptanes-2,3-dicarboxylic acid).

(e) Indirect or inadvertent residues in livestock commodities and fish. Tolerances are established for the indirect or inadvertent combined residues of the herbicide endothall in potable water resulting from uses to control aquatic plants in canals, lakes, ponds, and other potable water sources. Tolerances are established for the residues of endothall, including its metabolites and degradates, in or on the commodities in the table, below. Compliance with the tolerance levels specified, below, is to be determined by measuring only endothall (7-oxabicylco [2.2.1] heptanes-2,3-dicarboxylic acid) and its mono-methyl ester.

Table 2.2.2. Tolerance Summary for Endothall

Commodity	Established Tolerance (ppm)	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments *Correct Commodity Definition*
40 CFR § 180.293 (a) General (1)				
Alfalfa, seed[1]			2.0	
Clover, seed[1]			2.0	
Cotton, undelinted seed	0.1		0.2	
Cotton, gin byproducts			8.0	
Fish	0.1		0.1	Move to section (d)
Potato	0.1		0.2	

Table 2.2.2. Tolerance Summary for Endothall				
Commodity	**Established Tolerance (ppm)**	**Proposed Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments *Correct Commodity Definition***
Rice, grain	0.05		0.05	Move to section (d)
Rice, straw	0.05		0.05	Move to section (d)
40 CFR § 180.293 (a) General (2)				
Water, potable	0.2			Revoke
(d) Indirect or inadvertent residues in plant commodities.				
Almond, hulls	15.0			
Animal feed, nongrass, group 18, forage	4.0			
Animal feed, nongrass, group 18, hay	10			
Apple, wet pomace	0.15			
Beet, sugar, molasses	1.5			
Brassica, head and stem subgroup 5A	0.1			
Brassica, leafy, subgroup 5B	2.0			
Bushberry subgroup 13-07B	0.6			
Caneberry subgroup 13-07A	0.6			
Corn, field, grain	0.07			
Corn, pop, grain	0.07			
Corn, sweet, kernel plus cob with husks removed	0.3			
Citrus, dried pulp	0.1			
Feed commodities not otherwise listed	10.0			
Food commodities not otherwise listed	5.0			
Fruit, citrus group 10	0.05			
Fruit, pome, group 11	0.05			
Fruit, stone, group 12	0.3			
Grain, aspirated fractions	35.0			
Grain cereal, forage, fodder and straw, group 16	10.0			
Grain, cereal, group 15, except corn	4.0			
Grape	1.0			
Grape, raisin	5.0			
Grass, forage, fodder, and hay group 17, forage	3.5			
Grass, forage, fodder, and hay group 17, hay	18.0			
Herb and spice, group 19	5.0			
Nut, tree, group 14	0.05			
Okra	0.05			
Pea and bean, dried shelled, subgroup 6C	0.2			
Pea and bean, succulent shelled,	2.0			

Table 2.2.2. Tolerance Summary for Endothall				
Commodity	**Established Tolerance (ppm)**	**Proposed Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments *Correct Commodity Definition***
subgroup 6B				
Peppermint, tops	5.0			
Pistachio	0.05			
Rice, hulls	8.0			
Soybean, hulls	0.5			
Soybean, seed	0.2			
Spearmint, tops	5.0			
Tomato, paste	0.1			
Tomato, puree	0.1			
Vegetable, bulb, group 3-07	0.5			
Vegetable, cucurbit, group 9	1.5			
Vegetable, foliage of legume, group 7	4.0			
Vegetable, fruiting, group 8	0.05			
Vegetable, leafy, except brassica, group 4	2.0			
Vegetable, leaves of root and tuber, group 2	3.0			
Vegetable, legume, edible, podded, subgroup 6A	2.0			
Vegetable, root and tuber, group 1	1.0			
Wheat, milled byproducts	5.0			
40 CFR § 180.293 (e) Indirect or inadvertent residues in livestock commodities.				
Cattle, meat	0.03	0.05	0.05	
Cattle, kidney	0.2	0.06	0.05	
Cattle, liver	0.1	0.05	0.05	
Cattle, fat	0.01	0.05	0.05	
Milk	0.03	0.01	0.01	
Sheep, meat	0.015	0.05	0.05	
Sheep, kidney	0.15	0.06	0.05	
Sheep, liver	0.05	0.05	0.05	
Sheep, fat	0.005	0.05	0.05	
Goat, meat	0.015	0.05	0.05	
Goat, kidney	0.15	0.06	0.05	
Goat, liver	0.05	0.05	0.05	
Goat, fat	0.005	0.05	0.05	
Hog, meat	0.01	0.05	0.05	
Hog, kidney	0.1	0.06	0.05	
Hog, liver	0.05	0.05	0.05	
Hog, fat	0.005	0.05	0.05	
Poultry, meat	0.015	0.05	0.05	
Poultry, liver	0.05	0.05	0.05	
Poultry, fat	0.015	0.05	0.05	
Poultry, meat byproducts	0.2	0.05	0.05	
Egg	0.05	0.05	0.05	

Table 2.2.2. Tolerance Summary for Endothall				
Commodity	**Established Tolerance (ppm)**	**Proposed Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments *Correct Commodity Definition***
Fish-shellfish, crustacean[2]	N/A	1	1	
Fish-shellfish, mollusc[2]	N/A	4	4	
40 CFR § 180.319 (a) General				
Beet, sugar	0.2			Revoke (covered under 180.293 Vegetable, root and tuber, group 1)

[1] These tolerances for direct uses are not necessary if the use in alfalfa and clover is classified as non-food. In that case, tolerances may be established under section *(d) Indirect or inadvertent residues* to support residues resulting from irrigation with water treated with endothall.
[2] Tolerances for endothall in/on shellfish were proposed with Petition # 9F06015 at 1 ppm (crustacean) and 4 ppm (mollusc) based on the residue chemistry chapter D356315 (D. Soderberg, 10/22/2009).

2.2.3 Revisions to Petitioned-For Tolerances

The registrant has proposed updated tolerances for all livestock commodities at 0.05 ppm (LOQ of the proposed enforcement method) with the exception of milk for which the LOQ is 0.01 ppm, and ruminant kidney for which a tolerance of 0.06 ppm is proposed based on a residue of 0.051 ppm observed in the ruminant feeding study. These updated tolerances are higher than the tolerances currently established for all commodities with the exception of ruminant kidney. Residue levels in livestock commodities were re-evaluated following current procedures which make use of highest average field trial (HAFT) and median residues instead of tolerance level residues in feedstuff commodities. Based on these revised residue calculations, a tolerance at the LOQ level of the enforcement method is adequate for all livestock commodities.

2.2.4 International Harmonization

The International Residue Limits Table is included in Appendix E. Maximum residue limits (MRLs) for endothall have not been established by Codex or Mexico. Canada and the US have the same tolerance level for residues of endothall and its monomethyl esters in/on potato at 0.1 ppm. However, a higher tolerance for potato is recommended. It is not possible at this time to maintain the harmonized tolerance level of 0.1 ppm because the highest residue (0.113 ppm) estimated for potato is above the current tolerance level.

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

HED recommends in favor of the removal of the label restriction prohibiting livestock from drinking water treated with endothall.

The label of Desicate II (EPA Reg. No. 70506-190) includes a label restriction that states “Seed Crops Only - Seed from treated fields should be used for planting purposes only. Do not use seed for food, feed or oil purposes.” This restriction needs to be removed from the label unless its enforceability is demonstrated, refer to Section 3.3.

2.3.2 Recommendations from Occupational Assessment

For the agricultural uses, occupational handlers must wear the following personal protective equipment (PPE): long-sleeved shirts, long pants, chemical resistant gloves, protective eyewear and a dust mist respirator (TC-21C) for mixing/loading a liquid formulation for aerial application of endothall to alfalfa and clover. The 48-hour REI listed on the agricultural labels is appropriate. For aquatic uses, occupational handlers using a liquid formulation must wear long-sleeved shirts, long pants, chemical resistant gloves, and protective eyewear for all scenarios. All applicators of liquid formulations for aquatic uses should use a closed system, and mixer/loader/applicators of liquid formulations require a respirator for certain scenarios. Risk estimates for use of granular formulations in aquatic scenarios result in risk estimates of concern even using closed systems. There is no REI listed on aquatic labels (exempt under WPS).

2.3.3 Recommendations from Residential Assessment

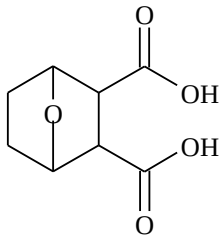
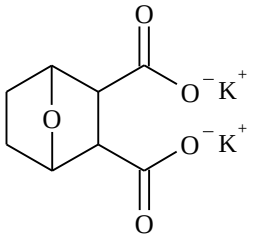
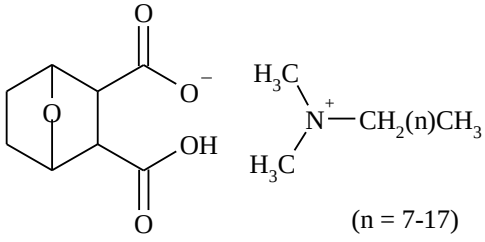
None.

3.0 Introduction

Endothall is a dicarboxylic acid that is a selective contact herbicide, defoliant, desiccant, growth regulator, and aquatic algaecide. The free acid of endothall (PC Code 038901) and its dipotassium (PC Code 038904) and monoalkylamine (PC Code 038905) salts are registered primarily as aquatic herbicides for the control of a variety of plants in water bodies, including irrigation canals. Tolerances are established for endothall and its monoethyl ester on food and feed items as a result of direct and inadvertent (aquatic) residues resulting from endothall products.

This memorandum serves as HED's scoping document and draft human health risk assessment in support of registration review for endothall. In addition, a petition from United Phosphorous Inc. to update the tolerances of endothall on meat, milk, poultry and eggs, and to support the removal of the restriction on consumption of water treated with endothall by livestock is considered. This label restriction would be removed from the label of the following end-use products: Hydrothol® Granular Aquatic Algicide and Herbicide (EPA Reg. No. 70506-174); Hydrothol® 191 Aquatic Algicide and Herbicide (EPA Reg. No. 70506-175); Aquathol® K Aquatic Herbicide (EPA Reg. No. 70506-176); and Aquathol® Super K Granular Aquatic Herbicide (EPA Reg. No. 70506-191).

3.1 Chemical Identity

Table 3.1.1 Structure and Nomenclature of Endothall-dipotassium.	
Chemical Structure	
Common name	Endothall acid
Molecular Formula	$C_8H_{10}O_5$
Molecular Weight	186.16
IUPAC name	7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid
CAS name	7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid
CAS #	145-73-3
PC Code	038901
Current Food/Feed Site Registration	Cotton, hops, potato, alfalfa grown for seed
Chemical Structure	
Common name	Endothall, di-potassium salt
Molecular Formula	$C_8H_8K_2O_5$
Molecular Weight	262.33
IUPAC name	7-oxabicyclo[2.2.1]heptane-2,3-dicarboxyilic acid, potassium salt
CAS name	3,6-endoxohexahydrophthallic acid, potassium salt
CAS #	2164-07-0
PC Code	038904
Current Food/Feed Site Registration	Cotton, hops, potato, alfalfa grown for seed, aquatic uses
Chemical Structure	 (n = 7-17)
Common name	Endothall, mono-N, N-dimethyl alkyl amine salt
Molecular Formula	Not available
Molecular Weight	Average: 422
IUPAC name	7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid, compound with N, N-dimethylcocoamine
CAS name	Not available
CAS #	66330-88-9
PC Code	038905
Current Food/Feed Site Registration	Cotton, hops, potato, alfalfa grown for seed, aquatic uses

3.2 Physical/Chemical Characteristics

The physicochemical properties of endothall are summarized in Appendix B. Endothall has a low vapor pressure (3.92 x 10^{-5} mm Hg at 24.3℃); therefore, is not volatile. Endothall is a diacid with high solubility in water (110 to 131 g/L at 25℃, depending on the pH). The environmental fate properties of endothall suggest that it degrades by biotic processes such as aerobic metabolism (N. Thurman, D356316, 09/09/2009). Laboratory studies measured first-order degradation half-lives of 14.5 days for aerobic soil metabolism, 10 days for aerobic aquatic metabolism, and 9 days for anaerobic metabolism. Terrestrial dissipation studies measured dissipation half-lives from the soil surface of 13 to 19 days. Dissipation/disappearance half-lives in aquatic studies ranged from 4 to 30 days in laboratory studies, and 0.5 to 20 days in ponds and lakes.

3.3 Pesticide Use Pattern

Endothall is a selective contact herbicide, defoliant, desiccant, growth regulator and aquatic algicide which belongs to the dicarboxylic acid chemical class. The free acid of endothall (PC Code 038901) is the active ingredient that forms from the breakdown of the endothall salts, and is not applied directly to use sites. Endothall dipotassium (PC Code 038904) and alkylamine (PC Code 038905) salts are registered primarily as aquatic herbicides to control a variety of plants including pondweed, naiad, coontail, milfoil, elodea, and algae, as well as plankton in water bodies. Moreover, the current labels allow for repeated broadcast applications to irrigation canals at rates yielding endothall concentrations of up to 5 ppm ae (acid equivalents) for the monoalkylamine salts and 3.5 ppm ae for the dipotassium salt. Endothall-treated water is used for irrigation purposes on non-food and food crops, established ornamentals, turf grass, lawns, and non-crop areas. There are also registered uses for desiccation/defoliation of alfalfa/clover (grown for seed only), cotton, and potatoes prior to harvest, and for reduction of sucker branch growth in hops. It is also registered as an apple blossom thinner.

A summary of the registered use directions is presented in Appendix D. The registered labels require occupational handlers to wear the following personal protective equipment (PPE): long-sleeved shirts, long pants, chemical resistant gloves, and protective eyewear. A 48-hour restricted entry interval (REI) is currently listed on the agricultural labels.

United Phosphorous Inc. submitted a petition to remove the label restriction that states "Do not use treated water for animal consumption within the following periods: 0.3 ppm - 7 days after application, 3.0 ppm - 14 days after application, and 5.0 ppm - 25 days after application." This label restriction would be removed from the label of the following end-use products: Hydrothol® Granular Aquatic Algicide and Herbicide (EPA Reg. No. 70506-174); Hydrothol® 191 Aquatic Algicide and Herbicide (EPA Reg. No. 70506-175); Aquathol® K Aquatic Herbicide (EPA Reg. No. 70506-176); and Aquathol® Super K Granular Aquatic Herbicide (EPA Reg. No. 70506-191).

The label of Desicate II (EPA Reg. No. 70506-190) includes a label restriction that states "Seed Crops Only - Seed from treated fields should be used for planting purposes only. Do not use seed for food, feed or oil purposes." This restriction needs to be removed from the label unless its enforceability is demonstrated (ChemSAC minutes of 03/07/2001). In general, restrictions imposed on Section 3 registration labels to preclude the need for residue data must be practical

and enforceable and are subject to the following criteria: (1) the food or feedstuff must remain under the control of the grower; (2) preferably the crop would be grown primarily as a feedstuff; and (3) the label restriction should cause no economic hardship. For alfalfa grown for seed, enforcement of the label restrictions necessary to achieve nonfood status would require the involvement of States and the establishment of adequate regulatory mechanisms such as might be prescribed under Section 24(c) registrations. In certain situations this label restriction has been allowed if the harvested seed is dyed.

3.4 Anticipated Exposure Pathways

The PRD and RD have requested an assessment of human health risk to support registration review and the proposed elimination of the label restriction prohibiting livestock from drinking water treated with endothall. Humans may be exposed to endothall in food and drinking water, since it may be applied directly or indirectly (i.e. resulting from irrigation with treated water) to growing crops and application may result in endothall reaching surface and ground water sources of drinking water. There are residential uses of endothall, so there is likely to be exposure in residential or non-occupational settings. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is a potential for post-application exposure for workers re-entering treated fields.

No new toxicity data have been received since the previous risk assessment (D403274, J. Liccione, 03/18/2013). A detailed description of the toxicity data and metabolism information may be found in the risk assessment dated 11/09/09 (David Soderberg, D370448). This risk assessment considers all of the aforementioned exposure pathways based on the proposed new uses of endothall, but also considers the existing uses as well, particularly for the dietary and residential exposure assessments.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the

development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

The most recent human health risk assessment was conducted for proposed use of the dipotassium form of endothall on apples (D403274, 3/18/2013). No new toxicity and/or metabolism data have been received since the last risk assessment. This assessment includes summaries of these data from previous assessments (D403274, 3/18/2013). No significant changes have been made to the hazard characterization and toxicity endpoints for risk assessment since the 2013 risk assessment.

4.1 Toxicology Studies Available for Analysis

The toxicology database for endothall is complete and sufficient for hazard characterization and no additional studies are required at this time. HASPOC waived the requirements of the acute and subchronic neurotoxicity studies, and an immunotoxicity study.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

In rats, at an oral 0.9 mg/kg dose, blood half-life elimination was 1.8 hrs in males and 2.5 hrs in females. At 4.5 mg/kg dose, the half-life elimination was 13.9 hours in males; the half-life in females could not be calculated because of a double blood peak. In single oral or intravenous dose studies, endothall did not undergo any metabolic transformation and was excreted unchanged. The results of a multiple (15-day) oral administration study indicated that endothall was absorbed and excreted largely unchanged in the feces and urine. At 24 hours, the tissue distribution of the compound was extensive but low. By 48 hours, the compound was mostly undetectable.

4.2.1 Dermal Absorption

Dermal absorption in rats treated dermally for 24 hours with 0.0125 mg/cm^2, 0.0625 mg/cm^2, and 0.125 mg/cm^2 was estimated at 3.9%, 2.2% and 7.3%, respectively. Urinary excretion of [^{14}C]-Endothall equivalents was 2.3% of the applied dose at 0.125 mg/cm^2 dose level. Fecal excretion amounted to <0.1% at all dose levels. It was noted in the study report that application of the direct formulation of the use product (23.4 % endothall) caused severe skin irritation and ulceration.

Since endothall is so toxic at the portal of entry (e.g., skin), quantification of systemic toxicity and risk resulting from dermal exposure will not be done, and a dermal absorption factor will not be estimated. In the 21-day dermal toxicity study (MRID 4346520), severe dermal effects were observed at the lowest dose tested. Effects included erythema, edema, and fissuring and sloughing off of the skin.

4.3 Toxicology Effects

Endothall is a caustic chemical with toxicity being the result of a direct degenerative effect on tissue. The most sensitive effect of endothall following oral administration is direct irritation of the gastrointestinal system. This effect was evident in several species and in several studies. The dog is particularly sensitive to endothall toxicity. Orally, it attacks the canine digestive tract at relatively low doses and then the liver and kidneys at lethal doses. Endothall caused gastric epithelial hyperplasia in dogs treated with orally with endothall for 52 weeks (a no observed adverse effect level (NOAEL) was not determined). Proliferative lesions of the gastric epithelium were observed in F_1 parental male and female rats treated orally with endothall in a 2-generation reproduction study (a NOAEL was not identified).

In a dermal irritation study, endothall was an extreme irritant (category I). Although it was classified as a category III in an acute dermal toxicity study, endothall has been shown to be a severe irritant in a dermal absorption study and in a 21-day dermal toxicity study after one application. Based on all available data, endothall is classified as a severe dermal irritant. Endothall is also an extreme irritant by the acute oral and acute ocular routes of administration (category I), and is a skin sensitizer. In the eye irritation study, endothall technical was extremely irritating to the eye, and was also lethal to 4/6 rabbits tested. In the acute inhalation study, it was classified as category III however, there was irritation and other respiratory effects observed in 5-day and 28-day inhalation toxicity studies supporting the conclusion of the irritant effects of endothall.

Besides gastric irritant effects, decreased body weight was also a sensitive effect following endothall administration. The decreased body weights were most likely attributable to the constant and direct irritation of the gastric lining. In a developmental rat study, pregnant rats exhibited decreased body weight following oral treatment. Decreased body weight was also apparent in a developmental toxicity study in the rabbit (maternal and offspring). Decreased body weight was noted in a 90-day dietary study in the rat. Body weight loss occurred in dogs following a 13 week oral treatment with endothall. Body weight decrement was also identified in an oral carcinogenicity mouse study.

Dermally, endothall destroys the stratum corneum and then the underlying viable epidermis. In the 21-day dermal toxicity study, severe dermal effects were observed at the lowest dose tested, i.e., erythema, edema, and fissuring and sloughing off of the skin at the dose site at the lowest tested.

Pulmonary toxicity was evident in 5-day and 28-day inhalation toxicity studies in the rat. Pulmonary effects observed in the 5-day inhalation study included rales, labored respiration, pale lungs (gross necropsy), increased absolute and relative lung weights, subacute inflammation, alveolar proteinosis, and hemorrhage. The rales and labored respiration were noted daily (0 -1 hrs post-dosing, prior to next exposure, and during detailed examinations) in addition, decreased body weights and food consumption, effects on clinical chemistry parameters were noted. Although nasal histopathology was not performed in the 5-day inhalation study, inflammation, erosion, and ulceration were noted in the nasal passages of rats that died during the study. In the 28-day inhalation study, acute effects indicative of pulmonary toxicity included rales and labored respiration, which were observed daily (0 -1 hrs post-dosing, prior to next exposure, and during detailed examinations) in rats. In addition, increased lung weights and alveolar macrophages in both sexes were observed at scheduled necropsy. Nasal effects consisted of minimal olfactory

epithelial degeneration and mild goblet cell hypertrophy. At higher concentrations, subacute inflammation of the trachea, and degeneration of the olfactory and respiratory epithelium of the nasal passages. Rales and labored respiration were noted in rats that died during the study

Endothall does not cause pre-natal toxicity following *in utero* exposure to rats or rabbits nor pre- and post-natal toxicity following exposures to rats for two generations.

Endothall is classified as "not likely to be carcinogenic to humans" based on lack of evidence of carcinogenicity in mice or rats. It has no mutagenic potential.

The HASPOC (December 19, 2012) recommended a waiver for acute and subchronic neurotoxicity studies in rats to support the proposed uses of endothall based on the lack of neurotoxicity in the endothall database as well as other carboxylic acid pesticides. The HASPOC (September 26, 2013) also recommended waiving the immunotoxicity study.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

The FQPA SF was reduced to 1X for all scenarios except the chronic dietary assessment. For the assessment of risk following chronic dietary exposure, the FQPA Safety Factor for increased susceptibility to infants and children is reduced to 3X for the following reasons:

1) A lowest observed adverse effect level (LOAEL) established in the two-generation reproduction study was used for assessing chronic dietary risks. Since a LOAEL was used, a 3X FQPA Safety Factor in the form of UF_L is retained for chronic exposure scenarios. A 3X factor (as opposed to a 10X) was determined to be adequate since the severity of the lesions were minimal to mild. HED is confident that the chronic Population Adjusted Dose (cPAD = 0.007 mg/kg/day) will not underestimate risks following exposure to endothall.
2) There is no indication of increased susceptibility of rats or rabbits *in utero* and/or postnatal exposure in the developmental and reproductive toxicity studies;
3) There are no concerns for neurotoxicity;
4) There are no residual uncertainties in the exposure database.

4.4.1 Completeness of the Toxicology Database

The toxicological database for endothall is complete and adequate for FQPA evaluation, selection of points of departure (PODs) for the various routes of exposure, and for dose-response evaluation. HASPOC recommended waiving the requirements for immunotoxicity, acute neurotoxicity and subchronic neurotoxicity studies.

4.4.2 Evidence of Neurotoxicity

There is no evidence of neurotoxicity in the endothall database. Acute and subchronic neurotoxicity studies are not available for endothall. However, the HASPOC (December 19, 2012) recommended waiving the acute and subchronic neurotoxicity studies in rats to support the proposed uses of endothall.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There is no quantitative or qualitative evidence of increased susceptibility following prenatal exposure to rats or rabbits in developmental toxicity studies, and pre- and post-natal exposure to rats in the 2-generation reproduction study.

4.4.4 Residual Uncertainty in the Exposure Database

Non-dietary exposure. The residential post-application exposure assessments are based upon the 2012 Residential Standard Operating Procedures (SOPs). These assessments of exposure are not likely to underestimate exposure to endothall.

Dietary exposure. There is no residual uncertainty in the exposure database for endothall with respect to dietary exposure. An adequate database with respect to both the nature and magnitude of residues expected in food has been provided. The chronic dietary food exposure assessment is conservative as field trial data along with 100% of crop treated assumptions for some commodities, and default processing factors for some commodities were used. Also, conservative modeled drinking water estimates of exposure were included in the assessments likely to generate the highest exposures (treatment of a reservoir).

4.5 Toxicity Endpoint and Point of Departure Selections

HED selected the following toxicity endpoints (and points of departure) for chronic dietary, incidental oral and inhalation scenarios which are the same that were used in the previous risk assessment. Additional studies in the database were not updated to reflect current policies since these changes would not affect current PoDs and the selected endpoints are protective of all effects seen in the endothall database.

Acute Dietary: An acute dietary hazard value was not identified for the general population or for females of child-bearing age (13-49 years old). This is because there is no appropriate endpoint attributable to a single dose in any of the studies submitted.

Chronic Dietary: For chronic dietary exposure, the toxicology endpoint was selected from a 2-generation reproduction toxicity study in rats in which the LOAEL was 2 mg/kg/day based on proliferative lesions of the gastric epithelium in both sexes. The Uncertainty Factor includes the 10x for interspecies extrapolation and 10x for intraspecies variation, and an additional 3x FQPA factor for the lack of a NOAEL in the study used for endpoint selection. A 3X FQPA factor (as opposed to a 10X) was determined to be adequate since the severity of the lesions were minimal to mild.

Dermal: Since endothall is so toxic at the portal of entry (e.g., skin), quantification of systemic toxicity and risk resulting from dermal exposure will not be done, and a dermal absorption factor will not be estimated. In the 21-day dermal toxicity study (MRID 4346520), severe dermal effects were observed at 30 mg/kg/day (the lowest dose tested). The NOAEL for dermal irritation was not established due to erythema, edema, and fissuring and sloughing off of the skin at the dose site at the lowest dose tested (30 mg/kg/day). Endothall is caustic dermally because it is an acid, and mitigation of any potential dermal effects can be addressed with precautionary

labeling recommending the use of gloves and other personal protection which limits contact of the material with the handler's body.

Inhalation: Residential handler exposure is expected to be short-term in duration. For this short-term inhalation exposure scenario, a NOAEL of 0.001 mg/L was selected from a 28-day inhalation toxicity study in the rat based on clinical signs of toxicity observed acutely at 0.005 mg/L. These signs, indicative of pulmonary toxicity, included rales and labored breathing and were seen daily (0-1 hr postdosing, prior to next exposure, and in detailed examinations). Although the 5-day inhalation study also revealed acute signs of pulmonary toxicity, a NOAEL was not identified, but the results of the study support the findings of the 28-day inhalation study. Therefore, the NOAEL for acute signs noted in the subchronic inhalation study was selected for the short-term residential exposure scenario. Intermediate-term exposures are not likely because of the intermittent nature of applications by homeowners.

For the short- and intermediate- term occupational inhalation risk assessment, a NOAEL = 0.001 mg/L was selected from a 28-day inhalation toxicity study in the rat in which the LOAEL was 0.005 mg/L based on indications of lung toxicity (rales in males and increased lung weights and alveolar macrophages in both sexes). Long-term inhalation exposures are not anticipated.

Incidental Oral: The short-term incidental oral risk assessment for endothall is based on a NOAEL of 9.4 mg/kg/day based on decreased pup body weight (both sexes) on Day 0 of the $F_1$and F_2 generations in a 2-generation rat reproduction (oral feeding) study. This endpoint is appropriate with respect to the duration and population of concern (i.e., swimmers incidental oral ingestion in adult and children). The current short-term incidental oral endpoint (NOAEL of 9.4 mg/kg/day) is protective of potential gastric lesions in the offspring. The development of gastric lesions is dependent on the duration of exposure. For example, in the 2-generation reproductive toxicity study in rats, the gastric lesions were seen in the F1 parental animals but not F0 parental animals. In addition, the toxicity database supports the conclusion that the short-term incidental endpoint is protective of gastric lesions in the offspring. It was noted that the acute oral LD_{50} (= 50.2 mg/kg) is greater than the offspring NOAEL. Additionally, no gastric lesions were observed in the subchronic oral rat and dog studies with endothall amine. Although there were no subchronic toxicity studies on the disodium or dipotassium endothall, at expected use conditions, all forms of endothall will be in the ionized state. The acute and subchronic oral toxicity studies in the rat, and the subchronic oral dog study, were conducted with a higher percentage of active ingredient compared with 2-generation reproductive toxicity rat study.

Intermediate- and long-term incidental oral exposures are not expected.

4.5.1 Recommendation for Combining Routes of Exposures for Risk Assessment

Dermal exposure was not quantitatively assessed due to a lack of toxicity via the dermal route. Post-application oral and inhalation exposure was assessed for adult and child swimmers; however, oral and inhalation exposure should not be combined because the endpoints are different. For occupational workers, only inhalation exposure and risk were assessed.

4.5.2 Cancer Classification and Risk Assessment Recommendation

HED classified endothall as "not likely to be carcinogenic to humans" according to the EPA *Draft Proposed Guidelines for Carcinogen Risk Assessment* (July 2, 1999). This classification is based on the lack of evidence of carcinogenicity in mice and rats.

4.5.3 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.3.1. Summary of Toxicological Doses and Endpoints for Endothall for Use in Dietary, Non-Occupational and Occupational Human Health Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment	UF/FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary	An appropriate endpoint attributable to a single dose was not available from any study. An acute RfD was not established.		
Chronic Dietary (All populations)	LOAEL= 2 mg/kg/day	UF_A = 10X UF_H = 10X FQPA UF_L = 3X **cRfD** = 0.007 mg/kg/day **cPAD** = 0.007 mg/kg/day	Rat 2-generation reproduction study LOAEL 2 mg/kg/day based on proliferative lesions of the gastric epithelium (both sexes)
Short-Term Incidental Oral	Offspring NOAEL = 9.4 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X **Residential** LOC for MOE = 100 **Occupational** = NA	Rat 2-generation reproduction study LOAEL 60 mg/kg/day based on decreased pup body weight (both sexes) on Day 0 $F_1$and F_2 generations
Short and Intermediate-Term Dermal	Since endothall is so toxic at the portal of entry (e.g., skin), quantification of systemic toxicity and risk resulting from dermal exposure will not be done, and a dermal absorption factor will not be estimated. In the 21-day dermal toxicity study (MRID 4346520), severe dermal effects were observed at 30 mg/kg/day (the lowest dose tested). The NOAEL for dermal irritation was not established due to erythema, edema, and fissuring and sloughing off of the skin at the dose site at the lowest dose tested (30 mg/kg/day). Endothall is caustic dermally because it is an acid, and mitigation of any potential dermal effects can be addressed with precautionary labeling recommending the use of gloves and other personal protection which limits contact of the material with the handler's body.		
Long-Term Dermal	NA - no exposure under use pattern		
Short-Term Inhalation	NOAEL = 0.001 mg/L Residential HEC = 0.00049 mg/L (HED = 0.0143 mg/kg/day)[A] Occupational	UF_A = $3X^C$ UF_H = 10X FQPA SF = 1X **Residential** LOC for MOE = 30	Subchronic inhalation toxicity study (MRID 47872201). Residential acute scenario: LOAEL = 0.005 mg/L based on clinical signs (rales and labored respiration) observed acutely (0-1 hr postdosing and prior to next exposure).

Table 4.5.3.1. Summary of Toxicological Doses and Endpoints for Endothall for Use in Dietary, Non-Occupational and Occupational Human Health Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment	UF/FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
	HEC = 0.0004 mg/L (HED = 0.021, 0.043, 0.074 mg/kg/day)[B]	**Occupational** LOC for MOE = 30	Occupational short-term scenario: LOAEL = 0.005 mg/L based on indications of lung toxicity (rales in males and increased lung weights and alveolar macrophages in both sexes). The NOAEL is 0.001 mg/L.
Intermediate-Term Inhalation	NOAEL = 0.001 mg/L Occupational HEC = 0.0004 mg/L (HED = 0.021, 0.043, 0.074 mg/kg/day)[B]	$UF_A = 3X^C$ $UF_H = 10X$ **Occupational** LOC for MOE = 30	Subchronic inhalation toxicity study (MRID 47872201). LOAEL = 0.005 mg/L based on indications of lung toxicity (rales in males and increased lung weights and alveolar macrophages in both sexes).
Long-Term Inhalation	NA no exposure under this use pattern		
Cancer (oral, dermal, inhalation)	Classified as a "Not Likely" human carcinogen.		

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

[A] Residential Exposures are anticipated only briefly (half hour) once a month and are acute. Residential HEC (pulmonary effect) = 0.001 mg/L * (6hr/6 hr; 1.0) * (1d/1d; 1) * pulmonary RDDR (0.499) = 0. 00049 mg/L

Residential HED = 0.00049 mg/L x ventilation rate (16.7 L/min) x relative specific activity (1.2) x human daily duration (2) = 0.0143 mg/kg/day.

[B] Refer to the table below. Occupational HEC (pulmonary effect) = rat POD * (daily duration adjustment) * weekly duration adjustment * RDDR = 0.001 mg/L * (6 hr /8 hr ; 0.75) * (5d/5d; 1)* pulmonary RDDR (0.499) = 0. 0004 mg/L.

Occupational HED (pulmonary) = HEC * human specific conversion factor * daily duration * relative activity factor (0.6 for 8.3 L/min ventilation rate; 1.2 for 16.7 L/min ventilation rate; and 2.1 for 29 L/min ventilation rate) = HEC (0.0004 mg/L) * 11.8 L/hr/kg BW * 8 hrs * relative activity factor (1.2).

Ventilation rates (L/min)	HED (mg/kg BW/day)
8.3	0.021
16.7	0.043
29	0.074

4.6 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for endothall, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), endothall are subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013 (final version published in June 26, 2014[1]) and includes some pesticides scheduled for Registration Review and chemicals found in water. 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.[2]

In the interim, EPA is making no human health or environmental safety findings associated with the EDSP screening of endothall. Before completing this Registration Review, the Agency will make an EDSP FFDCA section 408(p) determination.

5.0 Dietary Exposure and Risk Assessment

[1] See http://www2.epa.gov/endocrine-disruption/final-second-list-chemicals-tier-1-under-endocrine-disruptor-screening-program.
[2] http://www.epa.gov/endo/

5.1 Residues of Concern Summary and Rationale

Residue Chemistry Memo: K. King, D426753 and D428908, *In Progress*

The residues of concern for risk assessment and the tolerance expression are summarized in Table 5.1. The metabolism in plants and animals is qualitatively similar; parent endothall is the major residue while the major metabolite is the monomethyl ester with minor formation of the dimethyl ester. Upon further metabolism, endothall is rapidly broken down and incorporated into tissues as natural constituents. By combining information from soil and water metabolism, there is sufficient information on rotated crops to conclude that the residues of concern remain the same in rotated crops.

The residue of concern definition for endothall was reevaluated as part of registration review based on comments from the registrant indicating that the monomethyl ester is not a significant residue in plants and therefore it does not need to be quantitated by the data acquisition methods (e-mail communication from Garland Waleko, 11/18/2015). HED understands that parent endothall is an adequate marker of misuse in plants as it is the only or main residue observed in metabolism studies with sugar beets (64% TRR in tops and 37% TRR in roots), cotton (76-102% TRR in forage and 18% in seed) and alfalfa (99% TRR in forage, 103% TRR in seed) (S. Funk, 10/07/96). The monomethyl ester was observed in half mature sugar beets (48 day PHI) at 12% of the TRR (tops) and 22% of the TRR (roots) after soil application, in alfalfa forage (9 day PHI) at 3.6% of the TRR, and in alfalfa seed (9 day PHI) at 4.4% of the TRR. It was not observed in cotton and was not measured in mature sugar beets which showed a TRR lower than 0.016 ppm. Based on this, parent endothall is considered the residue of concern for tolerance enforcement. Although the tolerances established in the 40 CFR § 180.293 for plant commodities may have contribution from the monomethyl ester the metabolism studies suggest that the main residue is parent endothall and an appropriate marker of misuse as well. The tolerances are not likely to underestimate the residue levels and are considered adequate for enforcement purposes as are not likely to be significantly overestimated. Metabolism studies reflect the direct uses of endothall as an herbicide in sugar beets, desiccant in alfalfa and defoliant in cotton. Currently, tolerances for indirect uses (i.e. irrigation with water containing residues of endothall) are established for a great variety of crops with tolerances ranging from 0.01 ppm to 35 ppm. Because the analytical methods are based on the conversion of endothall and monomethyl ester to a common moiety is not possible to obtain additional information about the fate of endothall in crops (specially irrigated crops). Therefore, based on the lack of additional information and similar toxicity assumed for parent endothall and the monomethyl ester, both are still considered the residues of concern for risk assessment.

The monomethyl ester is a significant residue in livestock commodities, especially in poultry where it is at higher concentration than parent endothall. Therefore, parent endothall and its monomethyl ester are the residues of concern for tolerance and risk assessment in livestock commodities. Endothall acid is the major residue observed in the environmental fate studies so is included in the drinking water assessment. Endothall monomethyl ester has similar structure as the parent compound, so is assumed to have equal toxicity. Further information on the metabolism may be found in the residue chemistry chapter dated 08/30/2005 (DP# D321179, D. Soderberg).

Table 5.1. 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	Endothall and its monomethyl ester	Endothall
	Rotational Crop[2]		
Livestock	Ruminant	Endothall and its monomethyl ester	Endothall and its monomethyl ester
	Poultry		
Drinking Water		Endothall Acid	Endothall Acid[3]

[1] Endothall is 7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid.
[2] It is expected that the residues in crops resulting from irrigation with treated water cover those from crops planted in rotation with endothall treated crops (i.e. rice, cotton and potatoes); therefore, field rotational studies have been waived (D. Soderberg, D387313, 05/03/2011).
[3] A maximum contaminant level for endothall in water is established by the Office of Water.

5.2 Food Residue Profile

The nature of the residues in plants and livestock is adequately established based on acceptable alfalfa, cotton, sugar beet, poultry and goat metabolism studies. Tolerances are established in the 40 CFR § 180.293 for the use of endothall on apple, cotton, hop, potato and rice. In addition, tolerances are established for inadvertent residues of endothall in/on all crop commodities to support the use of water treated with endothall for irrigation purposes. Generally, tolerances for food commodities range from 0.05 for tree nuts to 5.0 ppm for herbs. In addition, tolerances established for endothall on meat, milk, poultry, eggs and fish range from 0.005 ppm for hog/sheep fat to 0.2 ppm for poultry by products.

As part of registration review, the residue chemistry database for endothall was reevaluated. Several deficiencies identified in the 2005 registration eligibility decision (D. Soderberg, D321179, 08/30/2005) have been satisfied with the submission of a livestock enforcement method, and irrigation, feeding, and storage stability studies. A summary of these deficiencies and a reference to the document in which these are resolved is included in Appendix F. Although recovery of the monomethyl ester of endothall by the data acquisition and enforcement methods used for plants has not been tested, recovery has been demonstrated for the parent compound. Based on the conservative nature of the dietary assessment it is not likely that the absence of these data will result in underestimation of the dietary risk.

5.3 Water Residue Profile

A drinking water exposure assessment was conducted by the Environmental Fate and Effects Division (EFED) to support the human health risk assessment for the proposed use of endothall-treated irrigation water on a variety of crops (J. Lin, D404321, 9/12/12). Based on personal communication between Brian Anderson of EFED and Michael Metzger of HED, the drinking water estimates from the 2012 assessment are still adequate for chronic dietary assessment. The estimated concentrations use the simple first-order degradation model, assuming either static (no flow) or varying water turnover rates in the farm water body. Endothall concentrations

degraded with first-order kinetics starting immediately after application. The maximum potential exposure of endothall in drinking water sources is expected to result from the direct application of endothall to drinking water reservoirs to control aquatic weeds. EFED assumed that the entire reservoir would be treated at the maximum rates, with no more than 10% of the reservoir treated at one time as stated on the label, so that 10 treatments were applied 7 days apart to treat the entire reservoir. Since the label specified that the community water system (CWS) could not supply treated drinking water unless the residues were below 0.1 ppm (100 µg/L), EFED assumed 100 µg/L (0.1 ppm) as the acute (peak) exposure and the constant exposure during the treatment period and then modeled residue decline by degradation after the final treatment. This resulted in a chronic (annual average) concentration of 31 µg/L (0.031 ppm) for endothall. This represents a conservative estimate of high-end chronic exposure from endothall from the use most likely to generate the highest exposures (treatment of a reservoir).

Table 5.3 Summary of Estimated Surface Water and Groundwater Concentrations for Endothall.

Scenario	Groundwater Conc., ppb
Acute	100
Chronic (non-cancer)	31
J. Lin, D404321, 9/12/12	

5.4 Dietary Risk Assessment

Dietary Exposure and Risk Memo: K. King, D426752, *In Progress*

5.4.1 Description of Residue Data Used in Dietary Assessment

Average residue values have been used for all crops. The residue and processing data used in this assessment are from residue field trials and processing studies designed to produce maximum residues for the purpose of setting tolerances. All treatments in the field trials with irrigated crops were performed by overhead irrigation (i.e. are sprayed on the crops). The processing data available were translated to the important processed commodities of all crops. Where data were not available, DEEM default factors were used.

Anticipated residues of meat, milk, poultry, and eggs have been estimated by using the maximum or average residues in feed stuffs as well as the maximum allowed 5 ppm concentration of endothall in livestock drinking water. Tolerance level residues were used for finfish and shellfish. Overall, the results are likely to be conservative.

The EFED used conservative modeling to estimate the levels of the chronically available residues in drinking water. The estimated drinking water concentration used represents a conservative estimate of high-end chronic exposure from endothall from the use most likely to generate the highest exposures (treatment of a reservoir).

5.4.2 Percent Crop Treated Used in Dietary Assessment

BEAD has provided percent crop treated (PCT) data for three crops with registered agricultural uses of endothall as well as another updated PCT assessment that had to be completed in order to

provide a better estimate of the percent of crops that are irrigated. The assessment is conservative because it assumes that all irrigated crops will use endothall treated water.

The following average percent crop treated estimates (LUIS Report of 12/31/2014) due to direct uses of endothall were used in the chronic dietary risk assessment for the following crops: alfalfa <1%, cotton <1%, and potatoes <2.5%. In addition, BEAD estimated PCT of irrigated crops. Estimated average percent crop treated for chronic dietary risk assessment was: apple 78%, fresh market apple 84%, processing apple 49%, apple juice 22%, canned apple 55%, barley for grain 40%, corn for grain 21%, dry beans 35%, grape 97%, fresh market grape 99%, processed grape 96%, green peas 42%, oats for grain 8%, peanut for nuts 34%, rice 100%, sorghum for grain 19%, soybean for beans 12%, strawberry 92%, fresh market strawberry 90%, processed strawberry 100%, sugarbeet for sugar 37%, sugarcane for sugar 54%, watermelon 38%, wheat for grain 13%.

5.4.3 Acute Dietary Risk Assessment

No acute exposure and risk assessment has been performed as no acute endpoint has been established for endothall.

5.4.4 Chronic Dietary Risk Assessment

A refined, chronic dietary exposure and risk assessment was conducted incorporating both food and water residues. Typically, HED has concerns regarding dietary risk when the exposure estimates exceed 100% of the chronic population adjusted dose (cPAD). The Summary Table 5.4.6 includes the exposure and risk estimates for endothall. The estimated exposure (food and water) to the U.S. population from the existing uses of endothall resulted in an estimated risk equivalent to 32% of the cPAD. The most highly exposed population subgroup is children 1-2 years of age with an exposure equivalent to an estimated risk of 90% of the cPAD. The estimated exposure (food only) to the U.S. population from the existing and proposed new uses of endothall resulted in an estimated risk equivalent to 23% of the cPAD. The most highly exposed population subgroup is children 1-2 years of age with an exposure equivalent to an estimated risk of 77% of the cPAD.

5.4.5 Cancer Dietary Risk Assessment

Endothall is classified as “Not likely to be carcinogenic to humans”; therefore, a quantitative cancer risk assessment was not performed.

5.4.6 Summary Table

Table 5.4.6. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Endothall		
Population Subgroup	**Chronic Dietary**	
	Dietary Exposure (mg/kg/day)	**% cPAD***
General U.S. Population	0.002247	32
All Infants (< 1 year old)	0.004492	64
Children 1-2 years old	**0.006317**	**90**
Children 3-5 years old	0.004636	66
Children 6-12 years old	0.002572	37
Youth 13-19 years old	0.001486	21
Adults 20-49 years old	0.001944	28
Adults 50+ years old	0.002008	29
Females 13-49 years old	0.001888	27

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Occupational and Residential Exposure and Risk Memo: S.Tadayon, D428969, *In Progress*

6.1 Residential Handler Exposure

There are no registered residential uses resulting in residential handler exposure to endothall. Therefore, a quantitative residential handler exposure assessment was not performed.

6.2 Residential Post-application Exposure/Risk Estimates

Endothall is registered for use in lakes and ponds for control of nuisance aquatic weeds. As a result, individuals can be exposed to endothall residues in water by entering these areas if they have been previously treated. Of the possible post-application exposures, swimming in treated water is considered by HED to be worse case and is used as a surrogate for all other possible post-application exposures, such as wading, water skiing, etc. The extent of exposure during recreational swimming is assumed to be short-term in duration. Risks estimates were calculated for inhalation and incidental oral ingestion while swimming in treated lakes or ponds. Post-application dermal assessments are not needed since there is no short-term systemic dermal hazard.

The scenarios, routes of exposure and lifestages assessed include:

- Inhalation exposure during recreational swimming (both adults and children 3 < 6 years old).
- Ingestion of water during recreational swimming (both adults and children 3 < 6 years

old).

The Agency considered residential post-application exposure for different segments of the population. The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[3]. These lifestages are not the only lifestages that could be potentially exposed for these post-application scenarios; however, the assessment of these lifestages is health protective for the exposures and risk estimates for any other potentially exposed lifestages.

The swimmer calculations have been updated from the previous assessment to reflect the revised body weights for adults and children. Also the water ingestion rates and the time spent in the water have been revised to correspond with the 2012 Residential SOPs. The average body weight of an adult female (i.e., 69 kilograms) is used for assessing incidental oral ingestion for adults since the toxicity endpoint selected is based on a reproductive study where developmental and/or fetal effects were observed. For children 3 to < 6 years old swimming in endothall treated water a body weight of 19 kg was used. The level of concern for adults and children (3 to < 6 years old) for short-term, inhalation exposures is MOEs < 30. The level of concern for adult females and children (3 to < 6 years old) for short-term, incidental oral exposures is MOEs < 100.

Residential Post-application Non-Cancer Exposure and Risk Equations

The equations and inputs are generally derived from SWIMODEL 3.0, developed by EPA as a screening tool to conduct exposure assessments of pesticides found in swimming pools and spas. It uses well-accepted screening exposure assessment equations to calculate the high end exposure for swimmers expressed as a mass-based intake value (mg/event). The model focuses on potential chemical intakes only and does not take into account metabolism or excretion of the chemical of concern. Detailed information and the downloadable executable file are available at http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/swimmer-exposure-assessment-model-swimodel, however, some of the inputs and parameters have been updated and are outlined below. The equations as provided in the SWIMODEL User's Manual (version 3.0) were used in a spreadsheet format to estimate the exposures.

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

Table 6.2.1 presents the post-application inhalation and incidental oral ingestion MOE values calculated for adults and children 3 to <6 years old after aquatic applications of endothall dipotassium. Post-application risk estimates do not exceed HED's level of concern for any of the scenarios assessed. MOEs for inhalation exposures were 5 x 10 ^{9} for adults and 3 x 10 ^{9} for children 3 to <6 years old. MOEs for oral exposures were 1,700 for adults and 250 for children 3 to <6 years old.

Table 6.2.1: Residential Post-application Non-cancer Exposure and Risk Estimates for Endothall (Swimmer Scenario)

Exposure Scenario	Level of Concern (LOC)	Maximum Concentration in Water [1] (mg/L)	Dose (mg/kg/day) [2,3]	Short-term MOE [4]
Inhalation, Adult-(Female)	30	5	2.7 x 10- ^{12}	5 x 10 ^{9}
Inhalation, Child 3 to <6 years old	30	5	5.1 x 10- ^{12}	3 x 10 ^{9}
Ingestion of water, Adult-(Female)	100	5	0.0056	1,700

[3] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Ingestion of water, Child 3 to <6 years old	100	5	0.0383	250

Notes: 1. Maximum concentration in water (top 1 ft.) = 5 mg/L. based on maximum application rate from registered labels for aquatic weed control: 0.00022 lb ai/ft^3 (EPA Reg.4581-388-82695).
2. Inhalation exposure dose (mg/kg/day) = chemical vapor concentration, v_p (7.8 x 10^{-11} mg/L) x inhalation rate, IR (0.64 m3 /hr adults and 0.42 m3/hr children 3 to < 6) x exposure time, ET (3.7 hr adults and 3 hr children 3 to < 6)
(hrs/d) x 1/BW (adult-female=69 kg; children (3 to < 6) = 19 kg)
3. Oral exposure dose (mg/kg/day) = concentration, C_w (5 mg/L) x ingestion rate (IgR), IgR (0.021 L/hr adults and 0.049 L/hr children 3 to < 6) x exposure time, ET (3.7 hr adults and 3 hr children 3 to < 6)
(hrs/d) x 1/BW (adult-female=69 kg; children (3 to < 6) = 19 kg)
4. MOE = NOAEL or HEC/Exposure dose; short-term inhalation HEC= 0.0143 mg/kg/day; short-term incidental oral NOAEL = 9.4 mg/kg /day. The LOC for adult females and children (3 to < 6) for short-term inhalation exposures is MOEs < 30; The LOC for adult females and children (3 to < 6) for short-term incidental oral exposures is MOEs < 100.

6.3 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.3.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for endothall.

- The recommended residential exposure for use in the adult short-term aggregate assessment reflects residential post-application incidental oral (water ingestion) exposure from swimming in treated aquatic areas.
- The recommended residential exposure for use in the children 3 to < 6 years old short-term aggregate assessment reflects incidental oral (water ingestion) exposure from post-application exposure to treated aquatic areas.

Table 6.3.1. Recommendations for the Residential Exposures for the Endothall Aggregate Assessment.[1] (Aquatic Scenarios)

Lifestage	Residential Post-application Total Exposure (mg/kg/day)[2]	Residential Post-application MOE[3] LOC = 100
Adult Female	**0.0056**	**1,700**
Child (3 to <6 years old)	**0.0383**	**250**

[1] Bolded risk estimates should contribute to the residential exposure portion of the aggregate assessment.
[2] Residential Post-application Dose = the highest post-application dose for each applicable lifestage of all scenarios assessed from Table 6.2.1. Total = incidental oral only.
[3] Residential Post-application MOE = the MOEs associated with the highest doses identified in Table 6.2.1. Total = incidental oral only.

6.4 Residential Bystander Post-application Inhalation Exposure

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219).

During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for endothall.

6.5 Spray Drift

Endothall is a systemic herbicide, meaning its herbicidal mode of action required it to be absorbed and translocated in the weeds. It is not a contact herbicide and thus the application method is not as a broadcast application meant to cover the surface area of the weeds. It is applied in a directed manner, usually using a hose, wand or meter, as a surface or subsurface application to water in order to maintain a specified herbicide concentration in the water body to control aquatic weeds systemically. The large/coarse droplet size and directed spray methods greatly reduce the spray drift potential for aquatic applications. As the application methods are not conducive to spray drift as described and assessed as part of the spray drift policy, a quantitative spray drift assessment is not required for the aquatic uses of the herbicide.

Endothall has direct uses on crops as well. Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment includes assessing exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an exposure scenario. Aside from the predicted residues available for transfer, the routes of exposure and assessment methodology is analogous to how exposures to turf products are considered in risk assessment.

No dermal endpoint was selected because the dermal irritation observed in a repeated-dose study is considered self-limiting. Therefore, dermal risk estimates were not calculated for children 1< 2 or adults. Incidental oral risk estimates for children 1<2 years old was calculated. The applicable LOC is 100 so MOEs < 100 represent risk estimates of concern. Children's (1<2 year old) incidental oral risk estimates from indirect exposure to endothall related to spray drift result in acceptable MOEs at the field edge for aerial, airblast and groundboom applications based on the screening level scenarios. Results are presented in Table 6.5.1, and indicate that there is no risk of concern from airblast, aerial or groundboom applications.

Table 6.5.1 Spray Drift Risk Estimate for Endothall

Crop/Rate Group	Spray Type/ Nozzle Configuration	Application Rate (lb ai/A)	Estimated TTRt (ug/cm^2)[a]	At Edge HtM MOE
Aerial	***Fine to Medium***	1	0.011	2,400
Groundboom	***High Boom Very fine to Fine***			3,300
Airblast	***Sparse***			4,300

a. TTR = Application Rate × F × $(1\text{-}D)^t$ × 4.54E8 µg/lb × 2.47E-8 $acre/cm^2$; where F = 0.1 and D = 0.10 per day

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

7.1 Acute Aggregate Risk

An appropriate acute oral endpoint attributable to a single dose was not available from any study, including the prenatal developmental toxicity study in rats. Based on the absence of an acute endpoint an acute aggregate risk assessment is not quantitatively assessed.

7.2 Short-Term Aggregate Risk

The oral endpoint selected to assess the risk of endothall from short-term incidental oral exposure is based on decreased pup weight. Moreover, orally, endothall damages the digestive tract at relatively low doses and then the liver and kidneys at lethal doses. On the other hand, the inhalation endpoint is based on lung toxicity. Based on the difference between the oral and inhalation endpoints, an assessment aggregating these different routes of exposure is not appropriate. However, an aggregate assessment adding exposures from food and water with those from incidental ingestion of treated water (swimmers) is needed. This assessment is presented in Table 7.2. Adult and children's post-application oral exposure (Table 6.3.1) were combined with the chronic dietary exposure from the mostly highly exposed adult (Adults 50+) and children's (Children 1-2 years old) subpopulations (Table 5.4.6), respectively, to determine aggregate exposure and risk as shown in Table 7.2. Despite the numerous conservative assumptions in developing these estimates, the MOEs are above the LOC of 100, and are not of concern.

Table 7.2 Short-Term Aggregate Risk Calculations

Population	Short- or Intermediate-Term Scenario						
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day[3]	Total Exposure mg/kg/day[4] Oral	Aggregate MOE (food, water, and residential)[5]
Adult	9.4	100	0.094	0.00201	0.0056	0.00761	1,200
Child	9.4	100	0.094	0.00632	0.0383	0.0446	210

[1] The LOC is based on standard inter- and intra- species uncertainty factors totaling 100.
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC
[3] Residential Exposure = Oral exposure from incidental ingestion of treated water while swimming, refer to Table # 6.3.1.
[4] Total Exposure = Avg Food & Water Exposure + Residential Exposure
[5] Aggregate MOE = NOAEL / (Avg Food & Water Exposure + Residential Exposure)

7.3 Intermediate-Term Aggregate Risk

Intermediate-term exposure is not expected to result from the residential uses of endothall.

7.4 Chronic Aggregate Risk

The chronic aggregate assessment is represented by the chronic dietary risk assessment which considers exposures from food and drinking water; refer to section 5.4.4. Chronic exposure is not expected to result from the residential uses of endothall.

7.5 Cancer Aggregate Risk

Endothall is classified as "Not likely to be carcinogenic to humans" through the oral, dermal and inhalation routes of exposure. Therefore, a quantitative cancer aggregate assessment is not needed.

8.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to endothall and any other substances and endothall does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that endothall has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Characterization

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the registered uses on agricultural crops and aquatic areas (S.Tadayon, D428969, *In Progress*).

9.1 Short- and Intermediate-Term Handler Risk

The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios which cover all the registered uses of endothall:

- Mixing/loading liquids to support aerial applications,
- Mixing/loading granular to support aerial applications,
- Mixing/loading liquids to support airblast applications
- Mixing/loading liquids to support groundboom applications,
- Applying sprays with groundboom equipment,
- Applying sprays with airblast application,
- Applying sprays with aircraft,
- Mixing/loading/applying with direct metering equipment (aquatic uses),
- Mixing/loading/applying with hose end sprayer (aquatic uses),

- Mixing/loading/applying with granular spreader (aquatic uses),
- Flagging to support aerial spray and spreader applications.

The registered labels require occupational handlers to wear the following personal protective equipment (PPE): long-sleeved shirts, long pants, chemical resistant gloves, protective eyewear and dust mist respirator (TC-21C).

The results of the occupational handler exposure and inhalation risk assessment for the agricultural scenarios (i.e., harvest aid and blossom thinner products) indicate that short- and intermediate-term inhalation risks do not exceed HED's LOC (i.e., an MOE > 30) at the label recommended PPE (i.e., dust/mist respirator). The MOEs range from 31 to 2,900.

The results of the occupational handler exposure and inhalation risk assessment for aquatic products indicate that some short- and intermediate-term inhalation risks exceed HED's LOC (i.e. an MOE < 30) at the label recommended PPE, and even with a closed system (i.e., engineering control). The MOEs range from 1 to 873.

Dermal handler and post-application exposure and risk assessments were not conducted because a systemic dermal hazard was not identified for endothall.

The inhalation toxicology study was conducted with a dust aerosol formulation which by far results in higher respirable particles than other formulations, and therefore higher exposure. Since the application the dipotassium salt, one of the two granular formulations, results in no respirable particles, there is no inhalation risk concern for this formulation Attrition studies or studies addressing the formation of respirable particles for other granular end-use products, e.g. Hydrothol 191 Granular, are not available. As such, risks of concern are associated with some aquatic uses of these formulations, as shown in Table 9.1.2.

Table: 9.1.1. Short- and Intermediate-Term Occupational Risk assessment for Agricultural uses Endothall

Exposure Scenario	**Crop or Target[a]**	**Baseline Inhalation Unit Exposure[b] (unless otherwise noted)**	**Maximum Application Rate[c]**	**Area Treated or Amount Handled Daily[d]**	**Baseline Inhalation Unless otherwise noted**	
					Dose[e]	**MOE[f]**
		µg/lb ai	***lb ai/A or lbai/gal***	***Acres or gals***	***mg/kg/day***	***LOC = 30***
Mixer/Loader Emulsifiable Concentrate						
Mixing/Loading Liquids for Aerial Application	Typical Field Crops[1]	0.219 (0.044 PF5)	1	350	0.00096	45
	High-Acreage Field Crops[2]		0.8	1200	0.00053 (PF5)	80
	High-Acreage Field Crops[3]		0.1		0.00033	130
Mixing/Loading Liquids for Groundboom Application	Typical Field Crops[1]		1	80	0.00022	200
	High-Acreage Field Crops[2]		0.8	200	0.00044	98
	High-Acreage Field Crops[3]		0.1		0.00005	780
Mixing/Loading Liquids for Airblast Application	Orchard Crop[4]		0.4	40	0.000044	980
			1		0.00011	390
Applicator						

Table: 9.1.1. Short- and Intermediate-Term Occupational Risk assessment for Agricultural uses Endothall						
Exposure Scenario	**Crop or Target[a]**	**Baseline Inhalation Unit Exposure[b] (unless otherwise noted)**	**Maximum Application Rate[c]**	**Area Treated or Amount Handled Daily[d]**	**Baseline Inhalation Unless otherwise noted**	
					Dose[e]	**MOE[f]**
		µg/lb ai	***lb ai/A or lbai/gal***	***Acres or gals***	***mg/kg/day***	***LOC = 30***
Applying Sprays for Aerial Application	Typical Field Crops[1]	0.0049 (engineering controls)	1	350	0.00002	980
	High-Acreage Field Crops[2]		0.8	1200	0.00006	360
	High-Acreage Field Crops[3]		0.1		0.0000074	2900
Applying Sprays for Groundboom Application	Typical Field Crops[1]	0.34	1	80	0.0003	62
	High-Acreage Field Crops[2]		0.8	200	0.0007	31
	High-Acreage Field Crops		0.1	200	0.00009	250
Applying Sprays for Airblast Application	Orchard Crop[4]	0.942(PF5)	0.4	40	0.0002	110
			1		0.0005	45
Flagger						
Flagging for Aerial Applications	Typical Field Crops[1]	0.35	1	350	0.00154	48
	High-Acreage Field Crops[2]		0.8		0.00123	60
	High-Acreage Field Crops[3]		0.1		0.000154	480

a Crop or Target
[1]Typical Field Crop, Potato at 1 lb ai/A.
[2]High-Acreage Field Crops Alfalfa and Clover at 0.8 lb ai/A
[3]High-Acreage Field Crop, Cotton at 0.1 lb ai/A
[4] Orchard crops, Apple blossom 0.4 lb ai/A, Hops 1.0 lb ai/A
b Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2012); Level of mitigation = Baseline, PF5 (dust mist respirator), or engineering controls.
c Based on the maximum application rates on the registered labels (Reg. 70506-175, 70506-174,70506-176 and 70506-191). See table 4.1).
d Exposure Science Advisory Council Policy #9.1.
e Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (kg).
f Short-term and intermediate-term Inhalation MOE = Inhalation HED (Human Equivalent Dose (0.021,0.043,0.074) mg/kg/day ÷ Inhalation Dose (mg/kg/day).

Table 9.1.2. Summary of Endothall Short- and Intermediate-Term Occupational Inhalation Handler Risks for Aquatic Uses								
Exposure Scenario	Target	Application Rate[a]	Surface Area or Length of Water Body (acres or miles)[b]	Depth of Water Body (feet)[b]	Width of Water Body (feet)[b]	Inhalation UE (ug/lb ai)[c] (PPE)	Short-term	
							Dose[d]	MOE[e]
Mixer/Loader								
Mixing/loading liquid for groundboom and aerial application (subsurface use)	Ponds/Lakes	13.6 lb ai/A-ft	30 Acres/day	5	NA	0.083 (EC)	0.0021	35
Mixing/loading granules for groundboom and aerial application (subsurface use)		30 lb ai/A-ft	30 Acres/day	5	NA	0.083 (EC)	0.0047	16

Table 9.1.2. Summary of Endothall Short- and Intermediate-Term Occupational Inhalation Handler Risks for Aquatic Uses

Exposure Scenario	Target	Application Rate[a]	Surface Area or Length of Water Body (acres or miles)[b]	Depth of Water Body (feet)[b]	Width of Water Body (feet)[b]	Inhalation UE (ug/lb ai)[c] (PPE)	Short-term	
							Dose[d]	MOE[e]
Mixing/Loading Emulsifiable Concentrate with Direct Metering	Flowing Water	0.56 lb ai / minute at 50 cfs(cubic feet per second)	300 minutes/day	NA	NA	0.219(NR)	0.0046	93
		0.15 lb ai / minute at 200 cfs (cubic feet per second)	120 minutes/day	NA	NA	0.219(NR)	0.000049	873
Applicator								
Applying liquid with Closed cab Groundboom (subsurface use)	Ponds/Lakes	13.6 lb ai/A-ft	30 Acres/day	5	NA	0.043 (EC)	0.00109	67
Applying liquid with closed cab aircraft (subsurface use)	Ponds/Lakes	13.6 lb ai/A-ft	30 Acres/day	5	NA	0.0049 (EC)	0.00013	168
Applying granules with closed cab Groundboom (subsurface use)	Ponds/Lakes	30 lb ai/A-ft	30 Acres/day	5	NA	0.22 (EC)	0.012	6
Applying granules with closed cab aircraft (subsurface use)	Ponds/Lakes	30 lb ai/A-ft	30 Acres/day	5	NA	1.3 (EC)	0.073	1
Mixer/Loader/Applicator								
Mixing/ Loading/ Applying Emulsifiable Concentrates with a Handgun Sprayer	Ponds/ Lakes	13.6 lb ai/A-ft	1 Acres/ day	2	NA	3.9(NR)	0.0013	56
	Canals	1.7 lb ai/canal--1 mile X 1 ft wide x 1 ft deep	1 miles long	2	20	0.78(PF5)	0.00066	112
		1.7 lb ai/canal--1 mile X 1 ft wide x 1 ft deep	1 miles long	2	5	3.9 (NR)	0.00083	89
Loading/ Applying granules (Push type rotary spreader)	Ponds/ Lakes	30.0 lb ai/A-ft	1 Acres/ day	5	NA	2(PF5)	0.00075	30
	Canals	1.6 lb ai/canal--1 mile X 1 ft wide x 1 ft deep	1 miles long	5	20	1(PF10)	0.00085	50
		1.6 lb ai/canal--1 mile X 1 ft wide x 1 ft deep	1 miles long	5	5	2(PF5)	0.00021	100

a Based on the maximum application rates on the registered labels (see Table 4.1).
b Amount handled per day values are HED estimates of acres, miles, or feet treated per day based on industry sources and HED estimates.
c Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2012);
d Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (kg).
e Short-term and intermediate-term Inhalation MOE = Inhalation HED (Human Equivalent Dose (0.021, 0.043, 0.074) mg/kg/day ÷ Inhalation Dose (mg/kg/day). **The Human Equivalent Dose (HED) was calculated with a breathing rates of 8.6, 16.7 and29 l/min**

9.2 Post-Application Risk Assessment

9.2.1 Inhalation Post-Application Risk Assessment

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain

pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its FIFRA SAP in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for endothall.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments.

9.2.2 Dermal Post-Application Risk Assessment

A quantitative dermal post-application assessment was not conducted because a systemic dermal hazard for endothall has not been identified.

Restricted-Entry Interval

The Environmental Protection Agency's requirements regarding Restricted-entry Intervals (REIs) are included in the 40 CFR 156.208. Guidance on applying these requirements are also included in Chapter 11 of the Office of Pesticide Programs' Label Review Manual. In accordance with the 40 CFR 156.208, the REI is based on the acute toxicity of the "technical active ingredient material". The toxicity categories of the active ingredient for acute dermal, eye irritation, and skin irritation potential are used to determine the interim Restricted-entry Intervals. If one or more of the three acute toxicity effects are in toxicity category I, the interim REI is established at 48 hours. The acute toxicity classification for primary eye irritation of endothall-dipotassium is Category I. Per the Worker Protection Standard (WPS), a **48-hour** restricted entry interval (REI) is required for chemicals classified under Toxicity Category I.

10.0 Public Health and Pesticide Epidemiology Data

Adapted from: S. Recore, D423761, 12/04/2014

IDS records incidents resulting in higher severity outcomes in more detail, in a module called the Main IDS module. This system stores incident data for death, major and moderate incidents, and it includes more details about the location, date and nature of the incident. Main IDS incidents involving only one pesticide are considered to provide more certain information about the potential effects of exposure from the pesticide. The less severe human incidents (minor, unknown, or no effects outcomes) are reported by registrants as counts called aggregate summaries and are recorded in a separate module called Aggregate IDS. The SENSOR-Pesticides database covers 11 states from 1998-2010, although reporting varies from state to state. Cases of pesticide-related illnesses are ascertained from a variety of sources. Although both occupational and non-occupational incidents are included in the database, SENSOR-Pesticides focuses on occupational pesticide incidents, and is of particular value in providing that information. For this evaluation, both the IDS and SENSOR database were consulted for pesticide incident data on the active ingredient endothall (PC Codes: 038901, 038904, and

038905). In addition, we sought information from the Agricultural Health Study (AHS); however, endothall is not included in the AHS.

Endothall and salts were previously reviewed in 2004 (J. Blondell and M. Hawkins, 6/24/2004, D304467). In this earlier review, it was concluded that "Relatively few incidents of illness have been reported due to endothall." For the Main IDS, from January 1, 2009 to November 13, 2014, there were 0 incidents reported for single chemical only in the database. In Aggregate IDS, from January 1, 2009 to November 13, 2014, there were 31 reported incidents involving endothall. These incidents were classified as minor severity. Overall, there are few incidents involving endothall reported to IDS. SENSOR-Pesticides identifies 16 cases from 1998 to 2010. Six cases, stemming from six separate events, involve a single active ingredient. Five cases were low in severity and one case was moderate in severity due to dermal burns following a spill of the product onto skin. The remaining five cases were low in severity. Three cases experienced ocular irritation and three cases experienced dermal irritation. Four cases were related to spills or splashes. Two cases exposed to the product as it was being applied by another individual.

Conclusions: Based on the low frequency and severity of incident cases reported for endothall in both IDS and NIOSH SENSOR-Pesticides in the current analysis, there does not appear to be a concern at this time that would warrant further investigation. The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be included in the risk assessment.

11.0 References

Endothall: Residue Chemistry Chapter to Support Registration Review and the Petition to Remove the Label Restriction for Livestock to Drink Treated Water; K. King; D426753 and D428908; *In Progress*.

Endothall: Occupational and Residential Exposure and Risk Assessment for Registration Review; S. Tadayon; D428969; *In Progress*.

Endothall: Chronic Aggregate Dietary (Food plus Drinking Water) Exposure Assessment to Support permanent tolerance on Milk, Meat, Poultry, and Eggs; K. King; D428970; *In Progress*.

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The toxicological data requirements (40 CFR 158.340) for food uses for endothall are in Table A1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1 Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rat and mouse)	yes	yes
870.3150	Oral Subchronic (dog)	yes	yes
870.3200	21/28-Day Dermal (rat)	yes	yes
870.3250	90-Day Dermal	CR	yes
870.3465	28-Day Inhalation	no[A]	yes
870.3700a	Developmental Toxicity (rat)	yes	yes
870.3700b	Developmental Toxicity (rabbit)	yes	no[C]
870.3800	Reproduction (rat)	yes	yes
870.4100a	Chronic Toxicity (rat)	yes	chronic/onco
870.4100b	Chronic Toxicity (dog)	yes	yes
870.4200a	Carcinogenicity (rat)	yes	chronic/onco
870.4200b	Carcinogenicity (mouse)	yes	yes
870.4300	Chronic/Carcinogenicity (rat)	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Mammalian Erythrocyte Micronucleus.	yes	yes
870.5500	Mutagenicity— Bacterial DNA Damage or Repair Test	yes	yes
870.5550	Mutagenicity—Unscheduled DNA Synthesis	yes	yes
870.6100a	Acute Delayed Neurotoxicity. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotoxicity Screening Battery (rat)	no[A]	-
870.6200b	90 Day Neurotoxicity Screening Battery (rat)	no[A]	-
870.6300	Developmental Neurotoxicity (rat)	CR	-
870.7485	General Metabolism (rat)	yes	yes
870.7600	Dermal Penetration (8-hour), *in vivo* (male rat)	CR	yes
870.7800	Immunotoxicity (rat)	no[B]	-

[A]HASPOC TXR No. 0056397. Waived.
[B]HASPOC TXR No. 0056794. Waived.
[C] Due to high mortality observed in a range finding study in rabbits even at low doses, a developmental toxicity study in this species was not conducted

A.2 Toxicity Profiles

Table A.2.a Acute Toxicity Profile – Endothall			
Guideline No./ Study Type	MRID No.	**Results**	**Toxicity Category**
870.1100 Acute oral toxicity	42289201	LD_{50} = 50.2/44.4[m/f] mg/kg	I
870.1200 Acute dermal toxicity	42289202	LD_{50} = >2000[m/f] mg/kg	III
870.1300 Acute inhalation toxicity	42169501	LC_{50} = 1.27/2.20[m/f] mg/L	III
870.2400 Acute eye irritation	42289203	Severe irritant; lethal 4/6 rabbits	I
870.2500 Acute dermal irritation	42289204	Unacceptable study	I [a]
870.2600 Skin sensitization	41871901	Sensitizer	N/A

Note: Studies in the database were not updated to reflect current policies since these changes would not affect current PoDs and the selected endpoints are protective of all effects seen in the endothall database.

A.2.b Subchronic, Chronic and Other Toxicity Profiles – Endothall[a]		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity rodents (rat)	43480810(1994) Acceptable/guideline 0, 150, 600, 1800 ppm M:0, 10, 39, 118 mg/kg/day F: 0, 12, 51, 153 mg/kg/day	NOAEL = 39 mg/kg/day LOAEL = 118 mg/kg/day based on treatment related deficits in body weight.
870.3150 13 week oral toxicity in nonrodents (dog)	43480802 (1994) Acceptable/guideline 0, 100, 400, 1000 ppm M: 0, 3.2, 11.7, 27.5 mg/kg/day F: 0, 3.2, 13.0, 28.9 mg/kg/day	NOAEL = 11.7 mg/kg/day LOAEL = 27.5 mg/kg/day based on decreases in body weight gain.
870.3200 21-Day dermal toxicity (rat) range-finding	42814101 (1992) Acceptable/nonguide -line 0, 80, 200, 500 mg/kg/day	NOAEL = not determined LOAEL = 80 mg/kg/day based systemic toxicity (death) LOAEL = 80 mg/kg/day based on dermal irritation
870.3250 21-Day dermal toxicity (rat)	43465201(1994) Acceptable/guideline 0, 30, 100, 300 mg/kg/day	NOAEL = not determined LOAEL = 30 mg/kg/day based on decreased body weight gains. LOAEL = 30 mg/kg/day based on dermal irritation
870.3700a Prenatal developmental in rodents (rat)	42776301 (1993) Acceptable/guideline 0, 6.25, 12.5, 25.0 mg/kg/day	**Maternal** NOAEL = 12.5 mg/kg/day LOAEL = 25 mg/kg/day based on decreased body weight gain. **Developmental** NOAEL =$\geq$ 25 mg/kg/day LOAEL = not determined HDT.
870.3700b Prenatal developmental in rabbit	42776301 (1993) Acceptable/guideline 0, 0.6, 1.5, 3.75 mg/kg/day	**Maternal** NOAEL = 1.5 mg/kg/day LOAEL = 3.75 mg/kg/day based on mortality, decreased body weights and food consumption. **Developmental** NOAEL = 1.5 mg/kg/day

A.2.b Subchronic, Chronic and Other Toxicity Profiles – Endothall[a]

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
		LOAEL = decreased body weight.
870.3800 Reproduction and fertility effects	43152101 (1993) 43629301 (1995) Acceptable/guideline 0, 30, 150, 900 ppm M: 0, 2, 10.2, 64 mg/kg/day F:0, 1.8, 9.4, 60 mg/kg/day premating 0, 3.1, 17.3, 104.7 mg/kg/day lactation	**Parental/Systemic** NOAEL = not established LOAEL = 2 mg/kg/day based on proliferative lesions gastric epithelium both sexes. **Developmental** NOAEL = 9.4 mg/kg/day LOAEL = 60.0 mg/kg/day based on decreased pup body weights
870.4100b Chronic toxicity dogs	40745202 (1987) supplementary/guideline 0, 150, 450,350 ppm. high dose lowered to 1000 ppm at the 7th M: 0, 5.7, 17 or 40 mg/kg/day F: 0, 6.5, 18, 33 mg/kg/day 52 weeks.	NOAEL = not determined LOAEL (LDT) = 6.5 mg/kg/day based on gastric epithelial hyperplasia.
870.4200b Carcinogenicity mice	40685301 (1988) supplementary/guideline 0, 50, 100, 300 ppm 0, 7.5, 15, 45 mg/kg/day 21 months	NOAEL =15 mg/kg/day LOAEL = 45 mg/kg/day based on decreased body weight gain and microscopic findings in male kidney. **no evidence of carcinogenicity**
870.4200b Carcinogenicity mice	43608301(1995) acceptable/guideline 0, 750, 1500 ppm M: 01, 124, 258 mg/kg/day F: 0, 152, 319 mg/kg/day 79 weeks	NOAEL = not determined LOAEL = 124 mg/kg/day based on decreased body weight gain in males. **No evidence of carcinogenicity.**
870.4300 chronic/onco rat	41040301(1989) acceptable 0, 150, 300, 900, 1800ppm M: 0, 6, 12, 37, 80 mg/kg/day F: 0, 8, 16, 49, 110 mg/kg/day	NOAEL = 8 mg/kg/day LOAEL = 16 mg/kg/day based on decreased body weight and body weight gain. **No evidence of carcinogenicity.**
Gene Mutation Guideline # OPPTS 870.5300 [§84-2]; OECD 476, study type *In vitro* Mammalian Cell Gene Mutation Assay	43437801 (1993) classification Acceptable equivalent = 11.6%) Dosed in (DMSO) at concentrations of 0.0116, 0.0580, 0.116, 0.580, 1.16, 2.32, 2.9, 3.48, 4.06, and 4.64 µg/mL (all concentrations expressed as active ingredient) without metabolic activation or at 0.116, 0.58, 1.16, 5.8, 11.6, 17.4, 20.3, 21.8, 23.2 and 26.1 µg/mL with metabolic activation (Initial Trial). For the confirmatory trial, levels of 0.0116, 0.0580, 0.116, 0.580, 1.16, 2.32, 2.90, 3.48. 4.06. 4.64, 5.22 and 5.80 µg/mL -S9 or 0.116, 0.580, 1.16, 5.80, 11.6, 17.4, 23.2, 26.1 and 29 µg/mL +S9 were processed.	Negative
Gene Mutation Guideline # Bacterial Gene Mutation Assay	43154801 (1993). Unacceptable in dimethyl sulfoxide (DMSO) (equivalent	Negative

A.2.b Subchronic, Chronic and Other Toxicity Profiles – Endothall[a]

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
(*Salmonella typhimurium*)/OPPTS 870.5100/[§84-2] OECD 471	to 1.93, 5.80, 19.3, 58.0, 116 or 193 µg/plate active ingredient) with or without S9 activation.	
Cytogenetics *In vivo* Mammalian Cytogenetics - Micronucleus Assay in Mice/OPPTS 870.5395/[§84-2]	43157401 (1994) Acceptable mice were administered 0.464, 0.928 and 1.86 mg/kg Endothall Technical amine salt (1.5:1 amine :salt ratio; Batch No. B46-44-1; endothall amine 30.3%;endothall acid equivalent = 11.6%) via intraperitoneal injection (IP) in deionized water;	Negative
Cytogenetics *In vivo* Mammalian Cytogenetics - Micronucleus Assay in Mice/OPPTS 870.5395/[§84-2]	41700301 (1989) Acceptable mice were administered 2,10 or 50 mg/kg Endothall	Negative
Cytogenetics *In vitro* Mammalian Cytogenetics OPPTS 870.5375 [§84-2]; OECD 473	41700302 (1989) Acceptable in dimethyl sulfoxide (DMSO) at concentrations of 2.5, 10.0, 20.0 and 40.0 µg/mL without metabolic activation or were exposed for 3 hours to 15.0, 60.0, 120.0 or 240.0 µg/mL with metabolic activation	Negative
870.7485 Metabolism and pharmacokinetics	42169502 (1990), acceptable a single i.v. dose at 0.9 mg/kg, a single oral dose at 0.9, 4.5 or 9.0 mg/kg and as a 15 day multiple dose at 0.9 and 9.0 mg/kg/day.	Intravenous administration of 0.9 mg/kg resulted in excretion mainly by the urine (69%) and feces. At an oral 0.9 mg/kg dose, blood half-life elimination - 1.8 hrs in males, 2.5 hrs females. At 4.5 mg/kg half-life - 13.9 hours in males; the half-life in females could not be calculated because of a double blood peak. Multiple oral or single administration indicated that the test material was rapidly absorbed and excreted in the feces (89-98%) and urine (5-9%). The compound did not bioaccumulate. At 24 hours tissue distribution of the compound was extensive but low, the highest amount (<10%) being found in the gastrointestinal tract. By 48 hours, the compound was mostly undetectable in the tissue. Bile elimination was only of minor importance. Absorbed or unabsorbed test compound in all groups was excreted mainly as chemically unchanged Endothall in the feces and urine.
870.7485 Metabolism and pharmacokinetics	44263501 (1997) acceptable Administered to 10 Sprague Dawley rats (5/sex/dose) in distilled water by gavage at a dose 9 mg/kg. Animals were sacrificed after 24 hours.	Following a single oral administration of [^{14}C}-Endothall to male and female rats (approximately 9 mg/kg), the majority of the radioactivity (70.8% males, 71.2% females) was excreted within the 0-24 hour time period, with most of the

A.2.b Subchronic, Chronic and Other Toxicity Profiles – Endothall[a]		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
		radioactivity being present in the feces (47.6% males, 47.5% females) At 24 hours after dosing, less than 0.21% of the dose was found in the stomach (+ contents), small intestine (+ contents) and pancreas and very little detected in the blood (below 15 ng eq/g). Higher levels of radioactivity were found in the caecum (3.0% males, 6. 1 % females) and the large intestine (3.2% males, 8.2% females). Analysis of extracts of the urine, feces, caecum and large intestine of both male and female rats gave a single radioactive component corresponding to unchanged Endothall which accounted for >86, >96, >74 and >69% of total recovery from the respective extracts.
870.7600 Dermal penetration	42169503 (1990) acceptable Dose levels were 0.0125 mg/cm^2 (0.3 mg/rat), 0.0625 mg/cm^2 (1.5 mg/rat) and 0.125 mg/cm^2 (3.0 mg/rat) respectively. Five (5) animals per time period (0..5, 1, 2, 4, 10 or 24 hours) in each dose	Approximately 55 to 82% of the applied dermal dose was washed from the application site. The rest of the [^{14}C]-Endothall equivalents was contained in the application site skin. Urinary excretion of [^{14}C]-Endothall equivalents increased in a dose related manner at 10 and 24 hours to a maximum of 2.3% of the applied dose at the 0.125 mg/cm^2 (3.0 mg/rat)dose level. Fecal excretion amounted to <0.1% at all dose levels. At the 0.0125 mg/cm^2 (0.3 mg/rat), 0.0625 mg/cm^2 (1.5 mg/rat) and 0.125 mg/cm^2 (3.0 mg/rat) dose levels, systemic bioavailability (absorption) of 3.9%, 2.2% and 7.3%, respectively, were noted at 24 hours. A time related increase in systemic bioavailability occurred only at the 1.5% dose level. The dose related pattern of absorption was typical of a chemical which directly damages the skin. The percent of dose absorbed increased with increasing dose. The total percent recovery of [^{14}C]-Endothall equivalents was 97.7 to 101.1% of the administered dose throughout the 24 hour period.
Special studies	None	
870.3465 28- day inhalation rat	47872201/47872202 acceptable 5 day: 0, 0.025, 0.075, and 0.152 mg/L, respectively) for 6 hours/day for 5 consecutive days.	5 day: LOAEL = 0.025 mg/L, based on decreased body weights and food consumption, effects on clinical chemistry parameters, liver effects (subacute inflammation and hepatocellular necrosis) and pulmonary effects (increased absolute

A.2.b Subchronic, Chronic and Other Toxicity Profiles – Endothall[a]		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
	28-day: 0 (air), 0.001, 0.005, or 0.025 mg/L for 6 hours per day, 5 days/week for 4 weeks	and relative lung weights, subacute inflammation, alveolar proteinosis, and hemorrhage). The NOAEL was not established. 28-day: LOAEL = 0.005 mg/L based on indications of lung toxicity (rales in males and increased lung weights and alveolar macrophages in both sexes). NOAEL is 0.001 mg/L.

[a] Studies in the database were not updated to reflect current policies since these changes would not affect current PoDs and the selected endpoints are protective of all effects seen in the endothall database.

Appendix B. Physical/Chemical Properties

Table C.1. Physicochemical Properties of Endothall and its Salts.		
Parameter	**Value**	**Reference**
Endothall (acid)		
Melting point	108-110℃	DP# 304026, D. Soderberg, 6/10/2004
pH	2.7 at 25℃ (1% solution)	
Density, bulk density, or specific gravity	0.481 g/cm^3 (bulk) at 25℃	
Water solubility at 25℃	109.8 g/L 13.1 g/100 mL in water, pH 5 12.7 g/100 mL in water, pH 7 12.5 g/100 mL in water, pH 9	
Solvent solubility at 25℃	3.4 g/100 mL in acetonitrile 2.4 g/100 mL in n-octanol 16.0 g/100 mL in tetrahydrofuran	
Vapor pressure	3.92 x 10^{-5} mm Hg at 24.3℃	
Dissociation constant, pK$_a$	4.32 for Step 1 and 6.22 for Step 2 at 20℃ (0.2% solution in 20% basic ethanol); dissociation rate 1.8-2.3 x 10^3 µmho within 3-5 minutes at ~25℃, by conductivity meter	
Octanol/water partition coefficient	Not applicable to endothall acid	
UV/visible absorption spectrum	Not available	
Endothall, dipotassium salt		
Melting point	>360℃	DP# 304026, D. Soderberg, 6/10/2004
pH	9.1 at 25℃ (1% solution)	
Density, bulk density, or specific gravity	0.766 g/cm^3 (bulk) at 25℃	
Water solubility	>65 g/100 mL in water, pH 5, pH 7, and pH 9	
Solvent solubility	<0.001 g/100 mL in acetonitrile, n-octanol, and tetrahydrofuran	
Vapor pressure	Not applicable. An organic acid K salt is anticipated to have an insignificant vapor pressure.	
Dissociation constant, pK$_a$	4.16 for Step 1 and 6.14 for Step 2 at 20℃ in water; dissociation complete at 5 mins (13.6 x 10^3 µmho)	
Octanol/water partition coefficient	K$_{OW}$ <0.02 and <0.3 at concentrations of 9 x 10^{-3} M and 9 x 10^{-4} M, respectively, at 25℃	
UV/visible absorption spectrum	Not available	
Endothall, mono-N,N-dimethylalkyl amine salt		
Boiling point	Not available	DP# 304026, D. Soderberg, 6/10/2004
pH	5.2 at 25℃ (1% solution)	
Density, bulk density, or specific gravity	1.028 g/mL at 25℃	
Water solubility at 25℃	≥49.2 g/100mL in water, pH 5 ≥51.6 g/100 mL in water, pH 7 ≥49.8 g/100 mL in water, pH 9	
Solvent solubility at 25℃	≥102.5 g/100mL in acetonitrile ≥95.4 g/100 mL in n-octanol ≥104.3 g/100 mL in tetrahydrofuran	
Vapor pressure	2.09 x 10^{-5} mm Hg at 25℃ (calculated; mixed mono- and dialkylamine (C8-C20))	
Dissociation constant, pK$_a$	4.24 for Step 1 and 6.07 for Step 2 at 20℃ for mixed mono- and dialkylamine (C8-C20) in acidified ethanol/water; dissociation complete ~17 minutes (1.7 x 10^3 µmho) at 25℃	
Octanol/water partition coefficient	K$_{OW}$ 2.097 at concentrations of 8.9 x 10^{-3} M and 8.9 x 10^{-4} M, at 25℃	
UV/visible absorption spectrum	Not available	

Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1), the Agricultural Handler Exposure Task Force (AHETF) database and, the Aquatic use Standard Operation Procedure (20-Sep-2013) and are subject to ethics review pursuant to 40 CFR 26, have received that review, and are compliant with applicable ethics requirements. For certain studies that review may have included review by the Human Studies Review Board. Descriptions of data sources as well as guidance on their use can be found at http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure.

Appendix D. Use Pattern Summary Tables

Table D. Summary of Registered Uses for Endothall				
Crop/Use Site	Application Timing and Type of Application	Registered Formulations	Maximum Application Rate	Personal Protective Equipment (PPE) and Restricted Entry Interval (REI),PHI
Registered Uses for Endothall				
Quiescent, slow moving, and flowing water aquatic sites (Drainage and irrigation canals, ponds, and lakes)	Aircraft- or boat-mounted spreader	Granular (G) 70506-174	5 ppm (30 lbs ai/acre ft)	PPE*
	Surface or injected; Drip or metering; Aerial	Liquid (SC) 70506-175	5ppm (3.6 pints/acre ft or 13.6 lb ai/per acre ft)	PPE*
	Surface or injected; Drip or metering; Aerial	Liquid (SC)70506-176	5 ppm (13.6 lb ai /acre ft for broadcast and for spot or lake margin treatment)	PPE*
	Aircraft- or boat-mounted spreader	Granular 70506-191	5ppm(13.9 lb ai/acre/ft)	PPE*
	Surface or injected; Drip or metering; Aerial	Liquid (SC)70506-302	1.8 ppm (4.9 lb ai/acre ft)	PPE* Closed mixing/loading for aerial application
Harvest Aid for Cotton	Preharvest, Defoliation, Aerial, ground	Liquid (SC) 70506-180	0.1(lb ai/A)	48 hr REI, 7 days retreatment interval
Harvest Aid for Alfalfa and Clover	Preharvest, Aerial, ground	Liquid (SC) 70506-190	0.8 (lb ai/A)	48 hr REI, 7 days retreatment interval
Harvest Aid Potato and Hops			1.0 (lb ai/A)	48 hr REI, 14 days retreatment interval
Apple blossoms	Airblast	Liquid SC 70506-296	0.4 (lb ai/A)	48 hr REI, 24 hr retreatment

PPE* - Label recommended PPE is long sleeve shirt, chemical resistance gloves, shoes plus socks, protective eyewear and PF5 dust/mist respirator

Appendix E. International Residue Limits Table

Endothall (PC Code 038901)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex
40 CFR 180.293: (a) General. (1) endothall (7-oxabicylco [2.2.1] heptanes-2,3-dicarboxylic acid) and its mono-methyl ester.		7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid, including its monomethyl ester		None
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex
Apple	0.05			
Apple, wet pomace	0.15			
Cotton, undelinted seed	0.1			
Fish	0.1			
Hop, dried cones	0.1			
Potato	0.1	0.1		
Rice, grain	0.05			
Rice, straw	0.05			
Completed: M. Negussie; 09/02/15				

[1] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

(2) An interim tolerance of 0.2 parts per million is established for residues of the herbicide endothall (7 -oxabicyclo[2.2.1] heptane-2,3-dicarboxylic acid) in water, potable from use of its potassium, sodium, di-*N, N*-dimethylalkylamine, and mono-*N*-*N*,-dimethylalkylamine salts as algicides or herbicides to control aquatic plants in canals, lakes, ponds, and other potential sources of water, potable.

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex
40 CFR 180.293: (d) Indirect or inadvertent residues. Tolerances are established for the indirect or inadvertent combined residues of the herbicide, endothall (7 -oxabicyclo[2.2.1] heptane-2,3-dicarboxylic acid) in potable water from use of its potassium, sodium, di-N, N -dimethylalkylamine, and mono- N-N, -dimethylalkylamine salts as algicides or herbicides to control aquatic plants in canals, lakes, ponds, and other potable water sources that may lead to endothall residues		None		None
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex
Almond, hulls	15.0			
Animal feed, nongrass, group 18, forage	4.0			
Animal feed, nongrass, group 18, hay	10			

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex
Apple, wet pomace	0.15			
Beet, sugar, molasses	1.5			
Brassica, head and stem subgroup 5A	0.1			
Brassica, leafy, subgroup 5B	2.0			
Bushberry subgroup 13-07B	0.6			
Caneberry subgroup 13-07A	0.6			
Cattle, fat	0.01			
Cattle, kidney	0.20			
Cattle, liver	0.10			
Cattle, meat	0.03			
Corn, field, grain	0.07			
Corn, pop, grain	0.07			
Corn, sweet, kernel plus cob with husks removed	0.3			
Citrus, dried pulp	0.1			
Egg	0.05			
Feed commodities not otherwise listed	10.0			
Food commodities not otherwise listed	5.0			
Fruit, citrus group 10	0.05			
Fruit, pome, group 11	0.05			
Fruit, stone, group 12	0.3			
Goat, fat	0.005			
Goat, kidney	0.15			
Goat, liver	0.05			
Goat, meat	0.015			
Grain, aspirated fractions	35.0			
Grain cereal, forage, fodder and straw, group 16	10.0			
Grain, cereal, group 15, except corn	4.0			
Grape	1.0			
Grape, raisin	5.0			
Grass, forage, fodder, and hay group 17, forage	3.5			
Grass, forage, fodder, and hay group 17, hay	18.0			
Herb and spice, group 19	5.0			
Hog, fat	0.005			
Hog, kidney	0.10			
Hog, liver	0.05			
Hog, meat	0.01			
Milk	0.03			
Nut, tree, group 14	0.05			
Okra	0.05			
Pea and bean, dried shelled, subgroup 6C	0.2			
Pea and bean, succulent shelled, subgroup 6B	2.0			
Peppermint, tops	5.0			

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex
Pistachio	0.05			
Poultry, fat	0.015			
Poultry, liver	0.05			
Poultry, meat	0.015			
Poultry, meat byproducts	0.20			
Rice, hulls	8.0			
Sheep, fat	0.005			
Sheep, kidney	0.15			
Sheep, liver	0.05			
Sheep, meat	0.015			
Soybean, hulls	0.5			
Soybean, seed	0.2			
Spearmint, tops	5.0			
Tomato, paste	0.1			
Tomato, puree	0.1			
Vegetable, bulb, group 3-07	0.5			
Vegetable, cucurbit, group 9	1.5			
Vegetable, foliage of legume, group 7	4.0			
Vegetable, fruiting, group 8	0.05			
Vegetable, leafy, except brassica, group 4	2.0			
Vegetable, leaves of root and tuber, group 2	3.0			
Vegetable, legume, edible, podded, subgroup 6A	2.0			
Vegetable, root and tuber, group 1	1.0			
Wheat, milled byproducts	5.0			
Completed: M. Negussie; 09/02/15				

Appendix F. Status of Residue Chemistry Issues Identified in the 2005 Chapter.

Deficiency	Status
Radiovalidation data to determine whether the current enforcement methods for plants and the required enforcement method(s) for animals can adequately extract and convert aged residues of the monomethyl ester to endothall.	Not resolved for plants; however, is not required as parent endothall only is an adequate marker of misuse. Waived for livestock in the current residue chemistry chapter (D428908, *In Progress*).
Data collection and regulatory analytical methods for the determination of endothall, per se, in animal commodities.	Resolved in the current residue chemistry chapter (D428908, *In Progress*).
Storage stability data for processed plant commodities, animal commodities, and fish.	Resolved for plants (D. Soderberg, D356315, 10/22/2009), animal commodities (current chapter, D428908), and fish (D. Soderberg, D324426, 02/27/2006).
Livestock (ruminant and poultry) feeding studies.	Resolved in D387313 (D. Soderberg, 05/03/2011)
A maximum seasonal rate of application to irrigation canal water must be proposed for the label. Depending upon this proposal, additional magnitude of the residue studies at the proposed seasonal rates may be required in irrigated crops. Additional magnitude of the residue studies are also required in some additional irrigated crops, pending discussion between HED and the registrant, to assure adequate coverage of all irrigated crops.	Resolved. Magnitude of residue studies in irrigated crops were reviewed in D356315 (D. Soderberg, 10/22/2009).
Magnitude of the residue studies in potato, alfalfa seed, undelinted cottonseed, and cotton gin byproducts. Magnitude of the residue studies in the RACs of sugar beet and rice if the registrant intends to support these uses.	Alfalfa: Two additional trials are required, tolerance recommended in this chapter. Potato and Cotton: Resolved in the current residue chemistry chapter (D428908, *In Progress*).
Processing studies on apples, corn (field), grapes, orange, rice, sorghum, soybeans, sugar beet, tomato, and wheat, to cover irrigation uses.	Resolved in the chapter that address studies in irrigated crops D356315 (D. Soderberg, 10/22/2009).
Submission of analytical reference standards for dipotassium and mono-N,N-dimethylalkyl amine salts of endothall.	Standards are available.
A confined rotational crop study identifying the residues of concern besides endothall is required or else limited rotational crop field trials may be performed in which the residues of concern for endothall (endothall and its monomethyl- and dimethyl- esters are tested.	The confined rotational study was waived in D387313 (D. Soderberg, 05/03/2011).
A radiovalidation study of the proposed enforcement method for determining endothall in fish is needed.	The radiovalidation was waived in D324426 (D. Soderberg, 02/27/2006).