Flumioxazin

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Massachusetts Department of Agricultural Resources
Pesticide Program

and

Massachusetts Department of Environmental Protection
Office of Research and Standards
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1 Chemical Overview

1.1. Chemical Identity

Flumioxazin is part of the N-phenylphthalimide class.

Flumioxazin is the common name for *N-(7-fluoro-3,4-dihydro-3-oxo-4-prop-2-ynyl-2H-1,4-benzoxazin-6-yl)cyclohex-1-ene-1,2-dicarboxamide*. The chemical structure is shown in Figure 2.1.

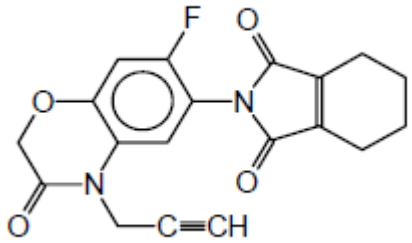

Figure 1.1 Flumioxazin Chemical Structure

1.2. Registration History

Flumioxazin is a broad-spectrum contact herbicide. It was first registered by EPA in 2001 for use on soy beans and peanuts (USEPA, 2001). As of 2011, it was registered for pre- and post-emergent weed control in a variety of fruit, vegetable and other agricultural crops, ornamentals, forestry, aquatic settings, and non-crop areas. Tolerances for flumioxazin have been established. In 2010, EPA approved the use of flumioxazin for the control of vegetation in aquatic sites. Registration review of flumioxazin was initiated in 2011 (USEPA, 2011A).

1.3. Registered Products in Massachusetts

The current list of aquatic herbicides containing flumioxazin that are registered in Massachusetts can be accessed at http://www.mass.gov/eea/agencies/agr/pesticides/aquatic-vegetation-management.html on the Massachusetts Department of Agricultural Resources (MDAR) Aquatic Vegetation Management website. MDAR updates this list regularly with changes. In addition, the MDAR can be contacted directly at (617) 626-1771 for more specific questions regarding these products.

1.4 Aquatic Use of Flumioxazin

Flumioxazin provides control of various submerged, emergent, and floating aquatic plants and filamentous green algae. Flumioxazin-based aquatic herbicides may be broadcast applied to the water surface or injected below the water surface.

1.5 Pesticide Type, Class, and Mode of Action

Flumioxazin is a member of the chemical family of N-phenylphthalimides (USEPA, 2001). They are light dependent peroxidizing herbicides (LDPH) which control plant growth by blocking heme and chlorophyll biosynthesis resulting in the accumulation of phototoxic porphyrins in plant and animal tissues (USEPA, 2010). They inhibit the enzyme protoporphyrinogen oxidase (PPO or protox) which is the last enzyme in the heme and chlorophyll biosynthetic pathway. Protox inhibition in plants results in a rapid accumulation of protoporphyrin IX. In the presence of ultraviolet light, protoporphyrin IX can become a powerful source of singlet oxygen which in plants causes lipid membrane peroxidation leading to a rapid loss of turgidity and foliar burns. Protox exists in both plants and animals and the enzyme from both sources has been shown to be highly sensitive to many LDPHs (USEPA, 2011B).

Studies with peroxidizing herbicides in rodents indicated that these substances act as protox inhibitors and interfere with the conversion of protoporphyrinogen to protoporphyrin. However, the inhibition is reversible and porphyrin levels returns to normal following cessation of exposure. Excess protoporphyrinogen is excreted in the bile and does not significantly accumulate in plasma at lower levels of exposure. Significant changes in plasma porphyrin spectrum were only observed in mice fed with a diet with high levels (> 10 mg/kg) of oxadiazon, a peroxidizing herbicide. Skin fluorescence was observed at dietary levels of oxidiazon higher than 50 mg/kg. In humans with a hereditary protox disorder (variegate porphyria) protox activity is reduced in all tissues. Symptoms may include porphyrin-related photosensitivity or acute porphyric crisis with neurological symptoms, but in most patients the metabolic defect never becomes clinically manifest. Krijt (1999) observed that a prolonged substantial inhibition of protox in all tissues is still compatible with life.

1.6 Physical and Chemical and Environmental Fate Properties

Several important physical, chemical, and fate and transport property values for flumioxazin are listed in Table 2.2 (USEPA, 2011B). The environmental fate of flumioxazin is characterized by rapid hydrolysis, photolysis, and aerobic metabolic degradation in soil and water. It has moderate mobility in soils, while its three major degradates are expected to be more mobile. Flumioxazin is expected to volatilize slowly from water and wet surfaces based on its Henry's law constant value. It is not expected to accumulate in fish based on its octanol-water partitioning constant (K_{OW}). More detailed information from EPA documents (USEPA, 2008 and USEPA 2011B) on the environmental fate properties is described below.

1.6.1 Hydrolysis

Flumioxazin hydrolyzes very rapidly in water. The hydrolysis rate increases as the pH of the solution increases. The average half-lives in hydrolysis studies with radio-labeled flumioxazin were 4.2 days, 23 hours, and 18.3 minutes for pH 5, 7, and 9 buffered solutions, respectively.

Four degradates were observed: 7-Fluoro-6[(2-carboxy-cyclohexenoyl)amino]-4-(2-propynyl)-1,4-benzoxazin-3(2H)-one (**482-HA**), 6-Amino-7-fluoro-4-(2-propynyl)-1,4,-benzoxazin-3(2H)-one (**APF**), 3,4,5,6-tetrahydrophthalic acid (**THPA**), and 3,4,5,6-Tetrahydrophthalic acid anhydride (Δ-TPA). Degradate 482-HA was found at high concentrations (97.3% of the applied) in the solution with pH 9. APF and THPA were not detected in the pH 9 solutions, but were important components in the pH 5 and 7 solutions (40-48%). Δ-TPA was a minor component (8.8% of the applied) in the pH 5 and 7 solutions. At the end of a 30-day hydrolysis study, the parent and major degradates were detected at the following percentages of applied radioactivity (at pH 7): flumioxazin at 4.7%, 482—HA at 9.3 %, APF at 40.0%, and THPA at 41.8%.

1.6.2 Photolysis

Flumioxazin degrades rapidly by photolysis in water. The half lives observed in three irradiation studies with differently radio-labeled flumioxazin that were reviewed and described by USEPA (2011B) were in the range of <1 to 26.3 hours. The results of the photolysis studies were summarized by stating that flumioxazin can degrade quickly via photolysis to 482-PHO (no chemical description for this and the following degradates available) which degrades to either 482-PHO-HA or 482-PHO-DC; 482-PHO can also degrade to 482-PHO-ISO which becomes 482-PHO-APF, or 482-PHO can degrade directly to 482-PHO-APF as can 482-PHO-HA; 482-PHO-ISO can degrade to both 482-PHO-HA and 482-PHO-DC which can further degrade to THPA. Further degradation occurs forming CO_2 and minor polar degradates. Shibata et al. (2011) identified two photo degradates: N-(2-propynyl)-4-[4-carboxy-3-fluoro-2-(3,4,5,6-tetrahydrophthalimido)-2-butenylidene]azetidine-2-one which can transform to N-(2-propynyl)-4-[4-carboxy-3-fluoro-2-(2-carboxy-1-cyclohexenecarbonylamino)-2-butenylidene]azetidine-2-one. The latter one degrades to THPA and CO_2 plus bound residues.

The half lives for the parent compound flumioxazin observed in two irradiation studies with differently radio-labeled compounds were 3.2 and 8.4 d, with various degradates identified (USEPA, 2011B).

1.6.3 Biotic Degradation

Aerobic soil metabolism studies in California sandy loam soils incubated with labeled flumioxazin showed half-lives of 11.9 and 17.5 days. Four minor degradates were detected (482-CA, 482-HA, APF, and IMOXA). Soil-bound residues increased to 74% of the applied dose by day 181. Studies with unlabeled flumioxazin in various soil types showed half-lives in the range of 5.0 to 18.9 days. Degradates were not monitored. Under anaerobic conditions, labeled flumioxazin degraded with half-lives of 4.2-4.3 hours in a flooded sandy loam. Major degradates identified were 482-HA and SAT-482-HA-2.

Anaerobic metabolism in aquatic systems was studied in a pond water-clay sediment system from Mississippi for 360 days in darkness. Radio-labeled residues appeared to rapidly partition into the sediment, in both labels, during the early part of the study. However, over the course of the study, the partitioning was variable in the [phenyl-^{14}C]-label, with the majority of the radioactivity in the sediment at 360 days, while radioactivity in the sediment of the [THP-^{14}C]-

labeled flumioxazin steadily declined, with the majority of the radioactivity in the water at 360 days. The significance of this difference was not further addressed in the review by USEPA. In the [phenyl-^{14}C]-flumioxazin, the water:sediment ratio was approximately 1:3 from 0 to 7 hours, 1:1 at 1 to 3 days, 1:3 at 21 days, and finally 1:5 at 360 days (study termination). In [THP-^{14}C]-flumioxazin, the water:sediment ratio was approximately 1:3 at 0 to 7 hours, 1:1 at 1 to 21days, 1:0.5 at 42 days, and finally 1:0.3 at 360 days. Based on first-order linear regression analysis, flumioxazin in the total system (combined labels) dissipated with a calculated half-life of 42.8 days; the individual half-lives were 45.9 and 40.1 days for the phenyl and THP labels (0-360 days), respectively. It should be noted that these half-life values seem very high based on the degradation data from which they seemed to have been calculated. In the same section, dissipation data for flumioxazin indicate much faster degradation. In the [THP-14C]flumioxazin, flumioxazin in the total system decreased from 90.4% of the applied concentration at time 0, to 85.7% at 7 hours, 38.5% at 1 day, 12.1% at 21 days, 0.4% at 268-360 days. In the [phenyl-14C]flumioxazin solutions, flumioxazin in the total system decreased from 98.7% of the applied concentration at time 0, to 89.0% at 7 hours, 41.9% at 1 day, 24.1% at 10 days, 2.6% at 59 days, and was 0.48% at 360 days (study termination). A much lower value for anaerobic metabolism half-life values was reported in an earlier EPA factsheet: a half-life of 0.2 d for anaerobic aquatic metabolism (USEPA, 2001).

The *aerobic aquatic metabolism* was studied in stream water-clay loam sediment (water pH 7.80, dissolved organic carbon 16.8 mg/L; sediment pH 7.28-7.7, organic carbon 8.0%) and lake water-sandy clay loam sediment (water pH 6.32, dissolved organic carbon 16.9 mg/L; sediment pH 5.3-6.4, organic carbon 3.6%) systems from the United Kingdom for 98 days under aerobic conditions in darkness at 20 °C. Labeled flumioxazin ([phenyl-U-^{14}C]- and [tetrahydrophthaloyl (THP)-1,2-^{14}C]) dissipated at similar rates in the two sediment systems. Summaries of these studies are available in the EPA review document (USEPA, 2011B). Calculated non-linear half-lives were 2 hours, 42-53 days and 3-5 days in the water layers, sediments and total systems, respectively.

1.6.4 Mobility of Flumioxazin

USEPA concludes that the overall potential for the parent compound to migrate into ground water and to move with surface runoff water is low. However, based on the organic carbon adsorption coefficients (K_{OC}) obtained from column leaching studies, flumioxazin can be classified as a chemical with "moderately mobile" soil mobility potential (mean K_{OC} = 557) (USEPA, 2013). Based on vapor pressure 3.2 mPA (25 °C), flumioxazin is classified as volatile. Based on its Henry's Law constant value of 6.32 x 10^{-2} Pa m^3 mol^{-1} (25 °C) flumioxazin is classified as non-volatile.[1]

1.6.5 Mobility of 482-HA, APF and THPA

No mobility information on 482-HA was available. Based on its chemical structure, this degradate is expected to be more mobile in alkaline environments than in acidic ones. No further

[1] Pesticide Properties DataBase (PPDB): http://sitem.herts.ac.uk/aeru/iupac/335.htm

absorption studies for 482-HA have been required by USEPA because it was found in the pH 7 hydrolysis study at a much lower level than the other two degradates (APF and THPA). APF and THPA were classified by USEPA as "moderately mobile" based upon adsorption study results (APF K_{OC} values in the range of 201 to 620; THPA K_{OC} values in the range of 13 to 191).

1.6.6 Bioconcentration

EPA granted a waiver for a bioconcentration study based on the following considerations: 1) the observed octanol/water partition coefficient is smaller than 1,000 (log Kow = 2.55); and 2) degradation is rapid in water with a half-life of about one day at pH 7 and about 20 minutes at pH of 9. Based on the low octanol water partition coefficient flumioxazin is not expected to accumulate in fish. According to a fish residue study submitted to EPA, BCFs between the edible tissue in bluegill and catfish and the static water treated with 800 µg/L flumioxazin during the seven samplings in the exposure period of 28 days ranged from 0.09-4.1 for flumioxazin, 0.2-1.3 for APF, and 0.04-2.6 for 482-HA. It should be noted that BCFs may be underestimated based on results of static water tests.

Table 1.1. Physical and Environmental Fate Properties of Flumioxazin (USEPA, 2011B)

Property	Value
CAS number	103361-09-7
Molecular weight	354
Molecular formula	$C_{19}H_{15}FN_2O_4$
Water solubility (mg/L)	1.8
Log Kow	2.55
Vapor pressure at 25°C (mmHg)	2.46×10^{-06}
Henry's Law constant at 25°C ($atm \cdot m^3 \cdot mol^{-1}$)	6.36×10^{-07}
Soil adsorption coefficient K_{OC} (L/kg) based on column leaching studies	112, 271, 656, 1190
Soil adsorption coefficient K_{OC} (L/kg) based on adsorption study	13, 66, 75, 191, 248, 339
Hydrolysis half-life (d) pH = 5 pH = 7 pH = 9	 4.2 1 0.01
Photolysis half-life in water, pH 5 (d)	1
Aerobic aquatic metabolism half-life (d)	3-5
Anaerobic aquatic metabolism half-life (d)	40.1 and 45.9[1]
Fish bioconcentration factors	The bioconcentration factor for the inedible tissue was <1X. In edible portions, BCF was 0.9-4.1

[1] A much lower value of 0.2 d was reported in USEPA (2001)

1.6.7 Metabolism Pathways

Two metabolism pathways in the aquatic environment have been proposed. In anaerobic conditions, flumioxazin degraded rapidly via hydrolysis of the phthalimide group to form 482-HA which further degraded to THPA and APF (Fig. 1.2). A second degradation pathway

proceeded via reduction of the cyclohexene double bond in 482-HA to form SAT-482-HA. It was also stated that it was possible, but unlikely that reduction preceded hydrolysis. THPA degraded to HPA by reduction of the double bond in THPA or hydrolyzed (Michael type reaction) to 1-OH-HPA. The side chain alkyne in APF was reduced to DAPF. Degradation continued to form multiple polar fragments, sediment-bound residues, methane and CO_2.Under aerobic conditions, the primary pathway involved hydrolytic cleavage and separation of the phthalimido and benzoxazin moieties at the amine bridge to yield APF and THPA. Other products identified included Δ-TPA, SAT-482-HA-2, IMOXA, 482-HA, 482-CA, and SAT-482. Mineralization to CO_2 occurred with both moieties, but was most significant with the phthalimido moiety. Formation of bound sediment residues was significant for both moieties.

1.6.8 Degradate Profile

Twelve degradates were detected in various laboratory abiotic and biotic fate studies. The major degradates are 482-A, APF, THPA, Δ-TPA, adipic acid, 482-PHO, 482-PHO-ISO, 482-PHO-DC, SAT-482-HA-2, DAPF, SAT-482-HA, HPA, and combined residues of THPA+ Δ-TPA. USEPA concluded that hydrolysis is a major route of dissipation for flumioxazin in the environment especially in alkaline aqueous media (half-lives = 4.2, 1, and 0.01 days, respectively, at pH 5, 7, and 9). As a result, the three major degradates generated with hydrolysis (APF, THPA, and 482-HA) are expected to occur as the major degradates in the environment and were considered in the human health and ecological risk assessments in this document.

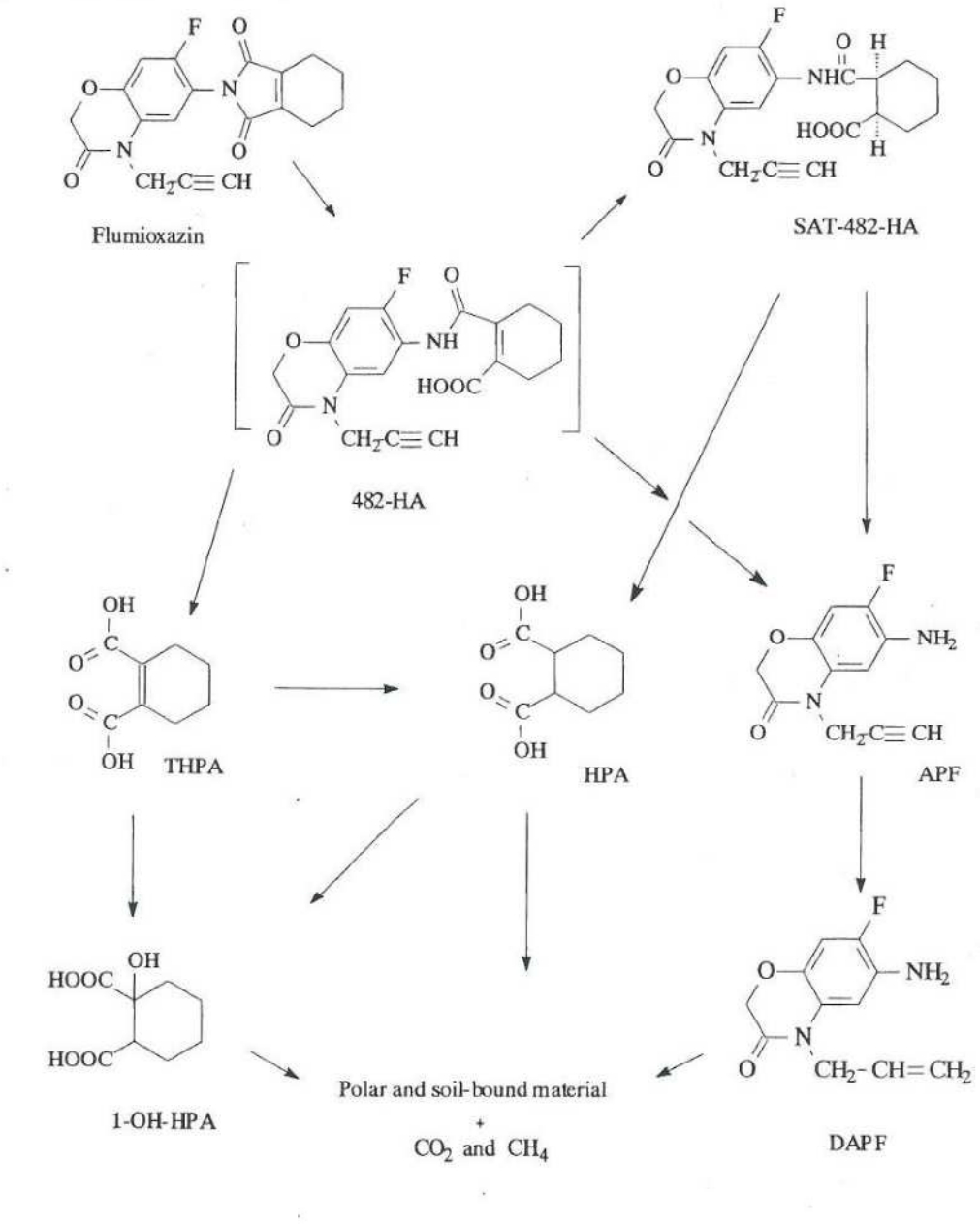

Figure 1.2. Proposed degradation pathway of flumioxazin in an aquatic anaerobic metabolism system (USEPA, 2011B)

A recent study provides additional information and insights into the aerobic aquatic dissipation and degradation profile of flumioxazin (Shibata et al., 2011). Water and sediments were collected from a pond in Japan and a lake in the UK and were used in laboratory-scale systems consisting of water or water plus sediments under illumination and in darkness. Flumioxazin was rapidly degraded in the overlying waters irrespective of illumination with half-lives of 0.1-0.4 days. Four major degradates were formed under illumination. The degradates 482-HA and THPA were formed through successive hydrolysis. Two other degradates (2-arizidinone derivatives)

were formed via photo-induced rearrangement. The presence of sediment under illumination greatly reduced the formation of these degradates and accelerated their degradation. The degradate APF was only detected as a minor fraction in one of the studied systems. The degradation profiles of flumioxazin in an illuminated water-sediment system are shown in Fig. 1.3 and Fig. 1.4. After 30 days, 50% of the applied radioactivity was present in the sediment phase and 17.3% was present in the water phase and 7.5% in the gas phase (CO_2), adding up to a total of 80.9% that was accounted for. The authors did not comment on this difference, but in comparison with their other studied systems, the fraction in the gas phase seems to be low in the system displayed in Fig. 1.3 and Fig. 1.4.

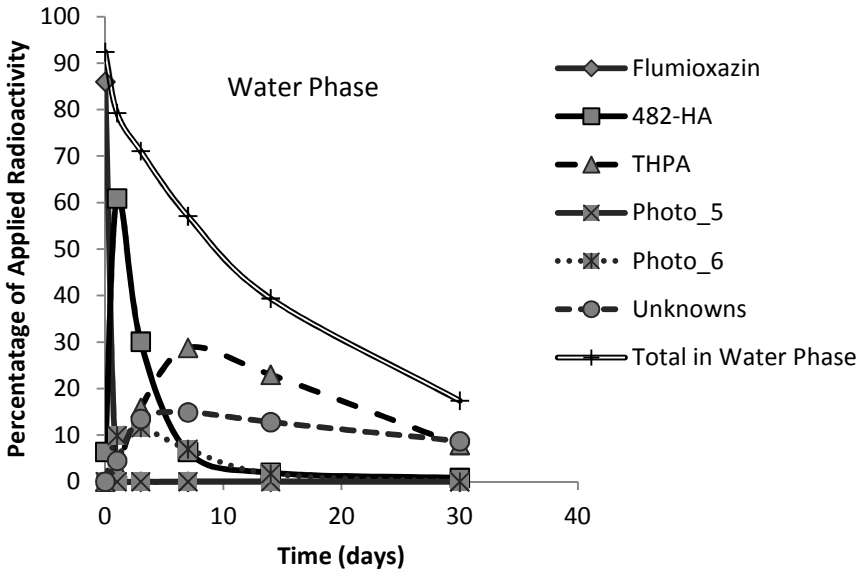

Figure 1.3. Distribution of ^{14}C-labeled flumioxazin and degradates in the **water phase** of the illuminated water-sediment system (Calwich Abbey system) generated based on data in Table 7 in Shibata et al. (2011). Symbols are the data points and smoothed lines were added to highlight trends.

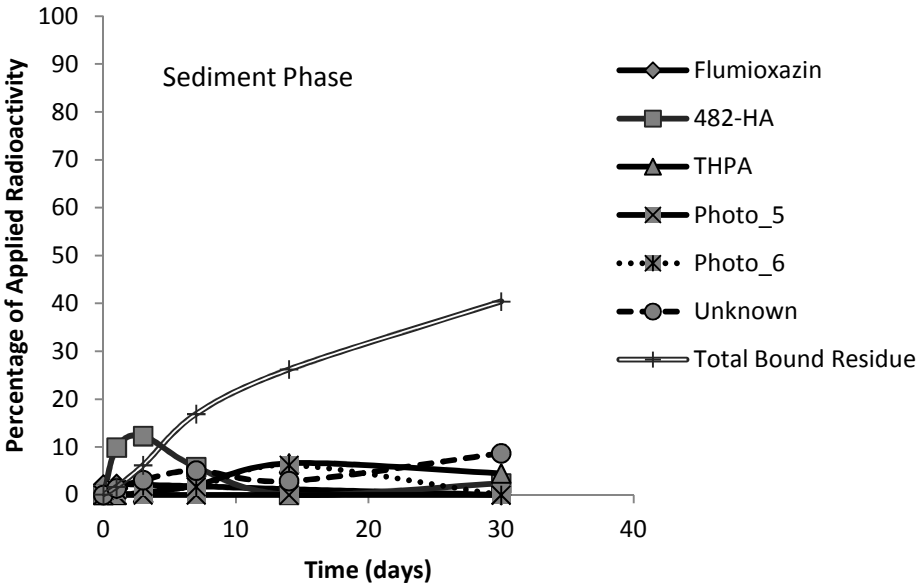

Figure 1.4. Distribution of ^{14}C-labeled flumioxazin and degradates in the **sediment** phase of the illuminated water-sediment system (Calwich Abbey system) generated based on data in Table 7 in Shibata et al. (2011). Symbols are the data points and smoothed lines were added to highlight trends.

1.6.9 Field Dissipation Studies

The environmental fate laboratory studies results indicate that the major routes of dissipation of flumioxazin in the environment appear to be rapid hydrolysis, photolysis, and metabolism of the parent compound. Field dissipation in soil was evaluated in field plots in Mississippi (silt loam), Illinois (silt loam), Iowa (silt loam), North Carolina (loamy sand), Indiana (loam soil) and California (soil type not reported). The application rates were in the range of 42-45 g flumioxazin /acre, except on the plot in California where the rate was 182 g flumioxazin/acre. The median of the half-lives was 12.5 days (range of 4.8 to 42 days). Flumioxazin generally did not leach below the 0- to 3-inch top soil layer, except for a single detection in the 3-6 inch depth layer in the Iowa plot. On the plot in California there were two detections in the 3-6 inch depth layer and a single detection in the 6-12 inch depth layer.

The aquatic field dissipation of flumioxazin was studied using a pond at one site in Iowa (average depth not specified; volume, 2.54 acre/ft) and a 0.469-acre pond at one site in Florida (average depth, 4 ft; volume, 1.88 acre/ft). These studies were conducted by the registrant of flumioxazin (MRID 47550605). Water and sediment samples were collected from each test site at 0-2 hours, 12-14 hours, and at approximately 1, 3, 5, 7, 14, 28, 60, and 90 days post-treatment. Pond water samples were collected at three depths: at 1 foot below the water surface, at mid depth, and at 1 foot above the pond bottom. Sediment samples were collected to a depth of 10 cm. Water and sediment samples were analyzed for flumioxazin and the two transformation products 482-HA and APF. The results from the Iowa study were available in EPA's review document and are summarized below.

The concentration profiles in water phase are shown in Fig. 1.5. It was not stated what the initially applied concentration was, but from the available information it can be inferred that the applied concentration likely must have been 400 µg/L (233 µg/L is 58.3% of 400). The measured levels of 482-HA of more than 300 µg/L are only possible with an initial concentration of higher than 233 µg/L).

The half-life of flumioxazin was not reported. *482-HA* had a reviewer-calculated linear, first-order half-life value of 4.9 days (r^2 = 0.94), and a nonlinear (one-compartment/two-parameter) half-life value of 2.6 days (r^2 = 0.98) in pond water, calculated based on the reviewer-calculated means across all sampling depths (0-28 day data). *APF* had a reviewer-calculated linear, first-order half-life value of 10.5 days (r^2 = 0.63), and a nonlinear (one-compartment/two-parameter) half-live value of 2.7 days (r^2 = 0.97) in pond water, calculated based on the reviewer-calculated means across all sampling depths (0-28 day data).

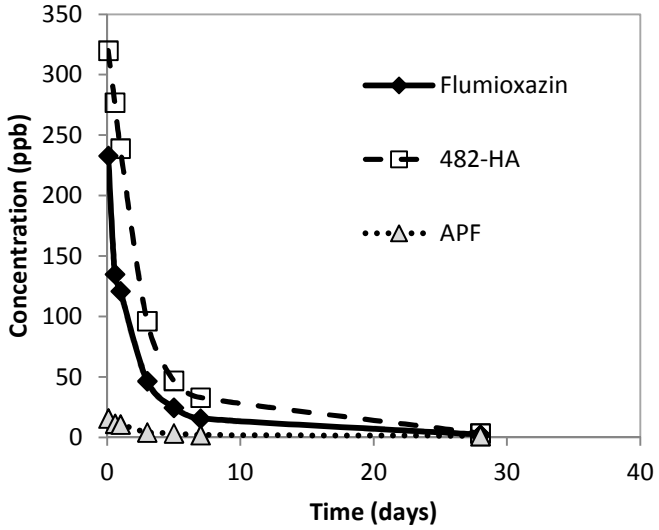

Figure 1.5 Concentrations of flumioxazin and degradates 482-HA and APF observed in the water phase of a pond in Iowa

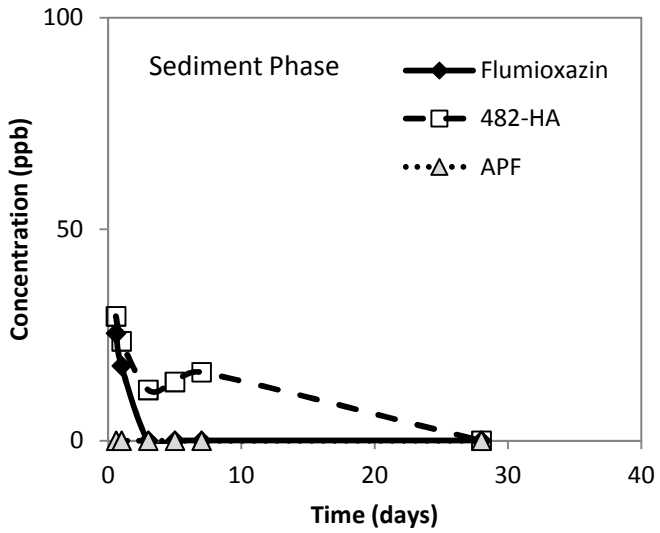

Figure 1.6. Concentrations of flumioxazin and degradates 482-HA and APF observed in the sediment phase of a pond in Iowa

The concentration profiles in sediment phase are shown in Fig. 1.6. *482-HA* had a reviewer-calculated linear, first-order half-life value of 3.3 days ($r^2 = 0.08$), and a nonlinear (one-compartment/two-parameter) half-live value of 2.5 days ($r^2 = 0.63$) in pond sediment, based on all replicate concentration data which occur on intervals with replicate values above the LOQ (0.5-7 days; replicate values below the LOQ were assumed at ½ LOQ). The transformation product APF was not detected in the pond sediment above the LOQ at any sampling intervals.

The registrant provided a field study conducted in two water bodies in the state of Michigan during 2011 (Fausey, 2011). The persistence of flumioxazin was monitored and the performance of this herbicide was evaluated. Selected areas in the two lakes with a depth of 5 feet were treated with 200 µg/L of flumioxazin. Water samples were taken at 0, 1, and 24 hours after treatment and were analyzed. The results showed that flumioxazin levels had declined to levels below 50 µg/L 24 hours after treatment.

2 Human Health Risk Assessment

The Health Effects Division (HED) of EPA conducted a risk assessment in conjunction with the registration of aquatic use for flumioxazin (USEPA, 2010C). That document was also the primary source of information for the registration review scoping document (USEPA, 2011C). These risk assessment documents are based on registrant-submitted studies which are generally not released or made available to individuals outside of the EPA Office of Pesticides. Summarized below are the hazard characterization and endpoint selection, assessments for dietary risk, risk associated with recreational use, and a drinking water assessment.

2.1. Hazard Characterization and Toxicity Endpoint Selection

Flumioxazin exhibited mild or no acute toxicity (categories III and IV) by oral, dermal and inhalation exposure routes. It also is classified in the same categories for primary eye and skin irritation and is not a dermal sensitizer. Subchronic and chronic toxicity studies demonstrated that toxic effects of flumioxazin exposure include anemia, and effects on the liver and the cardiovascular system. Developmental effects were observed in rat studies, but not in rabbit studies.

In utero exposure to flumioxazin has been associated with developmental and reproductive toxicity in rats. In one oral gavage developmental study with rats, animals were dosed daily on gestation days 6-15 at with 1,3,10 and 30 mg/kg study (Kawamura et al., 1995). No maternal effects were seen in the study. Developmental toxicity was seen at 30 mg/kg including significant increases in ventricular septal defects (VSD), embryolethality and skeletal defects (curvature of the scapula and wavy ribs) and decreased fetal growth.

The same study included a mechanistic study to identify the sensitive period during gestation to the herbicide. Rats were given single doses of 400 mg/kg on one of gestational days 11-15. The highest incidences of embryonic death and VSD and reduction of fetal body weight occurred when dosing took place on day 12.

In a dermal prenatal developmental study, no maternal effects were seen at the highest dose tested (300 mg/kg/day), but effects in fetuses were observed at a dose of 100 mg/kg/day. The effects were fetal cardiovascular anomalies, especially ventricular septal defects. Information on dosing regime was not available in EPA's summary document.

In a 2-generation reproduction study, systemic effects were observed in adult animals at the highest doses tested (HDT) of 18.9 mg/kg/day in males and 22.7 mg/kg/day in females. The observed effects included clinical signs and mortality as well as a decrease in body weight and body weight gain, and in food consumption. Offspring effects were also observed and included decreased pup body weights, a decrease in the number of live born, decreased mating index, and testicular atrophy in F1 males. Information on dosing regime was not available in EPA's summary document.

In contrast to the studies with rats, there was no evidence of susceptibility to developmental toxicity in rabbit studies. The absence of effects in rabbits was supported by literature studies indicating that rabbits are less susceptible to effects of PPO inhibitors.

No neurotoxicity studies are available. The review by the U.S. EPA Hazard Identification Assessment Review Committee stated that the acute, subchronic, chronic, developmental and reproduction studies did not indicate that flumioxazin had an effect on the nervous system (USEPA, 2004). According to new data requirements which became effective in 2007, neurotoxicity studies must be submitted. These studies will be required with registration review (USEPA, 2010C).

Flumioxazin was classified as "not likely to be a human carcinogen". This assessment was based on studies with rats and mice that indicated that flumioxazin did not induce significant increases in any tumor type in either rats or mice. In addition, it did not exhibit any mutagenic activity.

Flumioxazin is extensively excreted with urine and feces. Metabolism studies in rats indicated that recovery of flumioxazin in feces and urine was over 90%, with 4 – 5 times more excreted in feces than in urine. Highest levels of residues were found in blood cells (35.9-48.8 μg/L), which was much higher than the plasma levels (0.5-0.7 μg/L). In addition to untransformed parent compound, 7 metabolites were identified in urine and feces.

The EPA selected cardiovascular effects observed in oral developmental and pre-natal studies in rats as the basis for their acute dietary risk assessment. This endpoint is only applicable to females of child-bearing age (i.e., females of 13-49 years of age). The acute oral reference dose (aRfD) of 0.03 mg/kg was established for females in the 13-49 age group based on a NOAEL of 3 mg/kg for cardiovascular defects in rat fetuses seen at a LOAEL of 10 mg/kg. No acute oral endpoint was identified in the database for children or the general population. A chronic reference dose (cRfD) of 0.02 mg/kg/day was established for all populations based on a NOAEL of 2.0 mg/kg/day for increased chronic nephropathy in males and decreased hematological parameters in females. A NOAEL of 30 mg/kg/day from a rat dermal development toxicity study was selected for short- and intermediate-term dermal risk assessments for adults. For children exposed via the dermal route, the NOAEL of 6.3 mg/kg/day from the rat reproduction study was selected for risk assessment. For short- and intermediate oral exposure, the NOAEL of 6.3 mg/kg/day for reproduction and fertility effects in rat was selected as the dose for risk assessment. Since dosing information is not available in EPA's summary document, the dose units reported above cannot be verified.

Although the developmental and reproductive toxicity studies indicated that there was an increase in susceptibility for effects, HED's degree of concern for the susceptibility observed in the rat developmental and reproductive studies is low. This is because the regulatory endpoints for flumioxazin are based on clear no-observable-adverse-effect-levels (NOAELs) for developmental and reproduction studies. Doses and endpoints for risk assessment were chosen to be protective of cardiovascular and hematopoietic effects. It was concluded that there are no residual concerns for these effects. There are data that indicate differential species sensitivities to PPO chemicals. The Kawamura (1995) study showed a 100x difference in sensitivity between rats and rabbits (the insensitive ones for D/R toxicity). Pauli and Kennedy (2005) looked at

another endpoint (porphyria) using another herbicide having the same mechanism of action as flumioxazin and noted major differences in species sensitivities:(rats and hamsters were not affected whereas lab mice were strongly affected. Field mice and meadow voles were not affected. The authors concluded that the lab mouse strain was unique in its sensitivity to this herbicide.

2.2 Risk Associated with Recreational Uses of Water Bodies

Since there is no label restriction for swimming in treated water bodies, there is potential for exposure to flumioxazin with recreational activities. EPA used the SWIMMODEL to assess short-term post-application exposures and risks for children and adults. The SWIMMODEL uses well-accepted screening-exposure assessment equations to calculate the total worst-case exposure for swimmers expressed as a mass-based intake value (mg/event). The model considers dermal and oral exposures. The assessment was based on an exposure concentration of 400 μg/L. A margin-of-exposure (MOE) of 100 is considered sufficient to protect swimmers. The swimmer assessments indicated that all MOEs are above the level-of-concern (LOC) of 100 with values of 2,300 and 15,000 for oral and dermal exposure to a child, respectively. For an adult these values were 3000 and 84,000, respectively.

There are no label fishing restrictions in treated water and no fish consumption restrictions. Flumioxazin residues were measured in edible fish tissues (bluegill and channel catfish) over a 28-day period of exposure after flumioxazin application at 800 μg/L, which is equal to two times the maximum aquatic application rate of 400 μg/L. Total residues measured at the earliest sampling interval of 4 hours were 0.85-2.52 mg/L. Total residues declined rapidly by day 3 and then remained relatively steady up to day 28 in the range of 0.063-0.204 mg/L. Flumioxazin did not bioaccumulate in fish over the 28-day study. A tolerance of 1.5 mg/L has been established for freshwater fish. The data above indicate that the range of sampling results from the earliest sampling interval encompasses levels that exceed the tolerance of 1.5 mg/L. However, it seems unlikely that total residues of flumioxazin in fish would reach or exceed the tolerance level when the commonly used application rate of 200 μg/L is employed which is approximately 0.25 of the level used in the reported experiment.

Aggregate risk was assessed by combining residential exposures from swimming and handlers applying the herbicide for weed control with chronic dietary exposure. The MOE for adults was 694 and 470 for children. These exposure levels are above the LOC of 100 and aggregate risk is therefore not of concern.

2.3 Drinking Water Assessment

The drinking water residue profile was characterized by estimation of environmental concentrations of flumioxazin and its major degradates (482-HA, APF and THPA) in surface water following the application of flumioxazin (USEPA, 2010B). Ground water concentrations were not estimated by EPA since they judged the potential for flumioxazin to reach groundwater as low. Based on their Koc, the potential for APF and THPA to leach to groundwater is higher than the parent compound. However, the mobility of flumioxazin's major degradation product (482-HA) detected in the hydrolysis and the unidentified residues detected in the aqueous photolysis and anaerobic aquatic metabolism studies is unknown. These residues may persist in

the environment and may leach to groundwater.

Water concentrations of flumioxazin and its hydrolysis degradates 482-HA, APF, and THPA were estimated for the highest proposed aquatic use level of 400 μg/L of flumioxazin in a treated water body, six applications per year at an application interval of 28 days. The chronic EECs of flumioxazin and its degradates during a period of one year were calculated based on hydrolysis parameters for breakdown of the parent and formation the degradates. Since metabolism and field studies indicated that the degradates were not persistent, the degradate EECs would represent the worst case scenario.

THPA was not included in the residue of concern for drinking water because it was expected to have significantly lower toxicity than the parent and the other degradates. EPA did not provide further information or data to support this decision. For the purpose of the review presented here, information on the toxicity of flumioxazin and the three degradates was generated through the use of TOXTREE software [2]. TOXTREE is an application which is able to estimate toxic hazard and places chemicals into categories by applying a decision tree approach. The evaluation of flumioxazin and its degradates was done based on the option using the Cramer classification scheme which places compounds into one of three classes. Flumioxazin, 482-HA and APF were identified as Class III substances, which are those that permit no strong initial presumption of safety, or may even suggest significant toxicity or have reactive functional groups. THPA was identified as a Class I substance which are simple chemical structures with efficient modes of metabolism suggesting a low order of oral toxicity. These results support the decision by EPA to not include THPA in the drinking water assessment based on lower toxicity.

The acute exposure concentration used in EPA's assessment was 400 μg/L based on the initial concentration of flumioxazin immediately following the application. The total EEC at day 30 and after was calculated at 142 μg/L (10.4 μg/L flumioxazin + 21.6 μg/L 482-HA + 110.1 μg/L APF) as an estimated total residue level for chronic exposure. This represents a worst-case scenario for aquatic exposure levels.

For the purpose of this review, the risk of exposure through drinking water was assessed by comparing the EECs of flumioxazin to human health benchmarks that have been established for this active ingredient. These human health benchmarks for pesticides are levels of certain pesticides in water at or below which adverse health effects are not anticipated from one-day or lifetime exposures. EPA developed the human health benchmarks for pesticides to enable states, water systems and the public to better determine whether the detection of a pesticide in drinking water or source waters for drinking water may indicate a potential health risk (USEPA, 2012C). For flumioxazin, the acute benchmark value is 999 μg/L and 140 μg/L for chronic exposures. The acute value is based upon the prevention of developmental cardiovascular defects.

The assumed acute EEC of 400 μg/L is less than half of the acute benchmark value. The chronic EEC for flumioxazin of 10.4 μg/L is also much lower than the benchmark. However, the degradates APF and 482-HA are assumed to have similar toxicity to that of the parent. The total

[2] TOXTREE was developed for the European Commission's Institute for Health and Consumer Protection. Information is available at: http://toxtree.sourceforge.net/

EEC of 142 µg/L is therefore similar to the chronic benchmark. It should be pointed out that the EECs used by EPA represent worst-case scenarios assuming frequent applications and persistence of degradates. Field dissipation studies have indicated chronic residues are lower. For example, the dissipation data from a pond in Iowa (see Section 2.4) at day 7 showed 15.6 µg/L flumioxazin, 32.9 µg/L 482-HA and 1.99 µg/L APF, which makes a total of 50.5 µg/L. We modeled expected EECs for the typical single application concentration of 200 µg/L (Section 3.2.1) and projected a total 21-d average residue of 74.9 µg/L (sum of flumioxazin, 482-HA and APF concentrations) and a total 60-d average residue of 30.8 µg/L; both well below their respective duration specific benchmarks.

For groundwater exposure, one can consider a conservative screening-level scenario of the recharge of groundwater with surface water with no attenuation resulting in groundwater EECs with the same values as presented above for treated surface water.

The comparison of expected levels in water bodies and human health benchmark values indicate that effects on human health are unlikely to occur from exposure via drinking water containing residues of flumioxazin from aquatic applications.

2.4. Deficiencies and Data Gaps

HED has evaluated the status of the human-health assessments for flumioxazin to determine whether sufficient data are available and whether any updates are needed to support Registration Review (USEPA, 2011A). The Agency anticipates that acute and chronic neurotoxicity studies as well as an immunotoxicity study will be required to support registration review. These studies are new data requirements for pesticides. In addition, an inhalation study is required to fully characterize the toxic effects resulting from this route of exposure. Multi-residue Methods Testing for flumioxazin and water degradates 482-HA and APF are also required.

Aggregate assessments will be updated to include any changes that have been made in toxicological endpoints, or exposure estimates. Revised assessments will be conducted for all scenarios based on updated points of departure and procedures for ingestion, dermal and inhalation risk assessment.

3.0 Ecological Risk Assessment

USEPA conducted an ecological risk assessment as part of the evaluation associated with the registration for the use of flumioxazin to control vegetation in aquatic sites (USEPA, 2010A). The flumioxazin analysis consisted of assessment of exposure concentrations, and evaluating toxicity information to characterize potential risks to non-target species in the environment. The analysis is based on a screening-level assessment of estimated exposure concentrations combined with information from flumioxazin toxicity studies.

3.1 Ecological Hazard Characterization

The risk assessment document by USEPA (2010A) summarizes the effects characterization for flumioxazin as described below.

3.1.1 Toxicity to Aquatic Animals

Table 3.1 summarizes the toxicity data for aquatic animals. The data from the various categories of aquatic animals are described below.

Freshwater Fish: In acute toxicity studies conducted on coldwater and warm-water species, the 96-hour LC_{50} values for the technical grade material ranged from 2.3 to > 21 mg/L, suggesting that flumioxazin will be moderately to slightly acutely toxic to freshwater fish. An early life-stage toxicity test conducted on rainbow trout showed that flumioxazin significantly affected larval growth (length and weight) at concentrations with a lowest-observable-adverse-effect-concentration (LOAEC) of 16.0 µg/L and a no-observable-adverse-effect concentration (NOAEC) of 7.7 µg/L. Standard toxicity testing may not include light with the same wavelength or intensity as natural sunlight. LDPHs may be more toxic when exposed to natural sunlight, such as exposure conditions in the field. EPA has requested studies to address this uncertainty.

EPA typically uses fish as a surrogate for aquatic-phase amphibians when aquatic-phase amphibian toxicity data are not available. While EPA does not make reference to specific data in support of this practice, several reviews of acute and chronic toxicity data in the literature indicate that this approach is justified in most cases (Mayer and Ellersieck, 1986; Kerby et al., 2010; Weltje et al., 2013).

Freshwater Invertebrates: Acute toxicity studies conducted on freshwater aquatic invertebrates suggest that the active ingredient flumioxazin is moderately toxic. The 48-hour LC_{50} or EC_{50} value was 5.5 mg/L. The chronic data indicate that flumioxazin significantly reduced reproduction at concentrations equal to a LOAEC of 57 µg/L and a NOAEC of 28 µg/L and survival and growth (length and weight) at concentrations equal to 107 µg/L (LOAEC) and 57 µg/L (NOAEC).

Table 3.1 Toxicity of Flumioxazin to Aquatic Animals

Freshwater Fish Acute Toxicity			
Species	*96-hour LC50 (mg/L)*	*Toxicity Category*	
Rainbow trout *(Oncorhynchus mykiss)*	2.3	Moderately toxic	
Rainbow trout *(Oncorhynchus mykiss)*	>2.4 (OECD 21-day test)	Moderately toxic	
Bluegill sunfish *(Lepomis macrochirus)*	> 21.0	Slightly toxic	
Freshwater Fish Early Life-Stage Toxicity Under Flow-through Conditions			
Species	*NOAEC/LOAEC (*µg/L*)*	*MATC*[1] *(*µg/L*)*	*Endpoints Affected*
Rainbow trout *(Oncorhynchus mykiss)*	7.7/16.0	11.0	Growth (length and wt.)
Freshwater Invertebrate Acute Toxicity			
Species	*48-hour LC50/ EC50 (mg/L)*	*Toxicity Category*	
Waterflea *(Daphnia pulex)*	5.5	Moderately toxic	
Freshwater Invertebrate, Chronic			
Species	*21-day NOAEC/LOAEC (µg/L)*	*MATC*[1] *(µg/L)*	*Endpoints Affected*
Waterflea *(Daphnia magna)*	28.0/57.0	40.0	Reproduction, survival and growth
Estuarine/Marine Fish and Invertebrates Acute Toxicity			
Species	*96-hour LC50 (mg/L)*	*Toxicity Category*	
Sheepshead minnow *(Cyprinodon variegatus)*	>4.7	Moderately toxic	
Eastern oyster (Shell deposition) *(Crassostrea virginica)*	2.4	Moderately toxic	
Mysid *(Mysidopsis bahia)*	0.23	Highly toxic	
Estuarine/marine Aquatic Invertebrate Life-Cycle Toxicity			
Species	*21-day NOAEC/LOEAC (µg/L)*	*MATC*[1] *(µg/L)*	*Endpoints Affected*
Mysid *(Mysidopsis bahia)*	15.0/27.0	20.0	Reproduction, survival and growth

[1] Maximum Allowed Toxic Concentration, defined as the geometric mean of the NOAEC and LOAEC

Estuarine/Marine Fish: Testing on sheepshead minnow resulted in a 96-hour LC_{50} of >4.7 mg/L, which is considered to be moderately acutely toxic. No data were submitted to assess chronic risk to estuarine/marine fish.

Estuarine/Marine Invertebrates: Acute toxicity testing on estuarine/marine invertebrate species with the technical product resulted in 96-hour LC_{50} /EC_{50} values ranging from 2.4 to 0.23 mg/L which fall into the moderate to highly toxic acute classes for estuarine/marine invertebrates. The chronic data indicate that flumioxazin significantly reduced reproduction and growth (length and weight) at concentrations equal to 27 µg/L (LOAEC) and 15 µg/L (NOAEC) and survival at concentrations equal to 55 µg/L (LOAEC) and 27 µg/L (NOAEC).

Given that flumioxazin has been shown to produce developmental effects after exposure during one critical day early in the developmental stage in mammals, and given the similarities in developmental phases across all gestational organisms, developmental toxicity could actually be produced acutely in other aquatic species. Though this would be difficult to demonstrate given the types of tests typically conducted to assess toxicity, the developmental information showing this acute developmental toxicity for this chemical is noteworthy.

3.1.2 Toxicity to Terrestrial Species

Mammalian Species: Laboratory studies with rats indicated that flumioxazin was practically non-acutely lethal to small mammals with oral exposure (LD_{50} of 5000 mg/kg). Results from a chronic 2-generation reproduction study with rats at dietary levels of 0, 50, 100, 200, and 300 mg/kg indicate reproductive toxicity at a LOAEL of 200 mg/kg (NOAEL of 100 mg/kg) with decreased number of live-born pups and decreased pup weights. Increases in the incidence of reproductive organ abnormalities (predominately atrophied or hypoplastic testes and/or epididymides) were also noted that may imply an endocrine modulated pathway. Absolute organ weight for the testes, epididymides and prostate were significantly reduced at 300 mg/kg for F1 males. There was also decreased mating index and testicular atrophy in F1 males.

A more complete summary of mammalian toxicity studies was provided in Section 2.1, including identification of key rat studies used by the USEPA for identification of acute and chronic toxicity values (NOAELS of 0.3 and 0.2 mg/kg respectively) which can be used as the basis for identifying reference doses for terrestrial species derived from the rat data. *Avian Species:* In an acute oral toxicity study conducted on bobwhite quail, the LD_{50} for the technical product is >2250 mg/kg. The results suggest that flumioxazin is practically non-acutely toxic to birds via oral exposure. Subacute dietary toxicity studies conducted on mallard duck and bobwhite quail suggest that flumioxazin is also practically non-toxic, with LC_{50}s of > 5620 mg/kg for the technical grade active ingredient. An avian reproduction study on bobwhite quail indicated that there were no significant treatment related effects. The NOAEC and the LOAEC were 500 and >500 mg/kg, respectively. Also, an avian reproduction study using mallard ducks indicated that significant reductions in the number of viable embryos and live 3-week embryos were evident at the highest concentration (500 mg/L). The (NOAEC and the LOAEC were 250 and 500 mg/kg, respectively.

Non-target Insects: Flumioxazin is practically non-acutely toxic to bees (LD_{50} > 105 µg/bee).

3.1.3 Toxicity to to Plants

Flumioxazin belongs to a class of herbicides known to have a photo-toxic mode of action in plants. Plant toxicity data are summarized below.

A seedling emergence study with terrestrial plants indicated that the most sensitive monocot and most sensitive parameter were ryegrass and dry weight, respectively. The EC_{50} and NOAEL for the study was 0.0037 lb ai/A and 0.003 lb ai/A, respectively. The most sensitive dicot and most sensitive parameter was lettuce and also dry weight, respectively. The EC_{25} and NOAEL for the study was 0.0008 lb ai/A and 0.0004 lb ai/A, respectively.

A vegetative vigor study with terrestrial plants indicated that the most sensitive monocot and most sensitive parameter were oat and dry weight, respectively. The EC_{50} and NOAEL for the study was 0.0071 lb ai/A and 0.006 lb ai/A, respectively. The most sensitive dicot and most sensitive parameter were cucumber and phytotoxicity, respectively. The EC_{25} and NOAEL for the study were 0.00008 lb ai/A and 0.00005 lb ai/A, respectively.

Toxicity to the freshwater green alga (*Selenastrum capricornutum*) was characterized with an EC_{50} of 1.02 µg/L and a NOAEC of 0.79 µg/L. Toxicity to the freshwater diatom (*Navicula pelliculosa*) was characterized by a EC_{50} of 1.4 µg/L and a NOAEC of 0.041 µg/L. Toxicity to the marine diatom (*Skeletonema costatum*) was characterized by an EC_{50} of 19.2 µg/L and a NOAEC of 1.9 µg/L. The 5-day toxicity to the freshwater blue-green alga (*Anabaena flos aquae*) was characterized by an EC_{50} of 0.83 µg/L and a NOAEC of 0.022 µg/L. These toxicity values indicate that flumioxazin is from moderately to very highly toxic to marine and freshwater algae.

The toxicity to the aquatic vascular plant duckweed (*Lemna gibba*) was characterized by an EC_{50} of 0.49 µg/L and a NOAEC of 0.22 µg/L.

These data indicate that flumioxazin has a high, non-selective, acute toxicity to all plants from terrestrial to planktonic unicellular to vascular aquatic plants.

3.1.4 Degradate Toxicity

The major flumioxazin degradates of concern are 482-HA, APF and THPA. Few data are available to assess the potential toxicity of these compounds. Therefore EPA conservatively assumed that they are equally as toxic as the parent compound. The aquatic exposure to flumioxazin was addressed through a total residues approach that includes concentrations of the parent, 482-HA, APF, and THPA. However, due to limitations in terrestrial models in addition to the mobility and relative lack of persistence of the degradates, the parent flumioxazin was assessed in the terrestrial risk assessment.

MDAR staff estimated the aquatic toxicity of degradates using the ECOSAR program (Appendix 1). The results indicate that the degradates have generally lower toxicity to aquatic organisms than flumioxazin (10 – 1310 lower, mean 254), except the APF degradate whose predicted toxicity for invertebrates (*Daphnia*) is similar to that of flumioxazin.

3.2 Exposure Assessment for Direct Applications to Water

3.2.1 Aquatic Exposure Assessment

The aquatic exposure assessment by USEPA was based on the maximum application rate with a target concentration of 400 µg/L flumioxazin. The concentration of the major degradates was estimated based on the hydrolysis degradation profile of flumioxazin. This assessment was similar to the drinking water assessment described in Section 2.5. The estimated surface water concentrations are listed in Table 3.2.

MDAR staff noted that the 21-day and 60-day average values for flumioxazin reported by USEPA were not averages but calculated concentrations on day 21 and day 60. The true average values were calculated by MDAR staff and were found to be 38 µg/L and 39 µg/L, respectively.

Table 3.2. Estimated Environmental Concentrations (EECs) for flumioxazin and its major degradates in surface water resulting from aquatic herbicide application (3 applications with 400 ug/L at 28-day intervals (USEPA, 2010A). The EEC values for the degradates were based on the hydrolysis degradation profile.

Compound	Peak (µg/L)	21-day "average" [1)] (µg/L)	60-day "average" [1)] (µg/L)
Flumioxazin	400	0.0002 (38)	25 (39)
482-HA	21.6	21.6	21.6
APF	110.1	110.1	110.1
THPA	88.9	88.9	88.9

[1] MDAR staff noted that these values were not averages but calculated concentrations for day 21 and day 60, respectively. The average values in parentheses were determined by MDAR staff.

To supplement the exposure assessment by USEPA described above, MDAR staff generated EECs of flumioxazin and its major degradates using simulations with the AQUATOX model. The degradation of flumioxazin and degradates was based on the half-lives observed in an aquatic field study in Iowa (see Section 1.4). The application scenario assumed a single application at 200 µg/L. The half-lives used for model input were 1 day for flumioxazin, 4.9 days for 482-HA and 10.5 days for APF. Since THPA was not monitored in the Iowa field study, it was assumed to have the same half-life as APF. This seems a reasonable assumption based on the hydrolysis degradation pattern that showed similar levels of these two degradates. Further details on the simulations can be found in Appendix 2. The AQUATOX model-generated concentration profiles are shown in Fig. 3.1. The concentration profiles show a rapid decline for flumioxazin with concurrent rapid appearance of 482-HA.This degradate, in turn, rapidly

declines and results in the simulated formation of APF and THPA. The AQUATOX estimated values for peak level, and 21-d and 60-d averages are listed in Table 3.3.

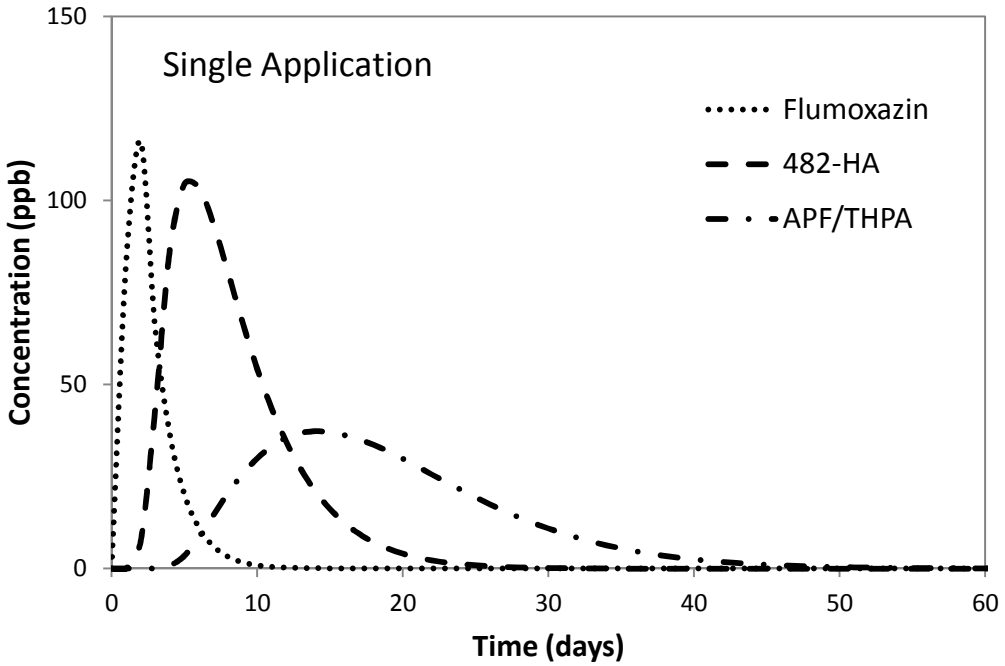

Figure 3.1 Aquatic concentrations of flumioxazin and its major degradates simulated by the AQUATOX model. The concentration profiles are the result of a single application at day 10 (May 10th). The degradation rates were based on half-lives observed in an aquatic field study in Iowa

Compared to the field data from an Iowa pond (Section 1.4) and the degradation profiles observed by Shibata et al. (2011), the model results show a somewhat more persistent flumioxazin and a slightly delayed appearance of the degradate 482-HA. The model also simulates a more prolonged presence in the water compared to the field and lab study results. The simulated dissipation profile for THPA is similar to the profiles observed in the field study and laboratory study by Shibata (2011). In the simulation, APF was assumed to be formed as a result from 482-HA degradation, but this degradate did not appear prominently in the Iowa field study or the laboratory study on aquatic fate by Shibata et al. (2011).

Table 3.3. Estimated Environmental Concentrations (EECs) for peak, 21-day and 60-day averages of Flumioxazin and major degradates based on AQUATOX simulated concentration in surface water. See Appendix 2 for more details on model simulations. Initially applied concentration of flumioxazin was **200** µg/L.

Compound	Peak (µg/L) (day)	21-day average (µg/L)	60-day average (µg/L)
Flumioxazin	200 (day 1)	15.7	5.6
482-HA	104 (day 4)	37.5	13.7
APF	37 (day 13)	21.7	11.5
THPA	37 (day 13)	21.7	11.5

Considering the exposure data review above, it is clear that overall the EPA assessment data represent a high-end exposure scenario. The peak value for flumioxazin assessed by EPA is the theoretical maximum concentration that may occur immediately following the application before any degradation would have taken place. In the Iowa field study, a peak concentration of 233 µg/L was observed two hours following the application, which was calculated to be 58% of the theoretical maximum of 400 µg/L. While the model-simulated peak concentration and field-measured peak concentration do not account for the initial brief exposure to maximum concentration, these results indicate that the exposure to the maximum concentration is very short. Uptake by target vegetation and degradation of flumioxazin results in a rapid decline of flumioxazin concentrations.

In contrast, the peak EEC for the degradate 482-HA used by EPA is much lower than the EEC based on AQUATOX simulation. The peak EEC for APF and THPA are also smaller than the EPA-assessed values, which is also attributable to the lower applied concentration. Overall, the values used by EPA for risk assessment are conservative. The AQUATOX simulated scenario represents a scenario that is used by vegetation management professionals. Comparison with the data from the Iowa field study and the laboratory study by Shibata et al. (2011) indicate that flumioxazin and its degradates are generally less persistent than indicated by exposure data from EPA or the AQUATOX simulation.

Partitioning between the water and sediment phases also affects the aquatic fate. The Iowa field study analyzed sediment which indicated that partitioning into sediment of flumioxazin and its major degradates did take place. Shibata et al. (2011) suggest that the presence of sediment reduced fractions of flumioxazin and degradates in the water phase and thereby reduced the potential for hydrolysis and photolysis. At the same time, these compounds are increasingly subjected to microbial degradation. Thereby, the sediment phase appeared to act as a sink for flumioxazin and degradates. The Shibata study points out that bound residue (detected by bound radioactivity) likely includes the fragments of advanced degradation to minor degradates. As the data indicate, the parent and major degradates were not present at significant levels.

3.2.2 Terrestrial Exposure Assessment

USEPA (2010A) assessed the risk to avian and terrestrial species based on a worst-case exposure scenario assuming that the entire application (0.383 lbs ai/A) is applied to the shoreline multiple times during the season. Exposure to birds and mammalian species was based on residues on various food items. This scenario would be highly conservative since the maximum surface application is not expected to be applied to any non-aquatic area. The maximum EEC on short grass was 206 mg/L, 116 mg/L on tall grass, 95 mg/L on broadleaf plants and insects, and 13 mg/L on seeds, fruits, and large insects.

Terrestrial plants inhabiting dry and semi-aquatic areas may be exposed to pesticides from runoff, spray drift or volatilization. Semi-aquatic areas are those low-lying wet areas that may be dry at certain times of the year. EFED's runoff scenario is: (1) based on a pesticide's water solubility and the amount of pesticide present on the soil surface and its top one inch, (2) characterized as "sheet runoff" (one treated acre to an adjacent acre) for dry areas, (3)

characterized as "channelized runoff" (10 treated acres to a distant low-lying acre) for semi-aquatic areas, and (4) based on % runoff values of 0.01, 0.02, and 0.05 for water solubility of <10 mg/L, 10-100 mg/L, and >100 mg/L, respectively. Spray drift exposure from ground application is assumed to be 1% of the application rate. Based on a single application of 0.38 lbs ai per acre, the total loading to an adjacent dry area was estimated to be 0.0077-0.0214 lbs ai/acre, 0.0421 lbs ai/acre to a semi-aquatic area, and 0.0038-0.0192 lbs ai/acre through spray drift.

Some ecologically important and common semi-aquatic terrestrial species such as muskrats and beaver may be exposed to herbicides applied to aquatic habitats through a variety of routes: water ingestion, dermal absorption, oral ingestion from preening activity and ingestion of contaminated vegetation. The risks to these 2 species from ingestion of water containing flumiozaxin and its degradates were assessed for the application scenario described in the human drinking water assessment (Section 2.4): a single 200 ug/L application giving peak, 21-day and 60-d average concentrations of the compounds (Table 3.3).

3.3 Risk Characterization and Risk Description

Ecological risk characterization integrates the exposure and ecotoxicity data to evaluate the likelihood of adverse ecological effects. EPA typically uses a deterministic approach to evaluate the likelihood of adverse ecological effects to non-target species. In this approach, risk quotients (RQs) are calculated by dividing EECs by ecotoxicity values for non-target species, both acute and chronic. RQs are then compared to established levels of concern (LOCs) (Appendix 3). These LOCs are criteria used by EPA to indicate potential risk to non-target organisms and the need to consider regulatory action or refined risk assessment. Terrestrial risk assessments were based on exposure to flumioxazin. Aquatic risk assessments were based on exposure to residues of flumioxazin and degradates 482-HA, APF and THPA.

3.3.1 Aquatic Animals

The individual compound RQs determined by EFED for freshwater fish and invertebrate species were in the range of 0.04 to 0.17 for acute risk and 2.8 to 14.28 for chronic risk (Table 3.4 and Appendix 3). The LOC for acute high risk is 0.5, 0.05 for endangered species, and 1 for chronic risk. Acute LOCs were exceeded for endangered freshwater fish and chronic LOCs were exceeded for all freshwater fish. The acute LOCs were exceeded for endangered invertebrates and chronic risk LOCs for flumioxazin, APF and THPA degradates.

Table 3.4 Summary of RQs for Aquatic Animals Determined by EPA-EFED. Shading indicates exceedance of LOC.

	Fish		Invertebrates	
Compound	Acute RQ	Chronic RQ	Acute RQ	Chronic RQ
Flumioxazin	0.170	1.500	0.070	1.350
482-HA	0.009	2.800	0.004	0.770
APF	0.047	14.280	0.020	3.930
THPA	0.038	11.540	0.010	3.170

The RQ values indicate that acute risk to endangered species is of concern, but chronic risk is of most concern. USEPA addressed the indicated risks by pointing out that the risks were calculated by using high-end EECs associated with the maximum application rates and degradation via hydrolysis. Real exposure levels are expected to be lower as is indicated by the results from monitoring concentrations in field studies. The highest RQs were determined for APF. As pointed out with the exposure assessment in Section 3.2.1, APF is expected *not* to occur as a prominent degradate based on data from field and laboratory aquatic fate studies. The next highest RQs were determined for THPA which is expected to occur based on field studies, but typically not at the levels as used in the USEPA risk assessment. Considering the conservative assumptions in the exposure assessments, EPA expected that real risks to aquatic organisms are lower than indicated by the RQ values discussed above.

Based on the indicated risks in EPA's risk assessment, MDAR performed a refined aquatic life risk assessment for the review presented here. Additional risk quotient calculations were performed for the exposure data from the field study in a pond in Iowa (Section 1.4) and for the refined exposure data from AQUATOX modeling (Table 3.3). The results of these calculations can be found in Appendix 4. Compared to EPA assessment, RQ values are generally lower, but certain LOCs are still exceeded.

EPA did not assess the combined effects of flumioxazin and its degradates. For the peak exposure data, a simple summation of all exposures is not realistic since the peak levels of the individual compounds do not occur at the same time (see also Table 3.3). For acute exposures, it is realistic to consider the peak concentrations of flumioxazin and its primary degradate 482-HA. For the 21-d and 60-d averaged exposure data, it is realistic to add the concentrations of flumioxazin and the three degradates to estimate the total exposure, although these longer term exposures are dominated by the occurrence of the APF and THPA degradates. Based on the assumption of equal toxicity, the RQ was calculated based on the total exposures. The results of this analysis are included in Table 1 and 2 in Appendix 4. Comparison of RQ with LOCs indicates acute risk for categories of endangered species and acute restricted use. However, the restricted use category does not apply to flumioxazin. The chronic risk LOC is exceeded for the EPA and DAR assessments, the assessment for the Iowa monitoring study data did not exceed the chronic LOC, but this is likely due to the lack of data for THPA exposure.

The risk characterization described above was based on the assumption of equal toxicity for flumioxazin and degradates. The risk assessment was further refined by use of ECOSAR-estimated toxicity endpoints for the degradates using the ECOSAR program. Details on this analysis are provided in Appendix 4. The results indicate that the degradates have generally a lower toxicity to aquatic organisms than flumioxazin, except the APF degradate for which the endpoints for invertebrates approach or are lower than the value for the parent.

The risk characterization was refined by adjusting the assumed toxicity endpoint values for the degradates. The ECOSAR-predicted toxicity endpoints were not directly used in the RQ calculation. Since the predicted toxicity values for flumioxazin were higher than the study data, a more conservative approach was used. The degradate endpoints were calculated by multiplying the endpoint point value for flumioxazin (study data) by the ratio of predicted degradate

endpoint/predicted endpoint for flumioxazin. RQ values were calculated for the AQUATOX-generated exposure data and the results can be found in Appendix 4. For the individual compounds acute LOC of 0.05 is only exceeded for flumioxazin exposure to endangered fish, and chronic LOCs of 1 is only exceeded with 21-d RQ for fish, the 60-d RQ does not exceed the chronic LOC. EPA uses 56 or 60-day RQ for chronic risk to fish[3].

The risk assessment was further refined by considering the concentration addition approach to estimate toxic unit (TU) summation for combined effect. Details on this assessment are described in Table 3 and 4 in Appendix 4. If one applies the same LOC thresholds for TU summation values, the LOCs for acute risk to endangered fish and 21-d TU for chronic effects to fish are exceeded. For invertebrates, the 21-d TU exceeds the LOC for chronic effects.

EPA did not assess the risks to estuarine/marine fish or invertebrates because the product may not be used in those areas. MDAR included a risk assessment for estuarine/marine organisms (Table 6 and 7 in Appendix 4). These data can be used as a reference point for evaluation of risks in situations where treated freshwater may enter into estuarine/coastal waters. Acute toxicity data for flumioxazin indicate that it is slightly less toxic to estuarine/marine organisms compared to freshwater organisms (Table 3.1). There are no chronic toxicity data available for estuarine/marine fish and therefore freshwater chronic toxicity data were used for risk characterization. Flumioxazin is highly toxic to marine invertebrates. RQs based on EECs in treated freshwater show LOC exceedances for 21-d chronic RQ for fish, and acute and chronic RQs for invertebrates from exposure to flumioxazin and APF degradate. The extent of dilution that would occur is an important factor to consider with an assessment of the potential for risk to estuarine/marine organisms in situations where treated freshwater mixes with saltwater . The length of time after herbicide treatment until mixing takes place with salt water is an important factor; flumioxazin dissipates rapidly and its levels decreases rapidly. Exposure levels used in the risk assessment of APF were based on modeling, but field studies have indicated that this degradate does not occur in significant concentrations.

As fish are used as a surrogate for aquatic-phase amphibians when aquatic-phase amphibian toxicity data are not available, the risk description of fish above also applies to aquatic-phase amphibians. The risk assessments do not specifically address benthic organisms.

3.3.2 Terrestrial Organisms

The RQs for birds (Appendix 3) are all below the LOCs for acute and chronic risks. These results indicate that no avian acute or chronic levels of concern are exceeded at registered maximum application rates.

USEPA's (2010A) discussion of acute risk to mammals states that the results suggest that mammalian acute levels of concern are not exceeded even under the highest multiple application

[3] Technical Overview of Ecological Risk Assessment Risk Characterization: EPA Office of Pesticide Programs; Information available at: http://www.epa.gov/oppefed1/ecorisk_ders/toera_risk.htm

rates. Flumioxazin is practically non-toxic to mammals (Section 3.1). Actual RQ values were not presented in the risk assessment document. The residues expected on mammalian food items after aquatic applications of flumioxazin products are based on the highest residue concentrations immediately after application. Furthermore, the exposure scenario would be highly conservative since the maximum surface application is not expected to be applied to any non-aquatic area, thus no risk is assumed.

The chronic LOC of 1.0 was slightly exceeded with RQs of 1.16 to 2.06 for small mammals eating short and tall grass in the multiple application of flumioxazin scenario. However, this exposure scenario was highly conservative since the product is to be used specifically on aquatic sites only. The exposure scenario used was a direct application to the shoreline.

For this report, we determined the risks from direct water ingestion of flumioxazin-treated waters by beavers and muskrats (see Appendix 4). RQ values were calculated as total daily ingested doses of flumioxazin and the degradates 482-HA and APF divided by the calculated duration-specific oral reference doses for those 2 species respectively. Exposures and risks from other routes were not quantitatively evaluated. Both acute and chronic ingestion risks for beavers and muskrats (0.02 – 0.05) were well below the LOC of 1. We do not believe that exposures from inhalation or dermal absorption could approach levels that would result in the total risks to these animals approaching the LOC (see discussion in Appendix 4). USEPA's analysis of contaminated vegetation ingestion risks noted above concluded no risk from that exposure route.

Currently, EFED does not assess risk of aquatic herbicides to non-target insects. Results of acceptable studies are used for recommending appropriate label precautions. As flumioxazin is practically non-toxic to honeybees, low risk is assumed.

3.3.3 Risk to Non-Target Plants

The maximum concentration in water (0.400 mg/L) and most sensitive endpoint (EC_{50} of 0.0005 mg/L for duckweed) were used to calculate the aquatic plant RQ. The RQ value of 800 exceeds the LOC of 1 and indicates that effects to aquatic plants from the application of flumioxazin to aquatic areas are likely. This is to be expected from the application of an herbicide to control targeted aquatic plants.

Endangered and non-endangered non-target plant species levels of concern are exceeded at maximum application rates. RQ values (Appendix 3) indicate that for single broadcast applications of flumioxazin, non-endangered non-target terrestrial and semi-aquatic plant species levels of concern are exceeded at maximum application rates (RQs ranged from 0.54 to 239.4); endangered species RQs ranged from 0.64 to 383 for single applications. A single maximum application rate of 0.38 lbs ai/acre is 54.7 to 7,660 times higher than the least (0.007 lbs ai/A) and most (0.00005 lbs ai/A) toxic NOAEL in submitted terrestrial plant studies, respectively. Since flumioxazin may exhibit phototoxicity and phytotoxicity, and RQs exceed LOCs, endangered and non-target terrestrial plant species are potentially at risk. This scenario is likely conservative since the maximum surface application is not expected to be applied to any non-aquatic areas where terrestrial plants may be exposed.

EPA does not specifically address the risk to planktonic unicellular algae. Based on the acute toxicity information for green algae (EC_{50} of 1.02 µg/L) and an acute exposure of 200-400 µg/L, the RQ would be approximately in the range of 200-400. This indicates that effects to green algae are likely from aquatic applications of flumioxazin.

A study by Umphres et al. (2012) provides information on effects of flumioxazin applications, including effects of flumioxazin on phytoplankton and zooplankton in a treated water body. The study evaluated the efficacy of flumioxazin for treatment of harmful algae blooms known as golden algae (*Prymnesium parvum*). In the US, golden algae occur mostly in brackish waters of the southern states and are of concern for causing extensive fish kills. Flumioxazin was applied to natural plankton communities during in-lake experiments using 20-L carboys filled with lake water and covered with 30% shade cloth to simulate natural *in-situ* light, temperature and turbulence conditions. The results from the experiment conducted during the pre-bloom period using application rates of 0-200 µg/L showed significant decreases in *P. parvum* densities, and total phytoplankton biomass. Adult copepod abundance slightly decreased compared to initial level at the highest rate of 200 µg/L. Adult copepod, copepod nauplii and rotifer densities all decreased in all flumioxazin concentrations. On the other hand, the cladocera abundance did not change significantly across doses levels. of inorganic nutrients showed opposite trends from phytoplankton, where declines in nitrogen and phosphorus were less with addition of flumioxazin. Effects from post-bloom treatment with flumioxazin were not as strong. *P. varvum* densities and total phytoplankton did not show significant differences with flumioxazin concentration. Nutrients showed a general increasing trend with flumioxazin concentration. Adult copepods increased compared to initial cove conditions, but less with flumioxazin concentration increase. Copepods nauplii decreased with higher flumioxazin concentrations. Cladocera and rotifers showed no trends with flumioxazin concentration increase. The absence of significant effects of flumioxazin treated during the post-bloom experiment was attributed to the limited light penetration due to higher turbidity which inhibits the light-sensitive mode of action of flumioxazin. The authors concluded that additional research is needed to better determine optimal application rates, timing, and factors such as cell density, light and pH. Ecosystem responses such as phytoplankton composition shifts also require further investigation.

3.3.4 Threatened and Endangered Species Concerns

In accordance with the Endangered Species Act, USEPA addressed the concerns for effects to federally threatened and endangered species (listed species) (USEPA, 2010A). For terrestrial and aquatic plant species as well as for freshwater fish and invertebrates evaluated in EPA's risk assessment, RQs exceeded the LOCs for the exposure scenarios considered (surface and subsurface applications to freshwater). Below is a summary of how USEPA plans to address the concerns during registration review.

The assessment of risk to listed species includes the identification of an action area, which for screening-level purposes, is conservatively assumed to be co-located with the pesticide treatment area.

An indirect effects analysis is done to assess the potential to exert indirect effects upon the listed organisms by, for example, perturbing forage or prey availability, altering the extent of nesting

habitat, and creating gaps in the food chain. In conducting a screen for indirect effects, direct effect LOCs for each taxonomic group are used to make inferences concerning the potential for indirect effects upon listed species that rely upon non-endangered organisms in these taxonomic groups as resources critical to their life cycle.

Because screening-level acute RQs exceeded the endangered species acute LOCs, USEPA uses the dose response relationship from the toxicity study used for calculating the RQ to estimate the probability of acute effects associated with an exposure equivalent to the EEC. This information serves as a guide to establish the need for and extent of additional analysis that may be performed.

Screening-level RQs for birds and mammals that feed on short grass, tall grass, broadleaf plants and small insects, and fruits, pods, and large insects that exceed the LOC may indicate a potential concern for indirect effects. USEPA considers this to be indicative of a potential for adverse effects to those listed species that rely either on a specific plant species (plant species obligate) or multiple plant species (plant dependent) for some important aspect of their life cycle. Alterations of habitats can affect the reproductive capacity of some terrestrial and aquatic animals. Due to the fact that terrestrial and aquatic plant RQs exceeded the endangered and non-endangered LOCs, all species may be affected due to indirect effects.

The screening-level risk assessment has identified potential concerns for indirect effects on listed species. In light of the potential for indirect effects, the next step for USEPA, and U.S. Fish and Wildlife Service and NOAA Fisheries Service (together referred to as the Services) is to identify which listed species and critical habitat are potentially implicated. At the time of the risk assessment, the information reviewed by USEPA did not permit a definitive identification of species that are potentially impacted indirectly or critical habitats that are potentially impacted directly by the use of the pesticide. USEPA and the Service(s) are working together to conduct the necessary analysis.

It should be noted that the potential impact to and protection of state-listed and endangered species in Massachusetts is addressed during the process of application for and review of aquatic herbicide applications licenses.

This approach is also used by the Department of Ecology in Washington State (WA) (Hamel, 2012). Risk mitigation of potential impacts to threatened and endangered species is done by requiring applicators to comply with timing windows. These windows either do not allow herbicide treatment or allow treatment at times when the herbicide will not affect the priority species or its food and habitat.

3.3.5 Uncertainties and Data Gaps

The uncertainties identified in the risk assessment for aquatic use of flumioxazin (USEPA, 2010A) are related to fate and toxicity of the degradates. The fate of the major degradates detected in the hydrolysis and the aqueous photolysis as well as those unidentified residues reported in the anaerobic aquatic metabolism study in the natural environments remains unknown.

At the time of the completion of the aquatic risk assessment (USEPA, 2010A), EFED did not require any additional fate data. In addition, the toxicities of the major degradates are unknown. EFED did not require toxicity studies at that time due to risk quotients indicating low concern. As pointed out in the review presented here, the RQs determined by USEPA can be considered to be of concern (Section 4.3). The refined risk assessment resulted in lower RQ values and fewer exceedances of LOCs.

USEPA (2010A) recommended that phototoxicity studies should be conducted on herbicides with the mode of action associated with LDPHs to determine if animals exposed to these LDPHs and intense light (similar to sunlight) show increased toxicity relative to controls exposed to LDPHs and low intensity light. The results of these studies will help to determine if animals that are exposed to sunlight in LDPH use areas are at higher risk than guideline toxicity studies suggest. USEPA expects that these data will become available for the registration review risk assessment of flumioxazin (USEPA, 2011A). At the time of the review presented here, these data were not available. Based on these data gaps, it is possible that risks to human health and aquatic life have been underestimated.

With the initiation of the registration review of flumioxazin, EFED performed a preliminary identification of data gaps (USEPA, 2011B). The data requirements for environmental fate of flumioxazin were all found to be satisfied. However, data gaps remain in the fate database for degradates. Relative to ecological effects, data gaps and uncertainties were identified and are described below. These data gaps will be addressed with the registration review. Missing information regarding anaerobic metabolism and information on benthic organism toxicity were not identified as data gaps by EPA.

Freshwater Invertebrate Acute LC_{50}: A study was submitted that examined the toxic effects of flumioxazin on freshwater invertebrates. However, the study showed high levels of precipitate in the solutions. These precipitates likely confounded the effects of the chemical itself. A new study is needed to address the uncertainty related to an accurate assessment of the toxicity of flumioxazin to freshwater free-swimming invertebrates.

No toxicity studies are available on flumioxazin effects on freshwater mussels. Massachusetts has a number of state-listed freshwater mussels and in general freshwater mussels are among the most endangered organisms in North America (Smith, n.d.)

Freshwater Fish Early Life-Stage: An additional study needs to address the potential UV light-enhanced toxicity for freshwater fish based on the LDPH nature of flumioxazin.

Estuarine/Marine Fish Early Life-Stage: It was determined that an early life-stage study is conditionally required. This determination was based on the condition of an EEC in water is ≥ 0.01 of the acute EC_{50} or LC_{50}. The 60 day average flumioxazin parent concentration was determined to be 25 µg/L, which is less than 0.01 of the acute LC50 of > 4.7 mg/L (0.01 * 4.7 mg/L = 47µg/L). However, the 60 day average concentration for the degradate APF was 110 µg/L (section 5.2.1.1). No data are available regarding the toxicity of any of the degradates.

Without these data, the degradates are assumed to be as toxic as the parent compound, and therefore the above condition is met. Considering that flumioxazin is an LDPH and may have enhanced toxicity under elevated light conditions, the results of the freshwater fish early life-stage test that addresses light-enhanced toxicity may be applied to the results of this study as appropriate.

Fish Full Life-Cycle: According to the CFR 40 part 158 guidelines, this study is conditionally required when "the end-use product is intended to be applied directly to water, or is expected to be transported to water from the intended use site, and when any of the following conditions apply:

- If the estimated environmental concentration (EEC) is ≥ 0.1 of the no-observed-effect level in the fish early-life stage or invertebrate life cycle test;
- If studies of other organisms indicate that the reproductive physiology of fish may be affected."

Flumioxazin has aquatic uses that indicate the chemical will be applied directly to freshwater systems, which meets the first part of the criteria. The peak EEC for parent flumioxazin based on the previous aquatic risk assessment (USEPA, 2010A) is 400 µg/L. The NOAEC in the fish early life-stage is 7.7 µg/L and in the invertebrate life-cycle is 28 µg/L. Therefore, 0.1 of the peak EEC (0.1*400 µg/L = 40 µg/L) is greater than both of these no effect levels, and therefore the second condition is also met. Furthermore, reproductive effects were observed in the freshwater invertebrate life-cycle test. A study on the fish full life-cycle is needed to address this remaining uncertainty of chronic risk to fish.

Avian Oral LD_{50}: CFR 40 part 158 guidelines require data on one passerine species and either a waterfowl or upland game bird species. Data has only been submitted for the Bobwhite quail. There is uncertainty as to the sensitivity of passerine species compared to other bird species. However, no mortality in any treatment group was reported in both the acute oral and dietary toxicity studies for avian species.

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APPENDICES

Appendix 1

Aquatic Toxicity Estimation of Flumioxazin, and its degradates 482-HA, APF, and THPA using ECOSAR Aquatic Toxicity Prediction Program

In absence of test data, the aquatic toxicity of THPA was estimated using the ECOSAR program. The Ecological Structure Activity Relationships (ECOSAR) Class Program is a computerized predictive system that estimates aquatic toxicity. The program estimates a chemical's acute (short-term) toxicity and chronic (long-term or delayed) toxicity to aquatic organisms such as fish, aquatic invertebrates, and aquatic plants by using computerized Structure Activity Relationships (SARs).[4)]

ECOSAR uses structure-activity relationships (SARs) to predict the aquatic toxicity of untested chemicals based on their structural similarity to chemicals for which aquatic studies are available. Application of structure activity relationships is a technique routinely used by the U.S. EPA Office of Pollution Prevention and Toxics under the New Chemicals Program. The toxicity data used to build the SARs are collected from publicly available experimental studies and confidential submissions provided to the U.S. EPA New Chemicals Program. The SARs in ECOSAR express correlations between a compound's physicochemical properties and its toxicity within specific chemical classes.

Through publication of the ECOSAR Model, the U.S. EPA provides public access to the same methods the EPA uses for evaluating aquatic toxicity. Many of the SARs have been validated through studies published in the open literature or through validation activities conducted by the U.S. EPA is conjunction with other regulatory agencies.

The results from the ECOSAR calculations for Flumioxazin, 482-HA, APF and THPA are included at the end of this document.

The predicted toxicity endpoint values as LC50/EC50s are summarized in Table 1. The values listed are the lowest predicted values for each compound. Comparison of the results indicates that the parent flumioxazin has generally the lowest endpoint values. The endpoint values for the degradates are generally higher, except the APF degradate for which the endpoints for *Daphnia* approach or are lower than the value for the parent flumioxazin.

[4] ECOSAR information available at: Ecological Structure Activity Relationships | New Chemicals Program | USEPA

Table 1 Summary of ECOSAR predicted toxicity endpoint values

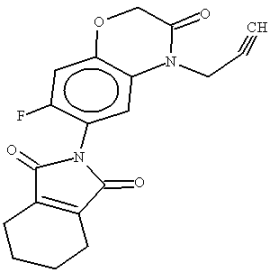
	Acute Toxicity Endpoints (mg/L)			Chronic Toxicity Endpoints (mg/L)		
	Fish 96-hr LC50	Daphnid 48-h LC50	Algae 96-h EC50	Fish	Daphnid	Algae
Flumioxazin[1]	16.7	11.4	0.55	0.10	0.15	0.59
482-HA[2]	1262	1022	19	32	88	6.2
APF[3]	395	5.5	16	3.1	0.16	11
THPA[4]	1259	712	341	131	83	131

[1] Lowest predicted values for ECOSAR class of amides
[2] Lowest predicted values for ECOSAR class of acrylamides-acid (fish, daphnid); class of amides-acid for green algae
[3] Lowest predicted values for ECOSAR class of anilines
[4] Lowest predicted values for ECOSAR class of neutral organic acids

Table 2 Ratios of Degradate endpoint (LC50/EC50)/Flumioxazin endpoint for values listed in Table 1.

	Ratio Degradate/Flumioxazin (acute)			Ratio Degradate/Flumioxazin (chronic)		
	Fish 96-hr LC50	Daphnid 48-h LC50	Algae 96-h EC50	Fish	Daphnid	Algae
Flumioxazin	1	1	1	1	1	1
482-HA	75.6	89.6	34.5	320.0	586.7	10.5
APF	23.7	0.5	29.1	31.0	1.1	18.6
THPA	75.4	62.5	620.0	1310.0	553.3	222.0

RESULTS FOR Flumioxazin:



SMILES : C#CCN1c2cc(c(cc2OCC1(=O))F)N3C(=O)C4=C(C3(=O))CCCC4
CHEM :
CAS Num: 635-08-5
ChemID1:
ChemID2:
ChemID3:
MOL FOR: C19 H15 F1 N2 O4
MOL WT : 354.34
Log Kow: 2.55 (User entered)
Melt Pt: 202.00 deg C
Wat Sol: 1.8 mg/L (measured)

ECOSAR v1.00a Class(es) Found

Imides
Amides

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Imides	: Fish	96-hr	LC50	38.448 *
Imides	: Daphnid	48-hr	LC50	44.288 *
Imides	: Green Algae	96-hr	EC50	3.390 *
Imides	: Fish		ChV	3.751 *!
Imides	: Daphnid		ChV	3.871 *!
Imides	: Green Algae		ChV	1.747
Amides	: Fish	96-hr	LC50	16.758 *
Amides	: Daphnid	48-hr	LC50	11.414 *
Amides	: Green Algae	96-hr	EC50	0.547
Amides	: Fish		ChV	0.099
Amides	: Daphnid		ChV	0.151 !
Amides	: Green Algae		ChV	0.592
Neutral Organic SAR	: Fish	96-hr	LC50	93.478 *
(Baseline Toxicity)	: Daphnid	48-hr	LC50	57.648 *
	: Green Algae	96-hr	EC50	31.146 *
	: Fish		ChV	8.767 *
	: Daphnid		ChV	5.868 *
	: Green Algae		ChV	12.463 *

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.

Note: ! = exclamation designates: The toxicity value was determined from

a predicted SAR using established acute-to-chronic ratios and ECOSAR regression techniques which are documented in the supporting Technical Reference Manual. When possible, this toxicity value should be considered in a weight of evidence approach.

Imides:

For Fish and Daphnid Acute Toxicity Values: If the log Kow of the chemical is greater than 5.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For Green Algae Acute Toxicity Values: If the log Kow of the chemical is greater than 6.4, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For All Chronic Toxicity Values: If the log Kow of the chemical is greater than 8.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

ECOSAR v1.00 SAR Limitations:

Maximum LogKow: 5.0 (LC50)
Maximum LogKow: 6.4 (EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

Amides :

No limitations known at this time.

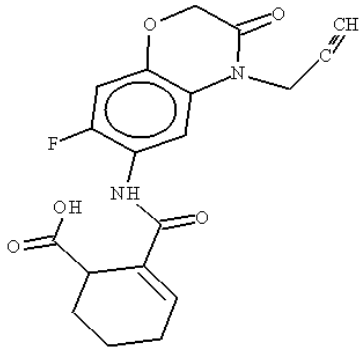
ECOSAR v1.00 SAR Limitations:

Maximum LogKow: >8.5 (LC50)
Maximum LogKow: >8.0 (EC50,ChV)
Maximum Mol Wt: 1000

Baseline Toxicity SAR Limitations:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

RESULTS FOR DEGRADATE 482-HA:



SMILES : C#CCN1c2cc(c(cc2OCC1(=O))F)NC(=O)C3=CCCCC3(C(=O)O)
CHEM :
CAS Num:
ChemID1:
ChemID2:
ChemID3:
MOL FOR: C19 H17 F1 N2 O5
MOL WT : 372.36
Log Kow: 0.72 (KowWin estimate)
Melt Pt:
Wat Sol: 1092 mg/L (WskowWin estimate)

ECOSAR v1.00a Class(es) Found

Acrylamides-acid
Amides -acid

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
--> Acid moeity found: Predicted values multiplied by 10				
Acrylamides-acid	: Fish	96-hr	LC50	1262.728 *
Acrylamides-acid	: Daphnid	48-hr	LC50	1022.147
Acrylamides-acid	: Fish		ChV	31.760
Acrylamides-acid	: Daphnid		ChV	88.081 !
Acrylamides-acid	: Fish (SW)	96-hr	LC50	1119.478 *
Acrylamides-acid	: Mysid Shrimp (SW)	96-hr	LC50	472.667
Acrylamides-acid	: Fish (SW)		ChV	62.509 !
Acrylamides-acid	: Mysid Shrimp (SW)		ChV	0.358
Amides -acid	: Fish	96-hr	LC50	4901.646 *
Amides -acid	: Daphnid	48-hr	LC50	1776.507 *
Amides -acid	: Green Algae	96-hr	EC50	18.556
Amides -acid	: Fish		ChV	28.976
Amides -acid	: Daphnid		ChV	23.435 !
Amides -acid	: Green Algae		ChV	6.221
Neutral Organic SAR	: Fish	96-hr	LC50	3450.105 *
(Baseline Toxicity)	: Daphnid	48-hr	LC50	1706.145 *
	: Green Algae	96-hr	EC50	435.656
	: Fish		ChV	336.889
	: Daphnid		ChV	125.742
	: Green Algae		ChV	124.887

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.

Note: ! = exclamation designates: The toxicity value was determined from a predicted SAR using established acute-to-chronic ratios and ECOSAR regression techniques which are documented in the supporting Technical Reference Manual. When possible, this toxicity value should be considered in a weight of evidence approach.

Acrylamides:

For Fish and Daphnid Acute Toxicity Values: If the log Kow of the chemical is greater than 5.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For Green Algae Acute Toxicity Values: If the log Kow of the chemical is greater than 6.4, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For All Chronic Toxicity Values: If the log Kow of the chemical is greater than 8.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

ECOSAR v1.00 SAR Limitations:

Maximum LogKow: 5.0 (LC50)
Maximum LogKow: 6.4 (EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

Amides :

No limitations known at this time.

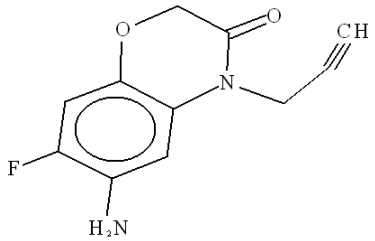
ECOSAR v1.00 SAR Limitations:

Maximum LogKow: >8.5 (LC50)
Maximum LogKow: >8.0 (EC50,ChV)
Maximum Mol Wt: 1000

Baseline Toxicity SAR Limitations:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

RESULTS FOR DEGRADATE APF:



SMILES : C#CCN1c2cc(c(cc2OCC1(=O))F)N
CHEM :
CAS Num:
ChemID1:
ChemID2:
ChemID3:
MOL FOR: C11 H9 F1 N2 O2
MOL WT : 220.20
Log Kow: -0.10 (KowWin estimate)
Melt Pt:
Wat Sol: 2055 mg/L (WskowWin estimate)

ECOSAR v1.00a Class(es) Found

Anilines (Aromatic Amines)
Amides

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)	
Anilines (Aromatic Amines) :	Fish	96-hr	LC50	395.527	
Anilines (Aromatic Amines) :	Fish	14-day	LC50	4398.546	*
Anilines (Aromatic Amines) :	Daphnid	48-hr	LC50	5.467	
Anilines (Aromatic Amines) :	Green Algae	96-hr	EC50	16.379	
Anilines (Aromatic Amines) :	Fish		ChV	3.060	
Anilines (Aromatic Amines) :	Daphnid		ChV	0.159	
Anilines (Aromatic Amines) :	Green Algae		ChV	11.728	
Amides :	Fish	96-hr	LC50	1303.225	
Amides :	Daphnid	48-hr	LC50	355.168	
Amides :	Green Algae	96-hr	EC50	1.863	
Amides :	Fish		ChV	7.704	
Amides :	Daphnid		ChV	4.685	!
Amides :	Green Algae		ChV	0.368	
Neutral Organic SAR :	Fish	96-hr	LC50	10189.535	*
(Baseline Toxicity) :	Daphnid	48-hr	LC50	4560.417	*
:	Green Algae	96-hr	EC50	829.939	
:	Fish		ChV	1013.287	
:	Daphnid		ChV	290.455	
:	Green Algae		ChV	204.628	

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.

Note: ! = exclamation designates: The toxicity value was determined from a predicted SAR using established acute-to-chronic ratios and ECOSAR regression techniques which are documented in the supporting Technical Reference Manual. When possible, this toxicity value should be considered in a weight of evidence approach.

Anilines (Aromatic Amines):

For Fish Acute Toxicity Values: 2,3,5,6-Tetrachloroaniline is 19 times more toxic than predicted by this SAR. Tetrabromoaniline may be more toxic than predicted by this SAR as well.

For Daphnid and Green Algae Toxicity Values: Tetrachloro- and tetrabrom-aniline may be 20 times toxic than predicted by this SAR.

N-Substituted anilines are less toxic than predicted by these SARs; for these compounds, Neutral Organic SARs are used.

ECOSAR v1.00 SAR Limitations:

Maximum LogKow: >7.8 (Fish 96-hr LC50, Daphnid 48-h LC50)
Maximum LogKow: >3.7 (Fish 14-day LC50)
Maximum LogKow: >4 (Green Algae 96-hr EC50 and ChV)
Maximum LogKow: >4.3 (Fish ChV)
Maximum LogKow: >2.4 (Daphnid ChV)
Maximum Mol Wt: 1000

Amides :

No limitations known at this time.

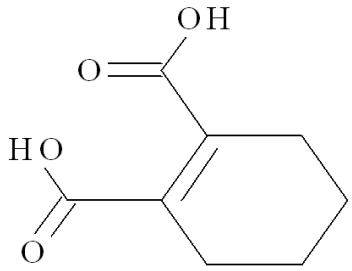
ECOSAR v1.00 SAR Limitations:

Maximum LogKow: >8.5 (LC50)
Maximum LogKow: >8.0 (EC50,ChV)
Maximum Mol Wt: 1000

Baseline Toxicity SAR Limitations:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

RESULTS FOR DEGRADATE THPA:



Input:

```
SMILES : C1CCC(=C(C1)C(=O)O)C(=O)O
CHEM   : 1,2,3,4-Tetrahydrophthalic acid
CAS Num: 635-08-5
ChemID1:
ChemID2:
ChemID3:
MOL FOR: C8 H10 O4
MOL WT : 170.17
Log Kow: 2.02  (User entered)
Melt Pt: 123.00 deg C
Wat Sol: 1580 mg/L  (WskowWin estimate)


ECOSAR v1.00a Class(es) Found
-----------------------------
Neutral Organics-acid
```

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
--> Acid moeity found: Predicted values multiplied by 10				
Neutral Organics-acid	: Fish	96-hr	LC50	1259.435
Neutral Organics-acid	: Fish	14-day	LC50	1273.843
Neutral Organics-acid	: Daphnid	48-hr	LC50	712.295
Neutral Organics-acid	: Green Algae	96-hr	EC50	341.061
Neutral Organics-acid	: Fish	30-day	ChV	131.389
Neutral Organics-acid	: Daphnid		ChV	82.839
Neutral Organics-acid	: Green Algae		ChV	130.761
Neutral Organics-acid	: Fish (SW)	96-hr	LC50	1748.300 *
Neutral Organics-acid	: Mysid Shrimp	96-hr	LC50	1238.169
Neutral Organics-acid	: Fish (SW)		ChV	185.553
Neutral Organics-acid	: Mysid Shrimp (SW)		ChV	106.391
Neutral Organics-acid	: Earthworm	14-day	LC50	2944.420 *

Note: * = asterisk designates: Chemical may not be soluble
enough to measure this predicted effect.

Neutral Organics:

For Fish LC50 (96-h), Daphnid LC50, Mysid: If the log Kow is greater than 5.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted.

For Fish LC50 (14-day) and Earthworm LC50: If the log Kow is greater than 6.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted.

For Green Algae Acute Toxicity Values: If the log Kow of the chemical is greater than 6.4, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For All Chronic Toxicity Values: If the log Kow of the chemical is greater than 8.0, or if the compound is solid and the ChV exceeds the water solubility
by 10X, no effects at saturation are predicted for these endpoints.

ECOSAR v1.00 SAR Limitations:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50, Mysid LC50)
Maximum LogKow: 6.0 (Fish 14-day LC50; Earthworm LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

Appendix 2

Estimated Environmental Concentrations (EECs) and Dissipation Behavior of Flumioxazin Following Direct Application to Water Using the AQUATOX Model

Modeling of Concentration and Dissipation of Flumioxazin in Standard Pond

AQUATOX is a model that is available from USEPA and has the capability to estimate the concentration in a water body from *direct application* of pesticides to a water body. AQUATOX is an ecosystem simulation model that predicts the fate of various pollutants, such as excess nutrients and organic chemicals, and their effects on aquatic ecosystems. An overview of the model is given below. For the purpose of the aquatic exposure assessment for the review presented here, the AQUATOX model was used to estimate the concentration and dissipation characteristics of flumioxazin in a standard pond. The fate portion of the model was used to here to characterize the dissipation of flumioxazin following an application to a standard pond.

Brief overview of the AQUATOX Model

AQUATOX is an ecosystem simulation model that predicts the fate of various pollutants, such as excess nutrients and organic chemicals, and their effects on aquatic ecosystems, including fish, invertebrates, and aquatic plants. AQUATOX is a valuable tool for ecologists, biologists, water quality modelers, and anyone who performs ecological risk assessments for aquatic ecosystems.

AQUATOX simulates the transfer of biomass, energy and chemicals from one compartment of the ecosystem to another. It does this by simultaneously computing each of the most important chemical or biological processes for each day of the simulation period; therefore it is known as a process-based or mechanistic model. AQUATOX can predict not only the environmental fate of chemicals in aquatic ecosystems, but also their direct and indirect effects on the resident organisms. Therefore it has the potential to establish causal links between chemical water quality and biological response and aquatic life uses.

AQUATOX is the only general ecological risk model that represents the combined environmental fate and effects of conventional pollutants, such as nutrients and sediments, and toxic chemicals in aquatic ecosystems. It considers several trophic levels, including attached and planktonic algae and submerged aquatic vegetation, invertebrates, and forage, bottom-feeding, and game fish; it also represents associated organic toxicants. It has been implemented for streams, ponds, lakes, estuaries, reservoirs, and experimental enclosures.

The fate portion of the model, which is applicable especially to organic toxicants, includes: partitioning among organisms, suspended and sedimented detritus, suspended and sedimented inorganic sediments, and water; volatilization; hydrolysis; photolysis; ionization; and microbial degradation. The effects portion of the model includes: acute toxicity to the various organisms modeled; and indirect effects such as release of grazing and predation pressure, increase in

detritus and recycling of nutrients from killed organisms, dissolved oxygen sag due to increased decomposition, and loss of food base for animals.

AQUATOX is the latest in a long series of models, starting with the aquatic ecosystem model CLEAN (Park et al., 1974) and subsequently improved in consultation with numerous researchers at various European hydrobiological laboratories, resulting in the CLEANER series (Park et al., 1975, 1979, 1980; Park, 1978; Scavia and Park, 1976) and LAKETRACE (Collins and Park, 1989). The MACROPHYTE model, developed for the U.S. Army Corps of Engineers (Collins et al., 1985), provided additional capability for representing submersed aquatic vegetation. Another series started with the toxic fate model PEST, developed to complement CLEANER (Park et al., 1980, 1982), and continued with the TOXTRACE model (Park, 1984) and the spreadsheet equilibrium fugacity PART model. AQUATOX combined algorithms from these models with an ecotoxicological construct borrowed from the FGETS model (Suárez and Barber, 1992); and additional code was written as required for a truly integrative fate and effects model (Park, 1990, 1993). In the late 1990s, AQUATOX was restructured and linked to Microsoft Windows interfaces to provide even greater flexibility, capacity for additional compartments, and user friendliness.

- AQUATOX Release 1 was produced in 2002 and was the first EPA release to run under Windows.
- AQUATOX Release 2 was completed in 2003 and included more state variables and multi-age-class fish along with a refined user-interface.
- AQUATOX Release 2.1 was completed in 2005 and included additional chemical modeling options and variable stoichiometry among numerous other refinements.
- AQUATOX Release 2.2 was completed in 2006 and included updated simulations and parameter databases along with minor interface enhancements.
- AQUATOX Release 3 was completed in 2009 and includes linked segments, simulations of estuaries, dramatically improved output capabilities, and many other model improvements.

In 2009, EPA released an enhanced version of AQUATOX, Release 3, which includes the capability to represent estuaries and to more realistically model nutrients. More information on the model and its applications, including references to peer-reviewed publications, is available at http://www.epa.gov/waterscience/models/aquatox/.

Model Input

The model package contains a number of scenarios. The model guidance suggests to select a scenario from the model package, and modify it as needed to make it more representative for a specific situation and conditions. The model results are suggested to be used for screening-level assessments. For the purpose of the review presented here, the model was used to simulate the fate of flumioxazin in the default Missouri farm pond. The study on esfenvalerate in a Missouri Farm Pond was selected as a starting scenario. The state variables defined for this model scenario and their initial values are listed in the attached Table A2.1. The site characteristics and chemical parameters are available upon request from H. Wijnja, MDAR.

The site characteristic for the latitude was adjusted to 42 degrees in order to make it more representative for the light situation in MA. The dimensions of the pond were modified to represent the dimensions of the EPA standard pond: Surface area of 1 ha (10000 m^2), a depth of 2 m (6.56 ft), and a resulting volume of 20,000 m^3. Subsequently, depths of 1.2 m (3.94 ft), 0.91 m (3 ft) and 0.304 m (1ft) (with associated volumes) of this pond were also simulated. Chemical Properties and Fate Data were adjusted to be representative of flumioxazin and its degradates. The following parameter values were used (see also Section 2.4 in main document): Molecular weight: 384; Henry's Law constant: 6.2E-7 atm m^3 mol^{-1}; Octanol-water partitioning constant (log): 2.55; Water partitioning coefficient: 50 L/kg; rate of aerobic and anaerobic microbial degradation: 0.00001 d^{-1}(set at a low value); maximum rate of hydrolysis: 0.693 d^{-1} (calculated using the half life value of 1 d and k = ln(2)/half life); and photolysis rate: 0.693 d^{-1} (based on half-life of 1 d). The model parameter input for degradation processes was conservative in that it assumed hydrolysis and photolysis as the major degradation processes. Modeling results that included simulation of aerobic microbial degradation with a half-life of 3 days indicated slightly faster degradation and a slightly lower peak value of flumioxazin. The model results presented below are therefore conservative estimates of flumioxazin concentrations.

The herbicide application was programmed to occur on May 10th considering a scenario with the highest aquatic exposure level of an application to submerged vegetation with a maximum concentration of 200 ppb. Repeat applications were not considered since these are not used in practice. The amount of flumioxazin for model input was determined based on the concentration of 200 ppb in the volume of the water body modeled, which is based on the depths considered. The amounts of flumioxazin applied was 1823 g for a pond with a depth of 0.91 m (3 ft) The model simulation was run from May 1st through August 31st.

The modeling also included the simulation of major degradates of flumioxazin. The load data and individual chemical parameters were defined in the model input.

The degradation of flumioxazin was assumed to take place by first degrading to 482-HA with a dissipation half-live of 1 day. Subsequently, it was assumed that 482-HA degraded to APF and THPA in equal fractions at a rate corresponding with a half-live of 4.9 days (corresponding rate is 0.138 d^{-1}). APF and THPA were assumed to degrade at a rate corresponding to a half-live of 10.5 days (corresponding rate is 0.066 d^{-1}). The degradation parameters for microbial degradation, hydrolysis and photolysis were all set at the same value representing the dissipation rate stated above.

The modeling was performed in three steps. First, the model was run with the application of flumioxazin taking place at the selected dates and application rates. The loss data for flumioxazin generated by the model were then used to determine the load data for the primary degradate 482-HA. The model was then run again, this time also with the load data for 482-HA (in addition to the loading of flumioxazin). The simulated loss data for 482-HA were then used to determine the loading of APF + THPA. The model was then run a third time to generate the concentration profiles that included also APF and THPA (sum of these two degradates).

Results

From the model output, the dissolved flumioxazin, 482-HA, and APF/THPA concentrations were selected. The results are presented in the graph below.

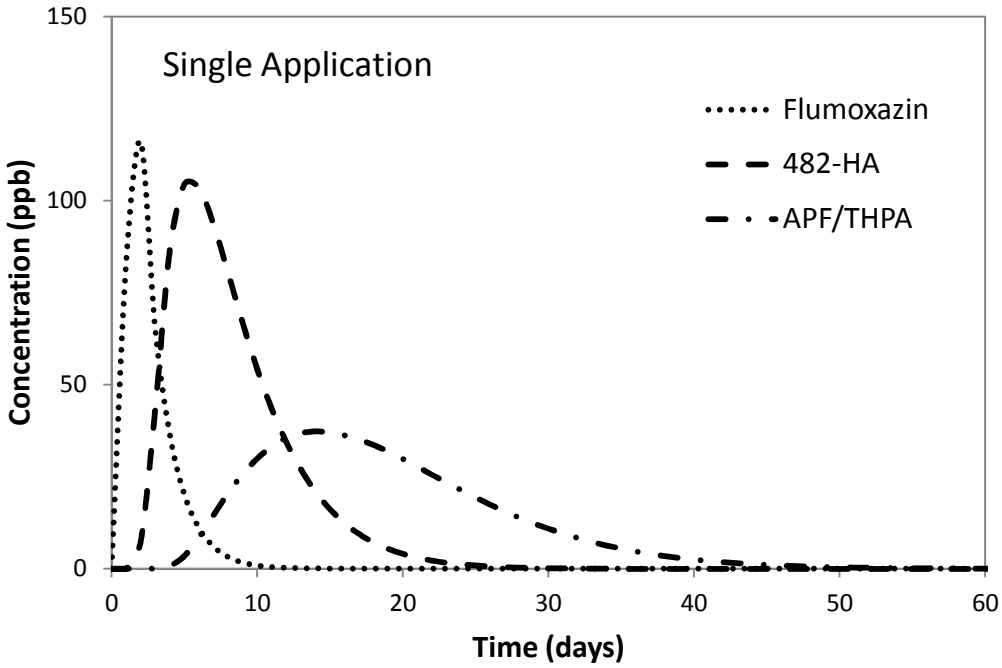


Figure A2.1 Aquatic concentrations of flumioxazin and its major degradates simulated by the AQUATOX model. The concentration profiles are the result of a single application at 200 ppb initial flumioxazin concentration on day 10 (May 10th). The degradation rates were based on half-lives observed in an aquatic field study in Iowa

Table A2.1 State Variables for Missouri Farm Pond and their initial values

State Variable Name	Init. Cond.	Units
NH3 & NH4+	0.08	mg/L
NO3	0.05	mg/L
Tot. Sol. P	0.05	mg/L
CO2	1.5	mg/L
Oxygen	12	mg/L
R detr sed	3	g/m2 dry
L detr sed	3	g/m2 dry
R detr diss	0.72	mg/L dry
L detr diss	0.18	mg/L dry
R detr part	0.08	mg/L dry
L detr part	0.02	mg/L dry
BuryRDetr	2	g/m2
BuryLDetr	2	g/m2
Peri High-Nut Diatom	36.86	g/m2 dry
Phyt High-Nut Diatom	0.00	mg/L dry
Peri, Green	0.01	g/m2 dry
Phyto, Green	0.00	mg/L dry
Phyt, Blue-Greens	0.00	mg/L dry
Cryptomonas	0.07	mg/L dry
Myriophyllum	36.67	g/m2 dry
Chironomid	2.29	g/m2 dry
Daphnia	0.05	mg/L dry
Copepod	0.32	mg/L dry
Sphaerid	2.46	g/m2 dry
Mayfly (Baetis)	0.24	g/m2 dry
Rotifer, Keratella	0.07	mg/L dry
Gastropod	3.68	g/m2 dry
Shiner	4.02	g/m2 dry
Largemouth Bass, YOY	0.21	g/m2 dry
Largemouth Bass, Lg	4.43	g/m2 dry
Water Vol	9114	cu.m
Temp	16	deg. C
Wind	0	m/s
Light	333	Ly/d
pH	6.8	pH

Appendix 3

Information Related to Exposure and Risk Assessment of Flumioxazin

The information is supplementary to the text in the main review document section on exposure and ecological risk assessment (Section 3.2 and 3.3) and was taken from USEPA (2010A).

Terrestrial Exposure Assessment

USEPA or EFED (2010) assessed the risk to avian and terrestrial species based on a worst-case exposure scenario considering that the entire application (0.383 lbs ai/A) being applied to the shoreline multiple times during the season. Exposure to birds and mammalian species was based on residues on various food items. This scenario would be highly conservative since the maximum surface application is not expected to be applied to any non-aquatic area. The maximum EEC on short grass was 206 ppm, 116 ppm on tall grass, 95 ppm on broadleaf plants and insects, and 13 ppm on seeds, fruits, and large insects.

The terrestrial exposure assessment is based on the methods of Hoerger and Kenaga (1972)[5] as modified by Fletcher et al. (1994)[6]. Uncertainties in the terrestrial EECs are primarily associated with a lack of data on interception and subsequent dissipation from foliar surfaces. EFED assumes that the foliar dissipation rate is equal to the aerobic soil metabolism rate. Open literature data suggest that foliar dissipation rates are generally less than 20 days[7].

Estimated Environmental Concentrations on Avian and Mammalian Food Items (ppm) following for scenario with 0.383 lbs ai/Acre x 6 applications with 28-day intervals (worst-case scenario)

	EEC (ppm) [1]
Food Items	*Predicted Maximum Residue*
Short range grass	206.57
Tall grass	116.2
Broadleaf plants and small insects	94.68
Fruits, pods, seeds, and large insects	12.91

[1] EECs are based on Hoerger and Kenega (1972), modified by Fletcher et al (1994). For multiple applications, EFED used EECs based on Hoerger and Kenega (1972) and Fletcher et al (1994), with first-order dissipation from foliage between applications (a 35 day default half life was used to calculate EECs)

1 Hoerger, F., and E.E. Kenaga. 1972. Pesticide residues on plants: Correlation of representative data as a basis for estimation of their magnitude in the environment. In F. Coulston and F. Korte, eds., *Environmental Quality and Safety: Chemistry, Toxicology, and Technology*, Georg Thieme Publ, Stuttgart, West Germany, pp. 9-28.

2 Fletcher, J.S., J.E. Nellessen, and T.G. Pfleeger. 1994. Literature review and evaluation of the EPA food-chain (Kenaga) nomogram, an instrument for estimating pesticide residues on plants. Environ. Tox. Chem. 13:1383-1391.

3 Knisel, W.G., ed. 1980. CREAMS: A field-scale model for chemicals, runoff, and erosion from agricultural management systems. USDA Conserv. Res. Rep. No. 26).

Risk presumptions, along with the corresponding Risk Quotients (RQs) and Levels of Concern (LOCs) are tabulated below:

Risk Presumptions for Terrestrial Animals

Risk Presumption	RQ	LOC
Birds		
Acute High Risk	EEC1/LC50 or LD50/sqft2 or LD50/day3	0.5
Acute Restricted Use	EEC/LC50 or LD50/sqft or LD50/day (or LD50 < 50 mg/kg)	0.2
Acute Endangered Species	EEC/LC50 or LD50/sqft or LD50/day	0.1
Chronic Risk	EEC/NOAEC	1
Wild Mammals		
Acute High Risk	EEC/LC50 or LD50/sqft or LD50/day	0.5
Acute Restricted Use	EEC/LC50 or LD50/sqft or LD50/day (or LD50 < 50 mg/kg)	0.2
Acute Endangered Species	EEC/LC50 or LD50/sqft or LD50/day	0.1
Chronic Risk	EEC/NOAEC	1

[1] abbreviation for Estimated Environmental Concentration (ppm) on avian/mammalian food items

[2] $\frac{mg/ft^2}{LD50 * wt. of bird}$ [3] $\frac{mg of toxicant consumed/day}{LD50 * wt. of bird}$

Risk Presumptions for Aquatic Animals

Risk Presumption	RQ	LOC
Acute High Risk	EEC[1]/LC50 or EC50	0.5
Acute Restricted Use	EEC/LC50 or EC50	0.1
Acute Endangered Species	EEC/LC50 or EC50	0.05
Chronic Risk	EEC/MATC or NOAEC	1

[1] EEC = (ppm or ppb) in water

Risk Presumptions for Plants

Risk Presumption	RQ	LOC
Terrestrial and Semi-Aquatic Plants		
Acute High Risk	EEC[1]/EC25	1
Acute Endangered Species	EEC/EC05 or NOAEC	1
	Aquatic Plants	
Acute High Risk	EEC[2]/EC50	1
Acute Endangered Species	EEC/EC05 or NOAEC	1

[1] EEC = lbs ai/A

[2] EEC = (ppb/ppm) in water

Risk Characterization Data
Freshwater Fish

Risk Quotients for Freshwater Fish Based On a EC50/LC50 of 2.3 ppm and a NOAEC of 0.0077 ppm

	LC50 (ppm)	NOAEC (ppm)	EEC Initial/Peak (ppm)	EEC 60-Day Ave. (ppm)	Acute RQ (EEC/LC50)	Chronic RQ (EEC/NOAEC)
Flumioxazin	2.3	0.0077	0.4	0.025	**0.17**	**3.25**
482-HA	2.3	0.0077	0.0216	0.0216	0.00	**2.80**
APF	2.3	0.0077	0.110	0.110	0.047	**14.28**
THPA	2.3	0.0077	0.0889	0.0889	0.038	**11.54**

Freshwater Invertebrates

Risk Quotients for Freshwater Invertebrates Based On a EC50/LC50 of 5.5 ppm and a NOAEC of 0.028 ppm.

Rate	LC50 (ppm)	NOAEC (ppm)	EEC Initial/Peak (ppm)	EEC 21-Day Average (ppm)	Acute RQ (EEC/LC50)	Chronic RQ (EEC/NOAEC)
Flumioxazin	5.5	0.028	0.4	0.00	**0.07**	0.00
482-HA	5.5	0.028	0.0216	0.0216	0.00	0.77
ADF	5.5	0.028	0.110	0.110	0.02	**3.93**
THPA	5.5	0.028	0.0889	0.0889	0.01	**3.17**

Birds: Acute and Chronic, Multiple Applications

Avian Acute and Chronic Risk Quotients for multiple Broadcast Applications of Flumioxazin, based on a n Avian LC_{50} of 5620 ppm and NOAEC of 250 ppm .

Use/App. Method	Rate (lbs ai/A) x No. Apps.	Food Items	Max EEC (ppm) [1]	Acute RQ (Max EEC/LC_{50})	Chronic RQ (Max EEC/ NOAEC)
		Multiple Applications[2]			
Aquatic Surface	0.383 x 6 (28-da interval)	Short grass	206.57	0.04	0.82
		Tall grass	116.2	0.02	0.50
		Broadleaf plants/Insects	94.68	0.02	0.38
		Seeds	12.91	<0.01	0.05
		Levels of Concern (LOC)			
Endangered species may be affected (acute risk)				≥ 0.1	
Acute risk may be mitigated through restricted use, in addition to endangered species risk				≥ 0.2	
High acute risk, including endangered species				**≥ 0.5**	
Chronic risk, including endangered species					**≥ 1**

[1] EECs are based on Hoerger and Kenega (1972), modified by Fletcher et al (1994).

[2] For multiple applications, EFED uses EECs based on Hoerger and Kenega (1972) and Fletcher et al (1994), with first-order dissipation from foliage between applications (a 35 day default half life was used to calculate EECs)

Mammals

Mammalian Acute

The residues expected on mammalian food items after aquatic applications of Flumioxazin products are based on the highest residue concentrations immediately after application (Fletcher, 1994). The results suggest that mammalian acute levels of concern are not exceeded even under the highest multiple application rate. This scenario would be highly conservative since the maximum surface application is not expected to be applied to any non-aquatic area, thus no risk is assumed.

Mammalian Chronic (multiple applications)

The following tables summarize the mammalian chronic risk quotients for single and multiple broadcast applications of non-granular products based on rat reproductive toxicity data.

Mammalian (Rat) chronic risk quotients for multiple broadcast spray applications of Flumioxazin, based on a rat NOAEC of 100 ppm in the diet using a 35 day halflife.

Use/App. Method	Rate (lbs ai/A) x No. Apps.	Food Items	Max/Ave EEC (ppm) [1]	Chronic RQ (EEC/NOAEC) Max/Ave
		Multiple Application[2]		
Aquatic Surface	0.383 x 6 x 28 da	Short grass	206.57	**2.06**
		Tall grass	116.19	**1.16**
		Broadleaf plants/Insects	94.68	0.94
		Seeds	12.91	0.12
		Levels of Concern		
Chronic risk				**> 1.0**

[1] EECs are based on Hoerger and Kenega (1972), modified by Fletcher et al (1994).
[2] For multiple applications, EFED uses EECs based on Hoerger and Kenega (1972) and Fletcher et al (1994), with first-order dissipation from foliage between applications. If foliar dissipation data are not available, a 35 day default value is used.

Risk to Plants

Terrestrial Plant Acute Risk Quotients For Flumioxazin (Endangered and Non-Endangered)

Crop Details/Rate	EECs (lbs a.i./acre)			[1]EC_{25} or NOEC		RQ		
	Total Loading to Adjacent Dry Areas	Total Loading to Semi-Aquatic Areas	Total Drift	Seedling Emergence (Monocots and Dicots)	Vegetative Vigor (Monocots and Dicots)	Emergence RQs-Adjacent Dry Areas (Monocots and Dicots)	Emergence RQs, Semi-Aquatic Areas (Monocots and Dicots)	Drift RQ (Monocots and Dicots)
Non-Endangered								
Aquatic 0.38 lbs ai/A	0.0077-0.0214	0.0421	0.0038-0.0192	0.0037 0.0008	0.0071 0.00008	**2.07-5.80** **9.58-26.81**	**11.39** **52.66**	0.54-**2.70** **47.88-239.4**
Endangered								
Aquatic 0.38 lbs ai/A	0.0077-0.0214	0.0421	0.0038-0.0192	0.003 0.0004	0.006 0.00005	**2.55-7.15** **19.15-53.62**	**14.04** **105.33**	0.64-**3.19** **76.60-383.00**

Acute Non-endangered Plant RQ = EEC/EC_{25}; Acute Endangered Plant RQ = EEC/EC_{05} or NOEC;
[1] EC_{25} for Non-endangered and NOEC for Endangered
Levels of Concern: RQ∃1.0 = Acute Risk

Appendix 4

Refined Aquatic Risk Assessment for Flumioxazin and Degradates

A refined aquatic risk assessment was conducted to supplement the results from EPA's aquatic risk assessment. EPA's aquatic risk assessment indicated LOC exceedances for various risk presumption categories, however, EPA did not provide a refined risk assessment. Results of refined assessments are presented below. The risk assessment was refined by additional exposure assessments (AQUATOX-modeling by DAR (Appendix 2) and Iowa Pond monitoring data), estimated ecotoxicological endpoints for degradates (Appendix 1), and concentration addition for assessing the risk of combined effects from flumioxazin and degradates.

A risk assessment for water ingestion by muskrats and beavers was also performed. In that case, in the absence of quantitative toxicity estimates for the degradates, the toxicities of all the degradates except for THPA were assumed to be equivalent to that of flumioxazin and risks were calculated in aggregate across compounds. THPA was omitted as USEPA has judged its toxicity to be less than that of the parent and other degradates.

Risk Assessment Based on Estimated Toxicity Endpoints for Degradates

The aquatic organism risk assessment was refined by considering the estimated ecotoxicity endpoints for the degradates. The adjusted values were calculated based on the toxicity endpoint point values for flumioxazin (available data for LC_{50} and EC_{50} data). The degradate endpoints were calculated by multiplying the endpoint point value for flumioxazin (study data) by the ratio of ECOSAR-predicted degradate endpoint / ECOSAR-predicted endpoint for flumioxazin (Table A1-2 in Appendix 1). The refined assessment was done for the DAR exposure assessment (AQUATOX estimated EECs). The results are shown in Table 3 for freshwater fish and Table 4 for freshwater invertebrates. The results for estuarine/marine fish and invertebrates are shown in Fig. 6 and 7.

The combined (totals) ecorisk quotients presented in Table 1 and 2 was based on the assumption that the toxicity of parent and degradates are the same. In addition, it was assumed that concentrations of parent and degradates are additive, but this may not be the case if, for example, peak concentrations of parent and degradates occur at different times.

Risk Assessment Based on Concentration Addition Approach for Combined Effects

The combined effect of multiple substances can also be assessed by using the concentration additions approach. The combined effect of multiple compounds or substances is calculated by summation of the concentration divided by an effect concentration. This approach is considered to provide a conservative estimate of the mixture effect (Junghaus et al., 2006; Backhaus and Faust, 2012; Lydy et al., 2004). The concentration addition is commonly applied by the use of

toxic units (TU). The TU is defined as the quotient c_i/ECx_i which rescales the absolute concentrations of substances to individual potencies. The combined effect is estimated by the summation of TUs. This approach was used in a refined assessment of the combined effect of flumioxazin and its degradates. The refined assessment was based on the AQUATOX-derived EECs and refined assessment of toxicity endpoints of the degradates based on ECOSAR predictions (Appendix 2).

The toxic unit summation results for fish and invertebrates are included in Table 3 and 4 (freshwater) and Table 6 and 7 (estuarine/marine).

Table 1. Comparison of Modeling and Monitoring Information for Risk Assessment in Freshwater Fish. Toxicity of degradates was assumed to be equal to flumioxazin. Total concentrations are summation of flumioxazin and all degradates (shading denotes trigger of acceptable LOC level)
(bolding represents total RQs that exceed LOCs for endangered fish (acute) or fish (chronic)

Compound		Peak[1] (ppb)	21-d avg (ppb)	60-d avg (ppb)	Acute RQ (EEC/LC50)[2]	Chronic RQ (EEC/NOAEC)[3]	
						21-d	60-d
Flumioxazin	EPA[5]	400	38	39	0.17	4.9	5.1
	DAR[6]	200	15.7	5.65	0.085	2.04	0.73
	Iowa[7]	233	15.6 (7-d)	2.21 (28-d)	0.10	2.03 (7-d)	0.29 (28-d)
482-HA	EPA	21.6	21.6	21.6	0.009	2.8	2.8
	DAR	104	37.5	13.7	0.045	4.87	1.8
	Iowa	320	12.4 (14-d)	3.31 (28-d)	0.14	1.61 (14-d)	0.43 (28-d)
APF	EPA	110.1	110.1	110.1	0.05	14.2	14.2
	DAR	37.3	21.7	11.5	0.02	2.82	1.5
	Iowa	15.8	1.99 (7-d)	1.21 (28-d)	0.007	0.26 (7-d)	0.16 (28-d)
THPA	EPA	88.9	88.9	88.9	0.04	11.5	11.5
	DAR	37.3	21.7	11.5	0.02	2.82	1.5
	Iowa	---	---	---	---	---	---
Totals	EPA	421.6[8]	220.6	245.6	**0.18**[9]	**28.7**	**31.9**
	DAR	220[8]	96.6	42.2	**0.13**	**12.6**	**5.5**
	Iowa	553[8]	---[4]	6.73	**0.24**	---[4]	0.87 (28-d)

[1]The peak value for the EPA study is the maximum immediately following application; for the DAR study, is the initial concentration that has been subject to degradation with a half-life of one day; and for the Iowa study, is the concentration 2 hours following application.
[2] LC50 = 2300 ppb; Acute High Risk LOC = 0.5; Acute Restricted Use = 0.1; Acute Endangered Species = 0.05: Acute EEC is peak level, chronic EEC used by EPA is 60-d average for fish (http://www.epa.gov/oppefed1/ecorisk_ders/toera_risk.htm)
[3]NOAEC = 7.7 ppb; Chronic Risk LOC = 1.0
[4]The total for this column for the Iowa study was not calculated because the individual values represent two different durations in time.
[5]Exposure data based on three consecutive applications at 400 ppb in 28-d intervals
[6]Exposure data based on a single application at 200 ppb and AQUATOX-modeling (Appendix 2)
[7]Exposure data based on single application of 400 ppb
[8] Total acute exposure is sum of flumioxazin and 482-HA
[9] Total RQ calculation assumed equal toxicity of flumioxazin and its degradates

Table 2. Comparison of Modeling and Monitoring Information for Risk Assessment in Freshwater Invertebrates. Toxicity of degradates was assumed to be equal to flumioxazin. Total concentrations are summation of flumioxazin and all degradates (shading denotes trigger of acceptable LOC level) (bolding represents total RQs that exceed LOCs for endangered organisms (acute) or (chronic)

Compound		Peak[1] (ppb)	21-d avg (ppb)	60-d avg (ppb)	Acute RQ (EEC/LC50)[2]	Chronic RQ (EEC/NOAEC)[2]	
						21-d	60-d
Flumioxazin	EPA[5]	400	38	39	0.07	1.35	1.39
	DAR[6]	200	15.7	5.65	0.035	0.56	0.20
	Iowa[7]	233 (2-h)	15.6 (7-d)	2.21 (28-d)	0.04	0.56 (7-d)	0.08 (28-d)
482-HA	EPA	21.6	21.6	21.6	0.004	0.77	0.77
	DAR	104	37.5	13.7	0.02	1.34	0.49
	Iowa	320	12.4 (14-d)	3.31 (28-d)	0.06	0.44 (14-d)	0.12 (28-d)
APF	EPA	110.1	110.1	110.1	0.02	3.9	3.9
	DAR	37.3	21.7	11.5	0.01	0.78	0.41
	Iowa	15.8	1.99 (7-d)	1.21 (28-d)	0.003	0.07 (7-d)	0.04 (28-d)
THPA	EPA	88.9	88.9	88.9	0.02	3.18	3.18
	DAR	37.3	21.7	11.5	0.01	0.78	0.41
	Iowa	---	---	---	---	---	---
Totals[5]	EPA	421.6[8]	220.6	245.6	**0.11**	**7.8**	**8.77**
	DAR	220[8]	96.6	42.2	**0.054**	**3.44**	**1.51**
	Iowa	553[8]	---[3]	6.73	**0.10**	---[3]	0.24 (28-d)

[1]The peak value for the EPA study is the maximum immediately following application; for the DAR study, is the initial concentration that has been subject to degradation with a half-life of one day; and for the Iowa study, is the concentration 2 hours following application.

[2] LC50 = 5500 ppb; Acute High Risk LOC = 0.5; Acute Restricted Use = 0.1 (LOC for acute restricted use does not apply in the case of flumioxazin since it is not classified as a restricted use pesticide); Acute Endangered Species = 0.05; [3]NOAEC = 28 ppb; Chronic Risk LOC = 1.0

[4]The total for this column for the Iowa study was not calculated because the individual values represent two different durations in time.

[5]Exposure data based on three consecutive applications at 400 ppb in 28-d intervals

[6]Exposure data based on a single application at 200 ppb and AQUATOX modeling (Appendix 2)

[7]Exposure data based on single application of 400 ppb

[8]Total acute exposure is sum of flumioxazin and 482-HA

[9] Total RQ calculation assumed equal toxicity of flumioxazin and its degradates

Table 3. Refined Risk Assessment for Freshwater Fish based on estimated toxicity for the degradates, AQUATOX-modeled exposure data, and toxic unit summation for combined effects. (shading denotes trigger of acceptable LOC level)(bolding represents total RQs that exceed LOCs for endangered species

Compound		Peak[1] (ppb)	21-d avg[1] (ppb)	60-d avg[1] (ppb)	Acute RQ (EEC/LC50)[2]	Chronic RQ (EEC/NOAEC)[3]	
						21-d	60-d
Flumioxazin	DAR[6]	200	15.7	5.65	0.085	2.03	0.73
482-HA	DAR	104	37.5	13.7	0.001	0.015	0.006
APF	DAR	37.3	21.7	11.5	0.001	0.091	0.048
THPA	DAR	37.3	21.7	11.5	0.0002	0.002	0.001
Toxic Unit Summation					**0.052**	**2.14**	0.789

[1]The exposure data are based on MDAR assessment using AQUATOX estimated concentrations for a single application at 200 ppb (see Appendix 2).

[2] Flumioxazin LC50 = 2300 ppb; Toxicity endpoints for 482-HA, APF and THPA were estimated by multiplying the flumioxazin endpoint value by the ratio of degradate value/flumioxazin value for ECOSAR predicted values listed in Table 5; Acute High Risk LOC = 0.5; Acute Restricted Use = 0.1; Acute Endangered Species = 0.05: Acute EEC is peak level, chronic EEC is 21-d and 60-d average

[3] Flumoxazin NOAEC = 7.7 ppb; 482-HA, APF and THPA: 7.7 ppb multiplied by the by the ratio of predicted endpoint of degradate/predicted endpoint of flumioxazin (see Table 5); Chronic Risk LOC = 1.0

Table 4. Refined Risk Assessment in Freshwater Invertebrates based on estimated toxicity for the degradates, AQUATOX-modeled exposure data, and toxic unit summation for combined effects. (shading denotes trigger of acceptable LOC level) (bolding represents total RQs that exceed LOCs for endangered invertebrates (acute) or fish (chronic)

Compound		Peak[1] (ppb)	21-d avg[1] (ppb)	60-d avg[1] (ppb)	Acute RQ (EEC/LC50)[2]	Chronic RQ (EEC/NOAEC)[3]	
						21-d	60-d
Flumioxazin	DAR[6]	200	15.7	5.65	0.035	0.56	0.202
482-HA	DAR	104	37.5	13.7	0.0002	0.002	0.001
APF	DAR	37.3	21.7	11.5	0.014	0.727	0.387
THPA	DAR	37.3	21.7	11.5	0.0001	0.001	0.001
Toxic Unit Summation					0.035	**1.29**	0.59

[1]The exposure data are based on MDAR assessment using AQUATOX estimated concentrations for a single application at 200 ppb (see Appendix 2).

[2] Flumioxazin LC50 = 5500 ppb; Toxicity endpoints for 482-HA, APF and THPA were estimated by multiplying the flumioxazin endpoint value by the ratio of degradate value/flumioxazin value for ECOSAR predicted values listed in Table 5; Acute High Risk LOC = 0.5; Acute Restricted Use = 0.1; Acute Endangered Species = 0.05: Acute EEC is peak level, chronic EEC is 21-d and 60-d average

[3] Flumioxazin NOAEC = 28 ppb; 482-HA, APF and THPA: 28 ppb multiplied by ratio of predicted endpoint of degradate/predicted endpoint of flumioxazin (see Table 5); Chronic Risk LOC = 1.0

Table 5. Ratios of degradate/flumioxazin for ECOSAR-estimated toxicity endpoint values (see also Table 2 in Appendix 1)

	Ratio Degradate/Flumioxazin (acute)			Ratio Degradate/Flumioxazin (chronic)		
	Fish 96-hr LC_{50}	Daphnid 48-h LC_{50}		Fish	Daphnid	
Flumioxazin	1	1		1	1	
482-HA	75.6	89.6		320.0	586.7	
APF	23.7	0.5		31.0	1.1	
THPA	75.4	62.5		1310.0	553.3	

Table 6. Refined Risk Assessment for Estuarine/Marine Fish based on estimated toxicity for the degradates, AQUATOX-modeled exposure data, and toxic unit summation for combined effects. (shading denotes trigger of acceptable LOC level)(bolding represents total RQs that exceed LOCs for endangered species

Compound		Peak[1] (ppb)	21-d avg[1] (ppb)	60-d avg[1] (ppb)	Acute RQ (EEC/LC50)[2]	Chronic RQ (EEC/NOAEC)[3]	
						21-d	60-d
Flumioxazin	DAR[6]	200	15.7	5.65	0.043	2.03	0.73
482-HA	DAR	104	37.5	13.7	0.0003	0.015	0.006
APF	DAR	37.3	21.7	11.5	0.0003	0.091	0.048
THPA	DAR	37.3	21.7	11.5	0.0001	0.002	0.001
Toxic Unit Summation					0.044	**2.14**	0.789

[1]The exposure data are based on MDAR assessment using AQUATOX estimated concentrations for a single application at 200 ppb (see Appendix 2).

[2] Flumioxazin LC50 = 4700 ppb; Toxicity endpoints for 482-HA, APF and THPA were estimated by multiplying the flumioxazin endpoint value by the ratio of degradate value/flumioxazin value for ECOSAR predicted values listed in Table 5; Acute High Risk LOC = 0.5; Acute Restricted Use = 0.1; Acute Endangered Species = 0.05: Acute EEC is peak level, chronic EEC is 21-d and 60-d average

[3] Flumoxazin NOAEC = 7.7 ppb (fresh water fish); 482-HA, APF and THPA: 7.7 ppb multiplied by the by the ratio of predicted endpoint of degradate/predicted endpoint of flumioxazin (see Table 5); Chronic Risk LOC = 1.0

Table 7. Refined Risk Assessment in Estuarine/Marine Invertebrates based on estimated toxicity for the degradates, AQUATOX-modeled exposure data, and toxic unit summation for combined effects. (shading denotes trigger of acceptable LOC level) (bolding represents total RQs that exceed LOCs for endangered invertebrates (acute) or fish (chronic)

Compound		Peak[1] (ppb)	21-d avg[1] (ppb)	60-d avg[1] (ppb)	Acute RQ (EEC/LC50)[2]	Chronic RQ (EEC/NOAEC)[3]	
						21-d	60-d
Flumioxazin	DAR[6]	200	15.7	5.65	0.87	1.045	0.377
482-HA	DAR	104	37.5	13.7	0.0051	0.004	0.002
APF	DAR	37.3	21.7	11.5	0.336	1.357	0.722
THPA	DAR	37.3	21.7	11.5	0.0026	0.003	0.001
Toxic Unit Summation					**1.213**	**2.409**	1.101

[1]The exposure data are based on MDAR assessment using AQUATOX estimated concentrations for a single application at 200 ppb (see Appendix 2).

[2] Flumioxazin LC50 = 230 ppb; Toxicity endpoints for 482-HA, APF and THPA were estimated by multiplying the flumioxazin endpoint value by the ratio of degradate value/flumioxazin value for ECOSAR predicted values listed in Table 5; Acute High Risk LOC = 0.5; Acute Restricted Use = 0.1; Acute Endangered Species = 0.05: Acute EEC is peak level, chronic EEC is 21-d and 60-d average

[3] Flumioxazin NOAEC = 15 ppb; 482-HA, APF and THPA: 28 ppb multiplied by ratio of predicted endpoint of degradate/predicted endpoint of flumioxazin (see Table 5); Chronic Risk LOC = 1.0

Risk Assessment for Terrestrial Animals – Muskrats and Beavers

The risks from exposures of beavers and muskrats to flumioxazin and its degradates were evaluated for drinking water exposures using an approach similar to that used for human drinking water exposures: compare duration-specific doses from herbicides in ingested water to duration-specific oral reference doses for these small mammals calculated from rodent studies reviewed in Section 2.1 of the main report.

Exposure parameters (body weights and daily water ingestion rates for muskrats and beavers (Table 8) were taken from compendia of wildlife exposure factors.

Table 8. Exposure Factors Used in Muskrat and Beaver Risk Assessments

Species	Body weight, kg	Water ingestion rate, L/d	Source
muskrat	1.4	1.372	US EPA, 1993
beaver	19.31	1.42	US EPA, 1999
rat (Sprague Dawley)	0.15 (6-7 wk old)	-	Charles River Laboratories (n.d.)

Species-specific reference doses of the flumioxazin/degradates together were calculated from the acute and chronic NOAELs identified by USEPA (2011a) from the developmental/reproductive rat study by Kawamura (1995) showing cardiovascular defects with short-term exposures and increased chronic nephropathy in males and decreased hematological parameters in females with longer-term exposures. In the absence of mammalian toxicity data for the degradates of flumioxazin, the toxicities of the major degradates 482-HA and APF were assumed to be equivalent to that for flumioxazin. THPA was not included in the risk evaluation because the USEPA in its review judged it to have significantly lower toxicity than the parent and the other degradates (Section 2.4 of main report).

Rat NOAELS (mg/kg) were converted from rat doses into beaver or muskrat equivalent doses using body weight scaling to the ¾ power following guidance provided by USEPA (2011b). These species specific equivalent NOAEL doses were then divided by a residual default uncertainty factor of 3 for interspecies differences to arrive at oral reference dose (RfD) values. Acute and chronic RQs were calculated by dividing the duration specific water-derived doses by the RfDs (Table 9).

Risks from other exposure routes such as dermal absorption, preening, inhalation, vegetation ingestion are likely insignificant given the very low RQs calculated for direct water ingestion. The exposures from these other routes would have to be almost two orders of magnitude greater

than that for ingestion for the total risks to approach the LOC of 1: a very unlikely event. For comparison, exposures of humans to volatile organic chemicals (VOCs) in the home from use of VOC contaminated water via dermal absorption and from inhalation of volatilized chemicals from water may be equivalent to that of that from ingestion, but these are for lipophilic, volatile chemicals whereas the flumioxazin and its degradates are relatively water soluble and therefore not amenable to dermal absorption. Also the more limited volatility of flumioxazin in the outdoor environment should also not result in any appreciable concentrations in outdoor air.

Table 9. Risk Assessment Parameters and Risk Quotients for Muskrats and Beavers

Species	Peak concentration, mg/L*	Acute RfD, mg/kg	Acute RQ	21-d avg. conc. mg/L	Chronic RfD, mg/kg	Chronic RQ
Muskrat	0.2	0.572	0.03	0.0749	0.381	0.02
beaver	0.2	0.297	0.05	0.0749	0.198	0.03

* assumed maximum initial concentration as applied.

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