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FINAL REPORT

Human Health and Ecological Risk Assessment (HHERA) for Flumioxazin

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EXECUTIVE SUMMARY

The United States Department of Agriculture (USDA) Forest Service (FS) anticipates utilizing the herbicide flumioxazin in various FS programs. Uses could include control of aquatic vegetation in surface water bodies and control of some terrestrial weeds and invasive plants, such as managing forest vegetation in roadsides, utility corridors, hardscapes, and conifer and hardwood production areas; as well as release or restoration of desirable vegetation in wildlife management areas, recreational areas, fire rehabilitation areas, natural areas, prairies, and fire breaks. The FS has not conducted previous risk assessments on flumioxazin. In accordance with FS procedures, a detailed Human Health and Ecological Risk Assessment (HHERA) is required to assess potential human health and ecological effects and estimate the nature and degree of risks prior to the use of flumioxazin in FS vegetation management programs. This HHERA follows the general approach of previous FS national HHERAs and FS risk assessment guidance, as posted on the FS Pesticide Management and Coordination website. The approach includes the development of both the written HHERA and accompanying workbook(s) that can be utilized to perform site-specific risk analyses for FS programs based on identified formulations of flumioxazin and anticipated program uses.

Flumioxazin is a light-dependent, peroxidizing N-phenylphthalimide herbicide used for pre- and post-emergence control of terrestrial and aquatic weeds. The herbicidal mechanism of flumioxazin is inhibition of protoporphyrin oxidase (PPO), the enzyme responsible for converting protoporphyrinogen IX to protoporphyrin IX. In plants, inhibition of PPO results in accumulation of phototoxic porphyrins in plant cells and decreased heme synthesis and chlorophyll biosynthesis.

The FS has identified representative flumioxazin products for this assessment from numerous available flumioxazin products. The following application methods are considered in this assessment: (1) backpack (foliar directed), boom ground, and aerial spray; (2) direct surface and subsurface application to water bodies; and (3) granular application to soil. The range of recommended labeled rates for terrestrial spray, granular, and surface water applications relevant to FS activities is 0.188 – 0.38 pounds active ingredient/acre (lb a.i./acre), with a maximum annual application rate of 0.765 lb a.i./acre/year. For subsurface applications, the recommended application rate is a target water concentration of 200 – 400 ppb (equivalent to 4.43×10^{-7} and 8.87×10^{-7} lb a.i./L), with a maximum of six applications/year. The maximum application rate of granular product is 0.375 lb a.i./acre, with a maximum of two applications/year. Flumioxazin is not persistent in the environment; as such, it does not accumulate in environmental media. Therefore, a single application is considered sufficient to characterize risks. The calculations used in the workbooks that accompany this risk assessment are based on a maximum single application rate of 0.38 lb a.i./acre.

The quantitative risk characterization for the human health and ecological risk assessments presented in this report is based on the hazard quotient (HQ), which is defined as the anticipated exposure (mg a.i./kg/day or mg a.i./L) divided by a non-carcinogenic toxicity value (mg a.i./kg/day or mg a.i./L) that is not likely to be associated with adverse effects. (Note that flumioxazin is not considered a carcinogen.) An HQ of greater than one is defined as the level of concern (LOC), such that HQs less than or equal to one indicate that adverse effects are not likely to occur. Concern level increases with increasing HQ values exceeding one. Hazard quotients greater than one and less than two, while above the LOC, might not represent significant risks, given the conservative nature of exposure estimates and no-observed-adverse-effect-level (NOAEL) to lowest-observed-adverse-

effect level (LOAEL) ratio for the critical effects used to derive toxicity values. For all non-accidental exposure scenarios, the HQs are linearly related to the application rate. HQs are calculated for three categories of exposure: central, lower bound, and upper bound. These categories account for uncertainties in the exposure estimates for specific exposure scenarios. FS risk assessments typically defer to the U.S. Environmental Protection Agency (U.S. EPA) on evaluation and selection of studies used in the dose-response assessment for both human health and ecological effects. Toxicity data used to assess risks of flumioxazin were obtained from Data Evaluation Records (DERs) of Master Record Identification (MRID) numbered studies submitted to U.S. EPA. Only data from DERs classified as "acceptable" or "supplemental"[1] were included in this risk assessment. Relevant data were also identified from searches of the peer-reviewed literature and were also reviewed. However, the critical toxicity data to assess risks were obtained from DERs, as these studies provided the lowest toxicity values reported.

Human Health Risk

As part of the human health risk assessment, risks related to the FS intended use of flumioxazin were characterized for workers (handlers and applicators) and the general public.

Workers. Risks to workers were characterized for general exposures and accidental acute exposure scenarios (Table ES-1). The most substantial risk to workers is for general exposure during foliar directed backpack application, with HQs ranging from 9 to 608 for lower to upper bound exposure estimates. For general exposure for other application methods (surface and subsurface water and granular applications), HQs exceeding the LOC are for upper bound exposures, with HQs of 1.7 and 3, respectively. The HQ of 28 for granular applications most likely represents an overestimate of risk due to conservative default input values in the exposure model. Risks associated with accidental acute exposure are much lower than for general exposure, with most HQs <1. The greatest risk is for a one-hour exposure from gloves contaminated with field solutions used for subsurface water application; HQs range from 13 to 32 for lower and upper bound exposures, respectively. Application of proper hygiene procedures to prevent accidental exposure should substantially reduce this risk.

Table ES-1: Hazard Quotients (HQs) for General and Accidental Exposures of Workers

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Workers: General Exposure				
	9 – 608 (Backpack)	<1 – 1.7	<1 – 3	<1 – 28
	<1 – 30 (Boom and Aerial)			
Workers: Accidental Acute Exposure				
Glove, 1 minute	<1	<1	<1	<1
Glove, 1 hour	<1	<1	13 – 32	<1

[1] According to U.S. EPA (2019) studies classified as "acceptable" are scientifically sound and considered acceptable for use in risk assessment. Studies classified as "supplemental" are considered scientifically sound; however, they were performed under conditions that deviated substantially from recommended protocols. Results do not meet guideline requirements; however, the information may be useful in a risk assessment.

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Spill on hands, 1 hour	<1 – 1.1	<1	<1	<1
Spill on lower legs, 1 hour	<1	<1	<1 – 1.5	<1

[1]HQ ranges are for lower to upper bound exposure estimates. HQs listed as <1 or ≤1 (with no range) indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Unless otherwise specified, values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).

Key: cells are colored for the highest HQ

	HQ ≤1
	HQ >1 – <2
	HQ ≥2

General Public. For the general public, risks were characterized for accidental acute exposures, non-accidental acute exposures, and chronic exposures. HQs for accidental acute exposures are summarized in Table ES-2. For accidental direct spray of a child (whole body) or an adult female (feet and lower legs), no HQs exceed one, indicating negligible risk. HQs for consumption of contaminated water by a child and consumption of contaminated fish by an adult male and subsistence populations indicate substantial risks resulting from spills of direct water subsurface field solutions and granular product; however, HQs also exceed the LOC for spills of spray solutions and direct surface water solutions. As shown in Table ES-1, marginal exceedances (>1 – <2) are observed for a few exposure scenarios, indicating a low risk of adverse effects. Note that although flumioxazin is not expected to bioconcentrate in fish, the high exposures from contaminated fish reflect the high flumioxazin concentrations in water predicted for spills into a small pond; risks would be reduced for the same volume of spill into a larger water body.

Table ES-2: Hazard Quotients (HQs) for Acute Accidental Exposures of the General Populations

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Direct spray of child, whole body	<1	NA	NA	NA
Direct spray of adult female, feet and lower legs	<1	NA	NA	NA
Water consumption (spill), child	<1 – 8	<1 – 5	9 – 213	6 – 79
Fish consumption (spill), adult male	<1 – 2	<1 – 1.4	6 – 64	5 – 24

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Fish consumption (spill), subsistence population	<1 – 12	<1 – 7	34 – 337	25 – 124

[1]HQ ranges are for lower to upper bound exposure estimates. HQs listed as <1 or ≤1 (with no range) indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).

Key: cells are colored for the highest HQ

	HQ ≤1
	HQ >1 – <2
	HQ ≥2

For non-accidental acute exposures to the general population, few HQs exceed 1 (Table ES-3). For non-accidental acute exposures by spray application, HQs for ingestion of treated or contaminated fruit and vegetation by an adult female range from 2 (upper bound) and 2 – 17 (central-upper bound estimates). Risks to females of childbearing potential are not surprising as developmental effects in offspring was the most sensitive toxicity endpoint observed in animal studies. For direct subsurface applications, the HQ for consumption of contaminated fish in a subsistence population is 1.4 .

Table ES-3: Hazard Quotients (HQs) for Nonaccidental Acute Exposures of the General Public

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Vegetation contact, shorts and T-shirt, adult female	<1	NA	NA	<1
Contaminated fruit, adult female	<1 – 2	NA	NA	<1
Contaminated vegetation, adult female	<1 – 17	NA	NA	
Swimming, 1 hour, adult female	<1	<1	<1	<1
Water consumption, child	<1	<1	<1	<1
Fish consumption, adult male	<1	<1	<1	<1
Fish consumption, subsistence population	<1	<1	1.4	<1

[1]HQ ranges are for lower to upper bound exposure estimates. HQs listed as <1 or ≤1 (with no range) indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).
Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ

	HQ: ≤1
	HQ: 1.1 – <2
	HQ: ≥2

For chronic/longer-term exposures, the only HQ exceeding 1 is the upper bound estimate for an adult female ingesting treated or contaminated vegetation (HQ: 2) (Table ES-4).

Table ES-4: Hazard Quotients (HQs) for Chronic/Longer-Term Exposures of the General Public

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Contaminated fruit, adult female	<1	NA	NA	<1
Contaminated vegetation, adult female	<1 – 2	NA	NA	<1
Water consumption, adult male	<1	<1	<1	<1
Fish consumption, adult male	<1	<1	<1	<1
Fish consumption, subsistence populations	<1	<1	<1	<1

[1]HQs listed as <1 or ≤1 only indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).
Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ

HQ ≤1
HQ >1 – <2
HQ ≥2

Ecological Risk

For the ecological risk assessment, risks are characterized for mammals, birds, terrestrial invertebrates, terrestrial plants, fish, aquatic invertebrates, and aquatic plants.

Terrestrial Organisms. The ecological risk assessment for terrestrial species indicates substantial risks to mammals and terrestrial plants. For mammals, the most significant risks are associated with accidental acute exposures and non-accidental acute exposures, with lower risks for chronic/longer-term exposures. HQs exceed 1 for accidental acute exposures as summarized in Table ES-5. HQ ranges encompass the smallest and largest mammals by weight, displaying a range of risks. Nearly all HQs exceed 1 for central and upper exposure estimates. The most substantial risks are for ingestion of fish contaminated by spills of subsurface field solutions and granular product into a small pond, with a wide range of exceedances. Significant risks for other exposure scenarios are also observed for direct spray application to small mammals and consumption of water contaminated by spills of subsurface field solutions and granular product, although risks are lower than for consumption of contaminated fish. For non-accidental acute and chronic/longer-term exposures, HQs exceed 1 for spray applications only (Table ES-6). For nonaccidental acute exposures, HQs exceed 1 for mammals consuming contaminated fruit, vegetation, and insects, indicating risk to mammals.

Table ES-5: Hazard Quotients (HQs) for Accidental Acute Exposures of Mammals to Flumioxazin

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Direct spray (100% absorption)	1.5 – 6	NA	NA	NA
Consumption of contaminated water	<1	<1	<1 – 5	<1 – 1.8
Consumption of contaminated fish	<1 – 6	<1 – 4	<1 – 177	<1 – 65

[1]HQ ranges are for lower to upper bound exposure estimates. HQs listed as <1 or ≤1 (with no range) indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).
Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ

HQ ≤1
HQ >1 – <2
HQ ≥2

Table ES-6: Hazard Quotients (HQs) for Non-Accidental Acute and Chronic/Longer-Term Exposures of Mammals to Flumioxazin

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Acute Exposure				
Contaminated fruit	<1 – 7	NA	NA	<1
Contaminated broadleaf foliage	≤1 – 49	NA	NA	<1
Contaminated tall grass	≤1 – 40	NA	NA	<1
Contaminated short grass	<1 – 88	NA	NA	<1
Contaminated insects	<1 – 12	NA	NA	<1
Contaminated water	<1	<1	<1	<1
Contaminated fish	<1	<1	<1	<1
Chronic/Longer Term Exposure				
Contaminated fruit	<1 – 1.1	NA	NA	<1
Contaminated broadleaf foliage	≤1 – 8	NA	NA	<1
Contaminated tall grass	<1 – 6	NA	NA	<1
Contaminated short grass	<1 – 14	NA	NA	<1
Contaminated water	<1	<1	<1	<1

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Contaminated fish	<1	<1	<1	<1

[1]HQ ranges are for lower to upper bound exposure estimates. HQs listed as <1 or ≤1 (with no range) indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Values are for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).
Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ

HQ ≤1
HQ >1 – <2
HQ ≥2

Low risks are anticipated for acute and chronic exposure scenarios for birds, with nearly all HQs <1 (data not shown). For direct spray and spray drift exposures to honey bees, all HQs are substantially <1 (data not shown). Quantitative risk characterizations were not developed for reptiles/terrestrial-phase amphibians or soil microorganisms because toxicity studies were not identified for these receptors.

For terrestrial plants, risks to sensitive and tolerant species are evaluated and quantified separately. The quantitative risk assessment for non-target terrestrial plants indicates substantial risks; this is anticipated as flumioxazin is an effective herbicide for both pre- and post-emergence applications. HQs for sensitive and tolerant species are summarized in Table ES-7. Substantial risks to plants are anticipated for direct spray and spray drift, runoff for spray and granular applications, and all application methods for contamination of irrigation water. Negligible risks are anticipated for exposure through wind erosion, with all HQs substantially below 1.

ES-7: Hazard Quotients (HQs) for Exposure of Terrestrial Plants to Flumioxazin

Exposure Scenario	HQs[1] for Application Type			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Direct spray and spray drift	S: <1 – 7600 T: <1 – 63	NA	NA	NA
Run-off	S: <1 – 285	NA	NA	S: <1 – 366
	T: <1 – 1.2			T: <1 – 1.5
Irrigation	S: <1 – 306	S: <1 – 63	S: 45 – 362	S: <1 – 612
	T: <1 – 3	T: <1	T:<1 – 3	T: <1 – 5

Exposure Scenario	HQs[1] for Application Type			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Wind erosion	<1[3]	<1[3]	<1[3]	<1[3]

[1]HQ ranges are for lower to upper bound exposure estimates. HQs listed as <1 or ≤1 (with no range) indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).
[3]HQs <1 for both sensitive and tolerant species.
Abbreviations: NA = not applicable; S = sensitive species; T = tolerant species

Key: cells are colored for the highest HQ
HQ ≤1
HQ >1 – <2
HQ ≥2

Aquatic Organisms. The ecological risk assessment for aquatic species indicates exposure to flumioxazin poses substantial risks to fish, aquatic invertebrates, aquatic macrophytes, and algae. HQs for exposure scenarios for accidental acute, non-accidental acute, and chronic/longer-term exposures are summarized in Table ES-8. For all species categories, the highest HQs are for accidental acute exposures. For fish, no risks of adverse effects are anticipated for non-accidental acute exposure (HQs <1), although risks are likely for chronic exposure of sensitive species. Risks for chronic exposure of fish may be overestimated. The toxicity value used to assess chronic risk was obtained from a study conducted under flow-through conditions (e.g., a constant concentration of flumioxazin over the exposure period). Under field conditions, a single application of flumioxazin would be expected to degrade rapidly in water. If studies had been conducted under static conditions, it is expected that toxicity values would be considerably higher. Thus, chronic HQs based on a flow-through toxicity values are likely to be overestimated and highly conservative. For aquatic invertebrates, risks are substantial for accidental acute exposure of sensitive and tolerant species and for non-accidental exposure of sensitive species. Risks for aquatic macrophytes and algae are substantial for all exposures and application methods. This is an expected outcome as flumioxazin is used as an aquatic herbicide.

ES-8: Hazard Quotients (HQs) for Exposure of Aquatic Organisms to Flumioxazin

Exposure Scenario	HQs[1,2] for Application Methods			
	Spray[3]	Direct Water Surface	Direct Water Subsurface	Granular
Fish				
Accidental acute	S: <1 – 4 T: <1	S: <1 – 2 T: <1	S: 11 – 107 T: 2 – 21	S: 8 – 39 T: 1.5 – 8
Non-accidental acute	<1[1]	<1[1]	<1[1]	<1[1]
Chronic/longer term	S: <1 – 6 T: <1	S: <1 – 9 T: <1	S: <1 – 53 T: <1 – 3	S: <1 – 15 T: ≤1.0

Exposure Scenario	HQs[1,2] for Application Methods			
	Spray[3]	Direct Water Surface	Direct Water Subsurface	Granular
Aquatic Invertebrates				
Accidental acute	S: 35 –348 T:1.3 – 13	S: 21 – 212 T: <1 – 8	S: 984 – 9.8E03 T: 36 – 364	S: 726 – 3.6E04 T: 27 – 134
Non-accidental acute	S: <1 – 3 T: <1	S: <1 – 7 T: <1	S: 40 T: 1.5	S: <1 – 7 T: <1
Chronic/longer term	<1[1]	<1[1]	S: 1.8	<1[1]
Aquatic Macrophytes[4]				
Accidental acute	1.6E03 – 1.5E04	963 – 9.6E03	4.4E04 – 4.5E05	3.3E04 – 1.6E05
Non-accidental acute	<1 – 154	31 – 314	1.8E03	<1 – 307
Chronic/longer term	<1 – 14	<1 – 21	<1 – 122	<1 – 35
Algae				
Accidental acute	S: ≥1.6E04 – 1.6E05 T: 183 – 1.8E03	S: 9.6E03 – 9.6E04 T: 112 –1.1E03	S: 4.5E06 – 4.5E06 T: 5.2E03 – 5.2E04	S: 3.3E05 – 1.6E06 T: 3.8E03 – 1.9E04
Non-accidental acute	S: <1 – 1.5E03 T: <1 – 18	S: 314 – 3.1E03 T: 4 – 36	S: 1.8E04 T: 211	S: 344 – 3.1E03 T: <1 – 36
Chronic/longer term	S: <1 – 140 T: <1 – 1.6	S: <1 – 212 T: <1 – 2	S: 4 – 1.2E03 T: <134	S: <1 – 348 T: <1 – 4

[1]HQs <1 for both sensitive and tolerant species.
[2] HQ ranges are for lower to upper bound exposure estimates. HQs listed as <1 or ≤1 (with no range) indicate that HQs for lower, central, and upper estimates are all ≤1.
[3]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).
[4]All toxicity studies were conducted in duckweed; sensitive and tolerant species were not identified.
Abbreviations: S = sensitive species; T = tolerant species

Key: cells are colored for the highest HQ

	HQ ≤1
	HQ >1 – <2
	HQ ≥2

Other Considerations. Flumioxazin is a light-dependent peroxidizing herbicide and its potency might increase under enhanced lighting conditions experienced in the field compared to standard lighting typically studied in the laboratory. No identified laboratory studies have evaluated the herbicidal activity of flumioxazin under enhanced lighting conditions in terrestrial or aquatic plants. However, numerous field studies on non-target terrestrial vegetation indicate that plant damage occurs at levels below the maximum single application rate of 0.38 lb a.i./acre. If enhanced lighting conditions increase the potency of flumioxazin to plants, risks to terrestrial and aquatic plants might be underestimated in this risk assessment. Similarly, risks to fish might also be enhanced under field lighting conditions. A single reproduction toxicity study in fish indicates that enhanced lighting increases the toxicity of flumioxazin compared to standard lighting conditions. These findings have not been corroborated in other identified laboratory or field studies or for other aquatic species.

However, if enhanced lighting does enhance the toxicity of flumioxazin, risks to fish might also be underestimated in this risk assessment.

Several studies have assessed the toxicity of environmental metabolites of flumioxazin in fish, aquatic invertebrates, aquatic macrophytes, and algae. Although most studies are not directly comparable due to differences in experimental designs (e.g., species and exposure duration), toxicity values (e.g., median lethal concentration [LC_{50}], no-observed-adverse-effect concentration [NOAEC] values, etc.) indicate that metabolites are less toxic than the parent compound. Therefore, if exposures are dominated by metabolites, rather than parent compound, risks to aquatic species could be overestimated in this risk assessment.

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ADR	absorbed dose rate
AFC	antibody forming cell
A/G	albumin/globulin ratio, or total serum protein
a.i.	active ingredient
ALP	alkaline phosphatase
APF	6-amino-7-fluoro-4-(2-propynyl)-2*H*-1,4-benzoxazin-3(4*H*)-one
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area-under-the-curve
BCF	bioconcentration factor
BLM	Bureau of Land Management
BPA	Blanket Purchase Agreement
bw	body weight
482-CA	2-[7-fluoro-3-oxo-6-(3,4,5,6-tetrahydrophthalimido)-2H-1,4-benzoxazin-4-yl]propionicacid
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CHO	Chinese hamster ovary
CICADS	Concise International Chemical Assessment Document
CRD	Crop Reporting Districts
cm	centimeter
DER	Data Evaluation Record
DI water	deionized water
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DNCB	dinitrochlorobenzene
DOI	Department of Interior
DT_{50}	time required for a 50% reduction in concentration
EC_{05}	concentration that affected 5% of tested organisms
EC_{25}	concentration affecting 25% of organisms tested
EC_{50}	median effects concentration
EDSP	Endocrine Disruptor Screening Program
EEB	Ecological Effects Branch
EFSA	European Food Safety Authority
EHC	Environmental Health Criteria
EOS	eosinophils
EPest	estimated pesticide use
F0	parent generation
F1	first generation
FDA	U.S. Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

FOB	Functional Observational Battery
FS	Forest Service
g	gram
gal	gallon
GD	gestational days
GLEAMS	Groundwater Loading Effects of Agricultural Management Systems
GOT	glutamic oxaloacetic transaminase
GSD	geometric standard deviation
ha	hectare
482-HA	7-fluoro-6-[(2-carboxyl-1-cyclohexenoyl)amino]-4-(2-propynyl)-1,4-benzoxazin-3-(2*H*)-one
HCO-40	polyoxyethylene hydrogenated castor oil
HERA	Human and Environmental Risk Assessment
HHERA	Human Health and Ecological Risk Assessment
HPV	High Production Volume
HQ	hazard quotient
HSG	Health and Safety Guidelines
IARC	International Agency for Research on Cancer
IC_{05}	concentration at which 5% of tested organisms are inhibited
IC_{50}	concentration at which 50% of tested organisms are inhibited
IMOXA	7-fluoro-6-(3,4,5,6-tetrahydrophthalimido)-2H-1,4-benzoxazin-3(4H)-one
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
IUPAC	International Union of Pure and Applied Chemistry
JECDB	Japan Existing Chemical Data Base
JEFCA	Joint Expert Committee on Food Additives
k_a	first-order dermal absorption rate coefficient
k_d	soil adsorption coefficient
kg	kilogram
K_{oc}	organic carbon-water partition coefficient
K_{ow}	octanol-water partition coefficient
K_p	zero-order dermal permeability rate
L	liter
LAP	leucyl aminopeptidase
lb	pound
LC_{50}	lethal concentration, 50% kill
LD_{50}	lethal dose, 50% kill
LLNA	Local Lymph Node Assay
LOAEC	lowest-observed-adverse-effect concentration
LOAEL	lowest-observed-adverse-effect level
LOC	level of concern
LOEL	lowest-observed-effect level
LOQ	limit of quantitation
LUC	leukocytes
m	meter

m^3/mol	cubic meter per mole
MATC	maximum acceptable toxicant concentration
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MeSH	Medical Subject Headings
µg	microgram
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
MMAD	mass median aerodynamic diameter
mmHg	millimeters of mercury
MOE	margin of exposure
MONO	monocytes
MRID	Master Record Identification Number
NAWQA	National Water-Quality Assessment
NEPA	National Environmental Policy Act
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIEHS	National Institute of Environmental Health Sciences
NITE	National Institute of Technology and Evaluation
NLM	National Library of Medicine
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NPIRS	National Pesticide Information Retrieval System
NRC	National Research Council
NTP	National Toxicology Program
NTRL	National Technical Reports Library
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organisation for Economic Cooperation and Development
OM	organic matter
OPP	Office of Pesticide Programs
OPPTS	Office of Prevention, Pesticides and Toxic Substances
PC	pesticide chemical
PCE	polychromatic erythrocyte
PFC	plaque-forming cell
ppb	parts per billion
ppm	parts per million
PPO	protoporphyrin oxidase
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RBC	red blood cells
RfD	reference dose
SD	standard deviation
SDS	Safety Data Sheet

SERA	Syracuse Environmental Research Associates
SIDS	Screening Information Data Set
sq ft	square foot
SRS	Substance Registry System
$t_{1/2}$	half-time
TDAR	T-cell dependent antibody response
T.G.	technical grade
THPA	3,4,5,6-tetrahydrophthalicacid
Δ-TPA	3,4,5,6-tetrahydrophthalicanhydride
TSCATS	Toxic Substances Control Act Test Submissions
TWA	time-weighted average
UF_A	interspecies uncertainty factor (extrapolation from animal to human)
UF_H	intraspecies uncertainty factor (intraspecies sensitivity)
USDA	U.S. Department of Agriculture
U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey
v/v	volume by volume
WB	workbooks
WBC	white blood cell
WDG	water dispersible granule
w/v	weight per volume
w/w	weight by weight

COMMON UNIT CONVERSIONS AND ABBREVIATIONS

To convert ...	Into ...	Multiply by ...
acres	hectares (ha)	0.4047
acres	square meters (m^2)	4047
atmospheres	millimeters of mercury	760
centigrade	Fahrenheit	1.8 °C+32
centimeters	inches	0.3937
cubic meters (m^3)	liters (L)	1000
Fahrenheit	centigrade	0.556 °F-17.8
feet per second (ft/sec)	miles/hour (mi/hr)	0.6818
gallons (gal)	liters (L)	3.785
gallons per acre (gal/acre)	liters per hectare (L/ha)	9.34
grams (g)	ounces, (oz)	0.03527
grams (g)	pounds, (oz)	0.002205
hectares (ha)	acres	2.471
inches (in)	centimeters (cm)	2.540
kilograms (kg)	ounces, (oz)	35.274
kilograms (kg)	pounds, (lb)	2.2046
kilograms per hectare (hg/ha)	pounds per acre (lb/acre)	0.892
kilometers (km)	miles (mi)	0.6214
liters (L)	cubic centimeters (cm^3)	1000
liters (L)	gallons (gal)	0.2642
liters (L)	ounces, fluid (oz)	33.814
miles (mi)	kilometers (km)	1.609
miles per hour (mi/hr)	cm/sec	44.70
milligrams (mg)	ounces (oz)	0.000035
meters (m)	feet	3.281
ounces (oz)	grams (g)	28.3495
ounces per acre (oz/acre)	grams per hectare (g/ha)	70.1
ounces per acre (oz/acre)	kilograms per hectare (kg/ha)	0.0701
ounces fluid	cubic centimeters (cm^3)	29.5735
pounds (lb)	grams (g)	453.6
pounds (lb)	kilograms (kg)	0.4536
pounds per acre (lb/acre)	kilograms per hectare (kg/ha)	1.121
pounds per acre (lb/acre)	mg/square meter (mg/m^2)	112.1
pounds per acre (lb/acre)	µg/square centimeter ($µg/cm^2$)	11.21
pounds per gallon (lb/gal)	grams per liter (g/L)	119.8
square centimeters (cm^2)	square inches (in^2)	0.155
square centimeters (cm^2)	square meters (m^2)	0.0001
square meters (m^2)	square centimeters (cm^2)	10,000
yards	meters	0.9144

Source: (SERA 2014a)

CONVERSION OF SCIENTIFIC NOTATION

Scientific Notation	Decimal Equivalent	Verbal Expression
1×10^{-10}	0.0000000001	One in ten billion
1×10^{-9}	0.000000001	One in one billion
1×10^{-8}	0.00000001	One in one hundred million
1×10^{-7}	0.0000001	One in ten million
1×10^{-6}	0.000001	One in one million
1×10^{-5}	0.00001	One in one hundred thousand
1×10^{-4}	0.0001	One in ten thousand
1×10^{-3}	0.001	One in one thousand
1×10^{-2}	0.01	One in one hundred
1×10^{-1}	0.1	One in ten
1×10^{0}	1	One
1×10^{1}	10	Ten
1×10^{2}	100	One hundred
1×10^{3}	1000	One thousand
1×10^{4}	10,000	Ten thousand
1×10^{5}	100,000	One hundred thousand
1×10^{6}	1,000,000	One million
1×10^{7}	10,000,000	Ten million
1×10^{8}	100,000,000	One hundred million
1×10^{9}	1,000,000,000	One billion
1×10^{10}	10,000,000,000	Ten billion

Source: (SERA 2014a)

1. INTRODUCTION

1.1. Background

The United States Department of Agriculture (USDA) Forest Service (FS) is responsible for protecting and managing natural resources on National Forest System lands. Forest management practices include the implementation of integrated pest and vegetation management programs to protect, restore, and maintain forest health. Pesticides are one of the various tools used by the FS to prevent, control, or manage forest insects, diseases, and invasive plants (USDA/FS 2020). When considering the use of pesticides on forest lands, it is FS policy that an analysis be conducted to assess potential human health and ecological risks and effects. FS pesticide risk assessments are referred to as Human Health and Ecological Risk Assessments (HHERAs). The FS uses HHERAs to evaluate the risks of harm from the use of a particular pesticide to FS personnel, the general public, and the environment. The FS also uses data and findings from HHERAs to prepare environmental documents required under the National Environmental Policy Act (NEPA). The project level NEPA assesses the potential effects from using pesticides. Additional information on the FS pesticide risk assessment process and a list of completed HHERAs can be accessed on the FS Pesticide Management and Coordination website.

The FS anticipates utilizing the herbicide flumioxazin in a number of FS programs to (1) control vegetation in surface water bodies; (2) control terrestrial weeds and invasive plants, such as managing forest vegetation in roadsides, utility corridors, hardscapes, and conifer and hardwood production areas; as well as for (3) the release or restoration of desirable vegetation in wildlife management areas, recreational areas, fire rehabilitation areas, natural areas, prairies, and fire breaks. The FS has not conducted previous risk assessments on flumioxazin. In accordance with FS pesticide procedures, the FS requested the preparation of a HHERA prior to using the herbicide. Kestrel Tellevate LLC, with support from our subcontractor, SRC Inc., prepared the flumioxazin HHERA. The work was conducted under Blanket Purchase Agreement (BPA) contract #AG-3187-B-17-0008, Call Order 123187180410.

1.2. Purpose of this HHERA

The purpose of this risk assessment is to estimate the nature and degree of potential risks associated with the use of the herbicide flumioxazin in FS terrestrial and aquatic vegetation management programs. Flumioxazin is used as a pre- and post-emergence herbicide in terrestrial and aquatic environments. This HHERA focuses on non-crop applications to soil, foliage, and water bodies for representative flumioxazin products, characterizing risks to workers (handlers and applicators), the general public, and environmental terrestrial and aquatic receptors. Risks are characterized for the following application methods: spray methods (e.g., backpack, boom, aerial) for application of aqueous solutions to soil, foliage, and water bodies; surface and subsurface instillation of aqueous solutions to water bodies; and soil applications of granular formulations.

The general framework, approach, and information included in this HHERA are consistent with previous national pesticide risk assessments developed for the FS. This includes the development of both a written HHERA and accompanying supporting materials that can be used to identify risks for FS programs based on anticipated program uses and formulations of flumioxazin. It is important to note that the HHERA is not intended to include summaries or evaluations of all available information

on flumioxazin. Instead, this document includes summaries and evaluations of available information that informs risk assessments and focuses on addressing technical areas and issues of specific importance to the Forest Service based on Forest Service intended uses.

In the future, the FS might update and/or expand this HHERA and welcomes input from the general public and other interested parties on the selection of studies included in the risk assessment. However, this input is particularly helpful if recommendations for including additional studies specify why and how the new or not previously included information would alter the conclusions reached in the risk assessment.

1.3. Supporting Materials (Excel Workbook)

Exposure and risk estimates are typically expressed as a central tendency estimate along with a range (low and high). In general, central tendency estimates are intended to represent the value predicted to have the highest probability of occurring (i.e., typical). The actual statistic used to represent the central estimate varies with the data underlying the estimate. Where normality is a reasonable assumption, the central estimate would be the mean. For skewed (i.e., lognormal) distributions, the central estimate would be the geometric mean. Because of the need to assess many different types of exposures for many types of receptors (human and ecological) and exposure scenarios, the risk assessment involves numerous calculations. Some of these calculations are relatively simple, while others are complex. Simple calculations and results are described in the body of the document. However, most of the exposure and risk calculations for human health and ecological receptors were conducted and are presented in customized Microsoft Excel® workbooks, which are included in Attachments 1 – 6. The workbooks were generated using the FS risk assessment tool called WorksheetMaker. The tool allows a user to develop pesticide-specific risk assessment workbooks by entering information on a chemical and formulation of interest, including chemical and physical-chemical properties, toxicity values, application rates, and application volumes. Once an Excel workbook is generated for a chemical and formulation, the workbook can be used to perform detailed calculations for quantitative exposures and risks for various human and ecological receptors.

The Excel workbook includes a series of worksheets designed to isolate the numerous calculations needed for the risk characterization. This includes the hazard quotient (HQ), which is used as the measure of risk and is further discussed in Sections 5.4 and 6.4. The HQ is the ratio of the estimated exposure compared to an appropriate comparable toxicity value (in the same units). The *WorksheetMaker Version 6.02 User Guide* (SERA 2016) includes additional information on WorksheetMaker and the use of Excel® workbooks in FS risk assessments.

1.4. HHERA Structure

The HHERA is organized into the following seven main sections:

1. Introduction
2. Chemical Information
3. Literature Search and Review
4. Fate and Transport in the Environment
5. Human Health Risk Assessment
6. Ecological Risk Assessment
7. References

The HHERA focuses on four general risk assessment steps, including (1) identification of the hazards associated with flumioxazin; (2) assessment of plausible exposure scenarios and exposures to the product after application; (3) assessment of dose-response relationships; and (4) characterization of risks. This framework is consistent with the basic steps recommended by the National Research Council (NRC) of the National Academy of Sciences for conducting and organizing risk assessments (NRC 1983).

While an effort is made to present the information in a manner that can be understood by a general audience, the information in this report, as well as the appendices and attachment, are intended to be detailed enough to support a technical review of the risk analyses. Additional information on the risk assessment process and terms used in the development of FS risk assessments are available in the *Preparation of Environmental Documentation and Risk Assessments for the USDA/Forest Service* guidance document developed by Syracuse Environmental Research Associates, Inc. (SERA) (SERA 2014a). The HHERA also follows the worker exposure methods described in the *Reassessment of Worker Exposure Rates* guidance document (SERA 2014b). In addition, the *Technical Comparison of EPA, BLM and Forest Service Pesticide Risk Assessments* document provides a comparison of the risk assessment methods used by the FS with risk assessments conducted by the U.S. Environmental Protection Agency/Office of Pesticide Programs (U.S. EPA/OPP) and the U.S. Department of Interior (DOI), Bureau of Land Management (BLM) (SERA 2009). SERA previously supported the FS in developing HHERAs, guidance documents, and tools for conducting FS-specific risk assessments. Interested parties should forward questions related to FS risk assessments and tools directly to the FS.

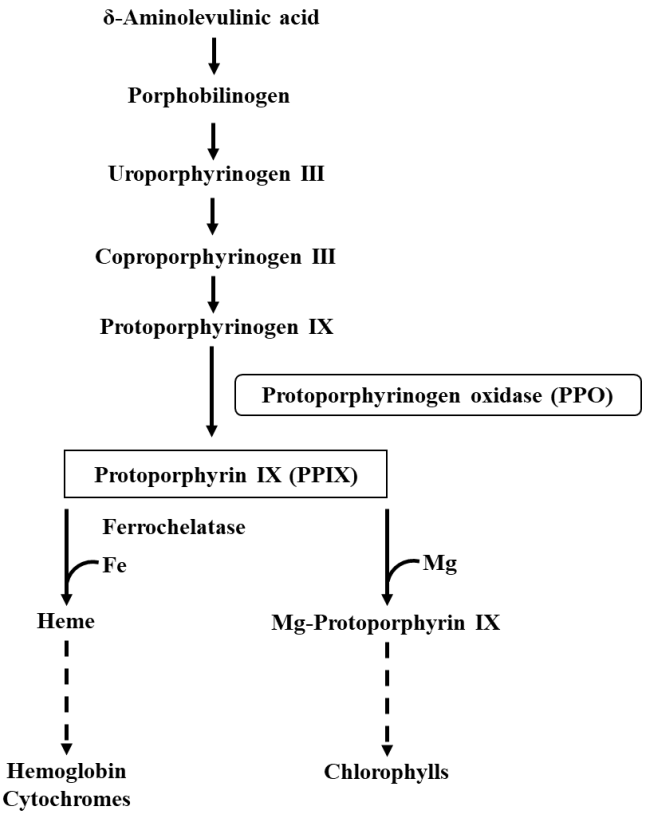
2. CHEMICAL INFORMATION

Numerous formulations of flumioxazin have been registered in the United States, including products that are formulated in combination with other herbicides. For this assessment, only products with flumioxazin as the sole active ingredient (a.i.) are considered. Inert ingredients commonly used in these formulations, listed in product Safety Data Sheets (SDSs), include kaolin clay and propylene glycol, and to a lesser extent aluminum oxide and sodium lauryl sulfate. The potential impact of "inert" ingredients is not separately evaluated in this risk assessment, but is considered jointly within product formulations, depending upon availability of technical information.

2.1. Chemical Description and Formulations

Flumioxazin (2-[7-fluoro-3,4-dihydro-3-oxo-4-(2-propynyl)-2H-1, 4-benzoxazin-6-yl]-4,5,6,7-tetrahydro-1H-isoindole-1,3(2H)-dione) is a light-dependent, peroxidizing N-phenylphthalimide herbicide used for the pre- and post-emergence control of terrestrial and aquatic weeds. Labeled uses include forestry-related applications, such as maintaining bare ground on conifer and poplar reforestation sites and managing undesirable aquatic vegetation in slow-moving or quiescent waters. Flumioxazin is active against both aquatic and terrestrial vegetation, including some grasses, broadleaf weeds, and sedges. The herbicidal mechanism of flumioxazin is inhibition of protoporphyrin oxidase (PPO), the enzyme responsible for converting protoporphyrinogen IX to protoporphyrin IX, a precursor of heme and chlorophyll in plants. Inhibition of PPO results in accumulation of phototoxic porphyrins in plant cells and decreases heme synthesis and chlorophyll biosynthesis, as shown in Figure 2.1-1 (U.S. EPA 2003; Kawamura et al. 1996). This mechanism of action also applies to some toxicological outcomes in mammals (e.g., hematological effects), as discussed in Section 5.1.2. Flumioxazin is somewhat unusual because typically, the mechanisms of herbicidal action and mammalian toxicity are not the same.

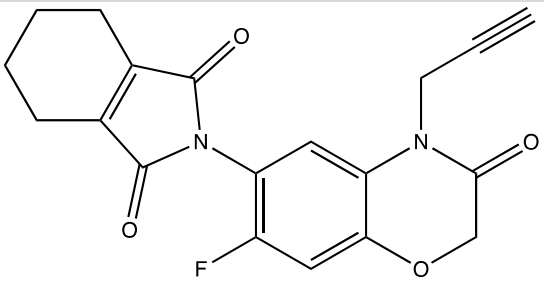
Selected chemical and physical properties of flumioxazin are summarized in Table 2.1-1. In the environment, flumioxazin photodegrades rapidly in water and in soil; it is classified as having moderate mobility in soil based on a K_{oc} value of 670 (U.S. EPA 2012). Flumioxazin is relatively volatile in water and soil and is not expected to bioaccumulate in fish. Additional data are presented in the workbooks provided in Attachment 1 (see Worksheet B01).



Source: Reprinted from Kawamura et al. 1996, with permission from Elsevier

Figure 2.1-1: Synthesis of Protoporphyrin IX, Heme, and Chlorophylls in Plants

Table 2.1-1: Chemical and Physical Properties of Flumioxazin

Parameter	Value	Reference
Common name	Flumioxazin	NA
Chemical name (IUPAC)	2-[7-fluoro-3,4-dihydro-3-oxo-4-(2-propynyl)-2*H*-1,4-benzoxazin-6-yl]-4,5,6,7-tetrahydro-1H-isoindole-1,3(2H)-dione	U.S. EPA (2012)
CAS Registry Number	103361-09-7	U.S. EPA (2012)
U.S. EPA PC Code	129034	U.S. EPA (2012)
Structure		U.S. EPA (2012)
Molecular formula	$C_{19}H_{15}FN_2O_4$	U.S. EPA (2012)
Molecular weight	354.34	U.S. EPA (2012)
Density (20 °C)	1.51 g/cm^3	U.S. EPA (2012)
Henry's Law constant	6.2 × 10^{-7} atm × m^3/mol	U.S. EPA (2012)
pH (23 °C)	pH = 7.29 at 25 °C	U.S. EPA (2012)

Parameter	Value				Reference
Vapor pressure (25 °C)	2.41×10^{-6} mmHg at 25 °C				U.S. EPA (2012)
Water solubility (20 °C)	1.8 mg/L				U.S. EPA (2003)
Dissociation constant (pK_a)	NA				Flumioxazin does not have any acidic or basic functional groups.
Octanol-water partition coefficient (K_{ow}) (pH 4, pH 7, and pH 9)	**Log (K_{ow})**	**K_{ow}**			U.S. EPA (2012) K_{ow} values based on antilog10 calculation.
	2.55	355			
Soil adsorption coefficient (K_d)	2.54 – 6.51 L/kg				U.S. EPA (2003) Alister et al. (2008)
K_d/K_{oc}	**Soil Texture**	**Organic Carbon Content %**	**K_d**	**K_{oc}**	Ferrel et al. (2005)
	Loamy sand	0.6	0.7	116	
	Sand	0.2	0.4	200	
	Sandy clay loam	2.6	3.8	146	
	Sandy loam	0.8	1.1	137	
	Sandy loam	0.9	1.5	166	
	Sandy loam	2.6	3.4	130	
	Silt loam	5.3	8.8	166	
K_d/K_{oc}	**Soil Texture**	**K_d**		**K_{oc}**	U.S. EPA (2003) MRIDs 42684907, 42684908, 42684909, and 42884010
	Sandy loam	0.8		112	
	Silt loam	7.7		1190	
	Sand	0.5		271	
	Clay loam	19.3		656	
Bioconcentration factor (BCF)	U.S. EPA waived the data requirement for bioaccumulation in fish[1] A minimal BCF value of 22.4 was modeled using Log K_{ow} of 2.55 for risk calculations[2].				NA
Photolysis in water half-life	1 day at pH 5				U.S. EPA (2003) MRIDs 44295036 and 44295039
Photolysis in soil half-life	3.2 – 9.4 days				U.S. EPA (2003)
Aquatic sediment half-life	**Water-Loam Sediment**				U.S. EPA (2003) MRID 44295041
	4.3 hours (flooded sandy-loam soil)				

Parameter	Value	Reference
Soil half-life	11.9 – 17.5 days in California sandy loam soil, 5.0 days in Wheeling sandy loam	U.S. EPA (2003) MRIDs 42684906 and 42884009

[1]Requirement waived; flumioxazin is not expected to bioaccumulate due to rapid degradation in water ($t_{1/2}$ = 1 day at pH 7, 20 minutes at pH 9) and the low K_{ow}.
[2]BCF is calculated using the following regression equation: Log BCF = 0.6598*log K_{ow} – 0.333 + CF, where CF may be an applicable structural correction factors (there are no factors for flumioxazin). Therefore, Log BCF = 0.6598*2.55 – 0.333 = 1.349, deriving a BCF of 22.
Abbreviations: atm = atmosphere; CAS = Chemical Abstracts Service; cm^3 = cubic centimeter; g = gram; IUPAC = International Union of Pure and Applied Chemistry; L = liter; m^3/mol = cubic meters per mole; mg = milligram; mmHg = millimeters of mercury; NA = not applicable; PC = pesticide chemical; $t_{1/2}$ = half-time

The FS intends to use flumioxazin for the treatment of non-crop areas of FS land to maintain bare ground or manage undesirable terrestrial vegetation, and to treat stagnant or slow-moving water bodies. For this risk assessment, several representative products have been selected; these are summarized in Table 2.1-2. The following formulations are used as proxies for modeling purposes: SureGuard™ Herbicide (51% a.i.) is used for spray applications of aqueous solutions to terrestrial vegetation; PondKlear Aquatic Herbicide (44% a.i.) is used for surface and subsurface applications to water bodies; and Broadstar™ Herbicide (0.25% a.i.) is used for granular applications to soil.

Table 2.1-2: Representative Flumioxazin Formulations

Formulation and U.S. EPA Registration No./Registrant	Application Method	Application Rate	Application Volumes
Formulation type: water dispersible granule (WDG) applied as a liquid			
Alligare Flumigard™ Herbicide (51.5% a.i.) 81927-68/Alligare, LLC	Boom sprayers, backpack applicators; broadcast, band, and aerial application; handgun sprayers; subsurface trailing hose	Terrestrial: 0.25 – 0.38 lb a.i./acre (maximum 0.38 lb a.i./acre, 2 applications/year) Aquatic surface: 0.19 – 0.38 lb a.i./acre Aquatic subsurface: 200 – 400 ppb a.i. (maximum 400 ppb [8.8×10^{-7} lb a.i./L], 6 applications/year)	10 – 20 gal/acre for boom sprayers; 50 – 100 gal/acre for backpack applications; 40 gal/acre for handgun sprayers; 10 gal/acre for aerial application; 30 gal/acre for aquatic application
Chateau® Herbicide WDG (51% a.i.) 59639-119/Valent U.S.A. LC	Sprayer: broadcast, band, and aerial application	0.188 – 0.38 lb a.i./acre (maximum rate of 0.38 lb a.i./acre, 2 applications/year)	10 – 60 gal/acre (5 – 10 gal/acre for aerial application)

Formulation and U.S. EPA Registration No./Registrant	Application Method	Application Rate	Application Volumes
Clipper™ Herbicide (51% a.i.) 59639-161/Valent U.S.A. LC	Surface sprayer: aerial, ground, or watercraft-based sprayer; backpack or handgun sprayer; subsurface: trailing hoses	Surface: 6 – 12 fl oz/acre Subsurface: 200 – 400 ppb (maximum rate of 400 ppb [8.8×10^{-7} lb a.i./L], 6 applications/year)	At least 5 gal/acre for aerial application; at least 30 gal/acre for surface spray application and subsurface application
Flumioxazin 51% WDG 85678-34/RedEagle International LLC	Ground boom; aerial, broadcast, and band application	0.188 – 0.38 lb a.i./acre (maximum 0.38 lb a.i./acre, 2 applications/year)	10 – 60 gal/acre
Lock Down™ Herbicide (51% a.i.) 71368-103/Nufarm Americas, Inc.	Boom sprayer (broadcast and band application); aerial application; backpack application; handgun sprayer	0.25 – 0.38 lb a.i./acre (maximum 0.38 lb a.i./acre, 2 applications/year)	10 – 30 gal/acre for boom sprayer application; 44 – 87 gal/acre for backpack application; 5 – 10 gal/acre for aerial application
Promenade™ Herbicide (51.5% a.i.) 81927-67/Alligare, LLC	Sprayer: aerial, broadcast and band application; ground booms; handgun sprayer	0.25 – 0.38 lb a.i./acre (maximum 0.38 lb a.i./a, 2 applications/year)	10 – 20 gal/acre for boom sprayers; 40 gal/acre for handgun application; 10 gal/acre for aerial application
SureGuard™ Herbicide (51% a.i.) 59639-120/Valent U.S.A. LLC	Sprayer: broadcast, band, and aerial application; Boom sprayer, backpack, and handgun application; Subsurface application	Terrestrial: 0.25 – 0.38 lb a.i./acre (maximum rate of 0.38 lb a.i./acre, 2 applications/year) Aquatic subsurface: 400 ppb (8.8×10^{-7} lb a.i./L) (maximum of 6 applications/year) Aquatic spray: 6 – 12 oz/acre	10 – 20 gal/acre for boom sprayer; 50 – 100 gal/acre for backpack application; 5 – 10 gal/acre for aerial application; 30 gal/acre for aquatic application

Formulation and U.S. EPA Registration No./Registrant	Application Method	Application Rate	Application Volumes
Warfox (51% a.i.) 66222-252/Makhteshim Agan of North America, Inc.	Sprayers (tanks, hoses, booms): broadcast, band, and aerial application	0.188 – 0.38 lb a.i./acre (maximum 0.38 lb a.i./acre; 2 applications/year)	10 – 60 gal/acre (7 – 10 gal/acre for aerial application)
Formulation type: liquid concentrate			
Alligare Flumigard SC Herbicide (42% a.i.) 81927-78/Alligare, LLC	Aerial application with boom sprayer; ground application with boom and handheld sprayers (backpack, handgun); broadcast and band application; trailing hoses for aquatic subsurface application	Terrestrial: 0.25 – 0.38 lb a.i./acre (maximum 0.38 lb a.i./acre, 2 application/ year) Aquatic surface: 0.19 – 0.38 lb a.i./acre Aquatic subsurface: 200 – 400 ppb a.i. (maximum 400 ppb [8.8×10^{-7} lb a.i./L], 6 applications/year)	5 – 10 gal/acre for aerial application; 30 gal/acre for aquatic application; 10 – 30 gal/acre for boom sprayer application; 40 gal/acre for handgun application; 44 – 87 gal/acre for backpack application
Panther® SC Herbicide (41.4% a.i.) 71368-113/Nufarm Americas, Inc.	Sprayer: broadcast, band, and aerial application	0.188 – 0.38 lb a.i./acre (maximum 0.38 lb a.i./acre, 2 applications/year)	10 – 60 gal/acre (7 – 10 gal/acre for aerial application)
PondKlear Aquatic Herbicide (44% a.i.) 8959-61/Arch Chemicals, Inc.	Sprayer via ground or watercraft; backpack or handgun sprayer	Surface: 1.5 – 3 fl oz/¼ acre Subsurface: 200 – 400 ppb (maximum concentration of 400 ppb [8.8×10^{-7} lb a.i./L], 6 applications/year)	16 gal/acre for surface spray application; 4 gal/acre-foot for subsurface application
SureGuard® SC Herbicide (41.4% a.i.) 71368-114/Nufarm Americas, Inc.	Sprayer: broadcast, band, and aerial application; backpack or handgun sprayer; airboat; ground booms	Terrestrial: 0.25 – 0.38 lb a.i./acre (maximum 0.38 lb a.i./acre, 2 applications/year) Aquatic surface spray: 6 – 12 oz/acre; subsurface application: 200 – -400 ppb (maximum 400 ppb [8.8×10^{-7} lb a.i./L], 6 applications/year)	5 – 10 gal/acre for aerial application; 30 gal/acre for aquatic application; 10 – 30 gal/acre for boom sprayer; 40 gal/acre for handgun sprayer; 44 – 87 gal/acre for backpack application

Formulation and U.S. EPA Registration No./Registrant	Application Method	Application Rate	Application Volumes
Valor® EZ Herbicide (41.4% a.i.) 59639-221/Valent U.S.A. LLC	Sprayer: broadcast, band, and aerial application	0.188 – 0.38 lb a.i./acre (maximum 0.38 lb a.i./acre; 2 applications/year)	10 – 60 gal/acre (7 – 10 gal/acre for aerial application)
Formulation type: granule applied to soil			
Broadstar™ Herbicide (0.25% a.i) 59639-128/Valent U.S.A. LC	Drop or rotary granular application equipment, hand-cranked spreader, hand shaker	0.375 lb a.i./acre, maximum 2 applications/year	150 lb product/acre or 3.5 lb/1000 sq ft

Abbreviations: a.i. = active ingredient; fl oz = fluid ounce; gal = gallon; lb = pound; oz = ounce; ppb = parts per billion; sq ft = square feet
Note: Trade product names are provided for example purposes only and should not be considered as endorsements by the Forest Service.

As shown in Table 2.1-2, Alligare, Valent, Nufarm, Arch Chemicals, Inc., RedEagle International, and Makhteshim Agan of North America are currently registrants of the representative flumioxazin products. These formulations are intended for pre- and post-emergence use for the control of undesirable vegetation to allow the re-establishment of desirable perennial grasses, forbs, shrubs and trees, as permitted by the product label. Flumioxazin product labels and SDSs for these products are available in the *U.S. EPA Pesticide Product and Label System*. Numerous formulations of flumioxazin are registered for residential and crop uses; however, as the FS does not anticipate residential or crop uses and those formulations are not considered in this risk assessment.

2.2. Application Methods

The most common methods for application of the flumioxazin products described in Table 2.1-2 are spray (backpack directed foliar spray, boom ground spray, and/or aerial aircraft spray), surface and subsurface applications to water bodies, and ground application of granules. Each of these is likely to be used by the FS and discussed in detail below.

2.2.1. Ground Broadcast Application

In terrestrial settings, FS workers might apply flumioxazin products to areas containing undesirable vegetation using boom sprayers (broadcast foliar application) or backpack and handgun sprayers (selective foliar application). Broadcast foliar application with booms is used primarily to treat rights-of-way or large swaths of FS land managed for regrowth of preferred species. Spray equipment is typically mounted on tractors or trucks carrying the herbicide in tanks. It is estimated that approximately eight acres can be treated in a 45-minute period (approximately 11 acres/hour). Some special truck-mounted spray systems might be used to treat up to 12 acres in a 35-minute period with approximately 300 gallons of herbicide mixture (approximately 21 acres/hour and

510 gallons/hour) (SERA 2014a). The flumioxazin products being evaluated in this risk assessment can be applied via ground boom sprayers either as broadcast or band foliar applications.

In selective foliar applications, the herbicide sprayer is carried by backpack or handgun and applied to selected target vegetation on a smaller scale. Application crews carrying backpacks or handgun sprayers might treat up to shoulder high brush, thereby exposing areas of the body that may not be covered by protective clothing (e.g., arms, hands, face) to flumioxazin. This HHERA conservatively assumes that arms, hands, and face are not covered by protective clothing. To reduce the likelihood of significant exposure, application crews should be directed not to walk through treated vegetation. Typically, a worker should be able to treat approximately 0.5 acres/hour with a plausible range of 0.25 – 1 acre/hour (SERA 2014a).

One of the flumioxazin products evaluated in this risk assessment, Broadstar™ Herbicide, is applied directly as a granule using drop or rotary granular application equipment (in a ground broadcast application) or using hand-cranked spreaders and hand shakers for more targeted application. Using this method, crews apply the product directly to the soil; because there is likely little direct application to foliage, worker exposure to flumioxazin from contact with contaminated vegetation is expected to be minimal. For granular applications using drop or rotary equipment mounted to trucks or tractors, approximately 6 – 15 acres can be treated in 35 – 45 minutes (approximately 8 – 26 acres/hour) (USFS 2005; SERA 2014a).

2.2.2. Aerial Broadcast Application

Aerial broadcast application of flumioxazin products can be used for both terrestrial and aquatic vegetation management. Aerial application involves the use of fixed wing or rotary wing aircraft, such as helicopters, and is employed in areas that are either not accessible by ground or are too large to efficiently cover using ground broadcast application methods. The herbicide is applied using specific spray nozzles and booms designed to reduce spray drift onto non-target areas by minimizing turbulence and maintaining a large droplet size. Product labels specify wind speeds, distance to dwellings or environmentally sensitive areas, nozzle type, and volume pressure, as well as steps to be taken to manage spray drift. For FS risk assessments, it is estimated that approximately 40 – 100 acres can be treated per hour in aerial herbicide applications (SERA 2014a).

2.2.3. Direct Water Application

Flumioxazin products might be directly applied to water bodies. Products can be applied to stagnant or slow-moving bodies of water via surface spray (similar to ground broadcast application) or by trailing hoses behind watercraft that directly apply the herbicide below the surface of the water to target submerged vegetation. Aerial application methods described above can also be implemented for these products except for PondKlear Aquatic Herbicide, whose label specifies that aerial application should not be used.

2.3. Mixing and Application Rates

Application methods described in Section 2.2 involve different estimates of the amount of flumioxazin used by FS workers in a single day based on the number of acres likely treated per day and the application rate. As summarized in Table 2.1-2, the range of recommended labeled rates for formulations of flumioxazin in single terrestrial applications relevant to FS activities is 0.188 –

0.38 pounds (lb) a.i./acre. Based on current product labels, the maximum annual application rate is 0.765 lb a.i./acre/year. For spray application to the surface of water bodies, the range of application rates is 0.19 – 0.38 lb a.i./acre, and for subsurface applications, the recommended application rate is 200 – 400 ppb (equivalent to 8.87×10^{-7} lb a.i./L), with a maximum of 6 applications/year. The maximum application rate of granular product is 0.375 lb a.i./acre, with a maximum of 2 applications/year. For this HHERA, only a single maximum-rate application is considered in the exposure assessments because flumioxazin is not persistent in the environment. To be conservative, calculations used in the Excel® workbooks that accompany this risk assessment are based on the maximum single application rate of 0.375 lb a.i./acre for foliar spray and soil granular applications. For surface and subsurface applications to water bodies, the maximum concentration is the water is 400 ppm (Attachments 1 – 6). This has been the standard approach used by the FS when developing national risk assessments (SERA 2014a). However, the application rate can be modified by users in Worksheet A01 of Attachments 1 – 6 to assess site-specific application rates.

Application volumes are also considered in FS risk assessments and refer to the number of gallons of pesticide solution applied per acre. Because most pesticides are diluted before field application, it is important to take the application volume into consideration as it might have an impact on dermal and direct spray scenarios, both of which depend on 'field dilution' (i.e., the concentration of pesticide in the applied spray) (SERA 2014a). The higher the concentration of flumioxazin, the higher the exposure and potential for risk. As shown in Table 2.1-2, application volumes vary by flumioxazin product, but in general, the recommended application volumes are 10 – 60 gallons/acre for boom sprayers in ground broadcast applications depending on pre- and post-emergence conditions; 50 – 100 gallons/acre for backpack sprayers; 40 gallons/acre for handgun sprayers; 5 – 10 gallons/acre for aerial application; and 16 – 30 gallons/acre for aquatic (surface and subsurface) application methods. The granular flumioxazin product is applied at a volume of 150 lb/acre, or 3.5 lb/1000 square feet.

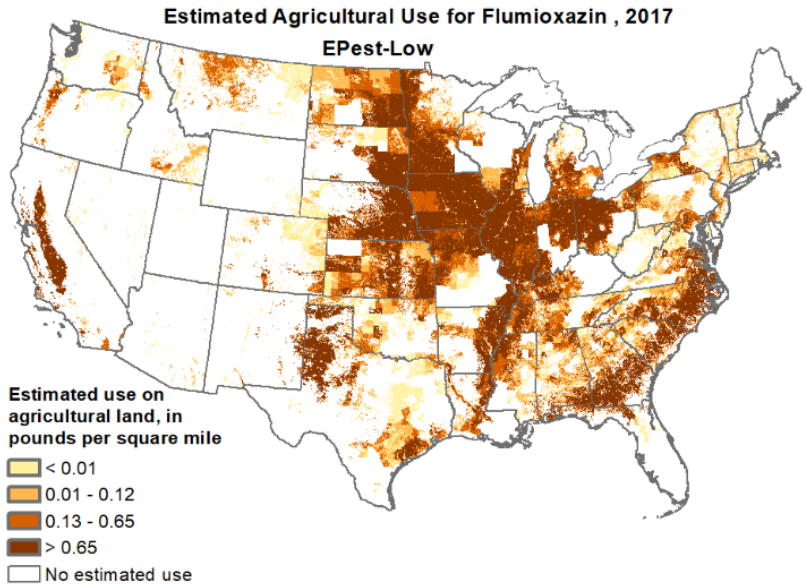
2.4. Use Statistics

FS risk assessments attempt to characterize the typical use of an herbicide or pesticide in FS programs relative to their use in agricultural applications. While the use statistics do not have a direct impact on the risk assessment assumptions and risk calculations, they can be useful in providing context as to where the herbicide is being used across the country and on what agricultural crops. FS pesticide use reports up to year 2004 are available on the *FS Pesticide Management & Coordination* website. Flumioxazin has been registered since April 2001.

Information on agricultural use is compiled by the U.S. Geological Survey (USGS) *National Water-Quality Assessment Project (NAWQA)*, which provides information on estimated annual agricultural pesticide use. Pesticide use data are compiled from proprietary surveys of farm operations located within USDA's Crop Reporting Districts (CRDs). County annual harvested-crop acres reported by the USDA are also collected and used to calculate use rates per harvested-crop acre, or an "estimated pesticide use" (EPest) rate, for each crop by year (Baker and Stone 2015). The county-use estimates are then calculated by multiplying EPest rates by harvested-crop acres for each pesticide crop combination.

A summary of the agricultural uses of flumioxazin is presented in Figures 2.4-1 and 2.4-2. These preliminary use statistics are for 2017, the most recent year for which data are available, and include

the EPest-low and high estimates. According to USGS, EPest-low estimates are based primarily on CRD surveyed data. When surveyed data are not available, EPest estimates are calculated from adjoining or nearby CRDs to ensure that pesticide use is estimated for all counties within CRDs. Therefore, EPest-high estimates include more extensive estimates of pesticide use not reported in CRD surveys, which sometimes include information from States or specific areas where use restrictions have been imposed (Baker and Stone 2015). All uses of flumioxazin reported by the USGS are for application on crops, including pasture and hay, alfalfa, orchards and grapes, rice, vegetables and fruit, cotton, wheat, soybeans, and corn. Use of flumioxazin has increased relatively steadily since registration (April 12, 2001), with approximately 1.25 – 1.5 million pounds used in 2017 (USGS 2017).



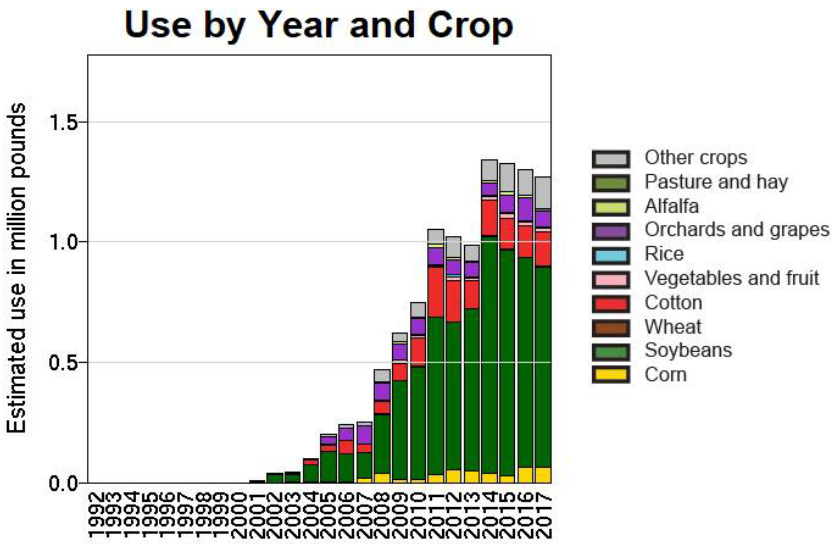
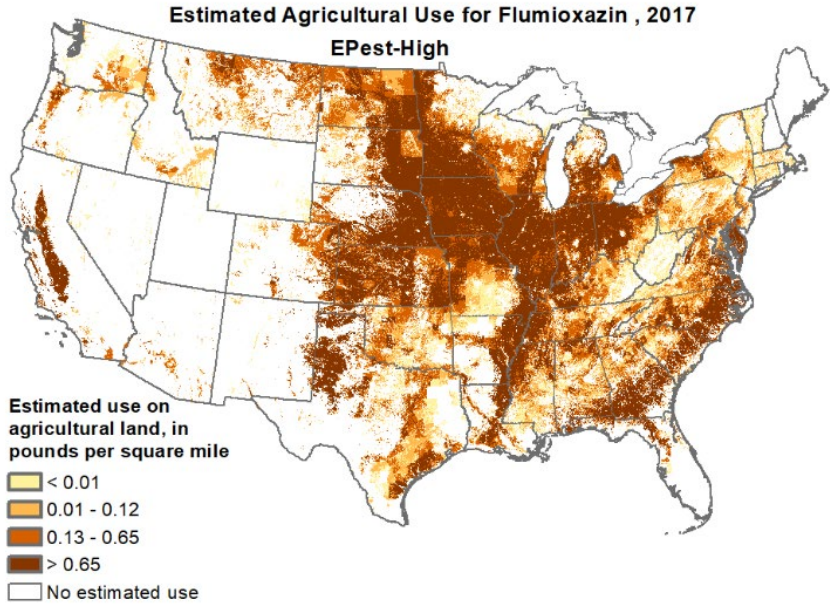


Figure 2.4-1: U.S. Geological Survey EPest-Low Agricultural Use Estimates for Flumioxazin in 2017

Source: USGS (2017)



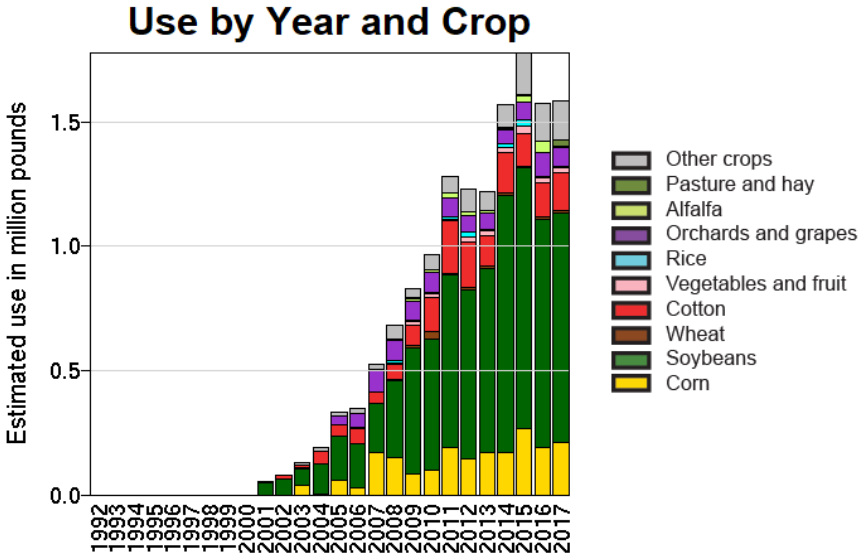


Figure 2.4-2: U.S. Geological Survey EPest-High Agricultural Use Estimates for Flumioxazin in 2017

Source: USGS (2017)

3. LITERATURE SEARCH AND REVIEW

3.1. Overview

A literature search was conducted to identify fate and transport, exposure, and toxicity information on flumioxazin. This section describes the methodology and tools used to conduct the search. Information on the screening, review, and documentation process are also described. In addition to obtaining studies from the open literature, relevant information was obtained from reputable reviews by the U.S. EPA and other agencies, as well as unpublished studies.

3.2. Open Literature

3.2.1. Data Search and Collection

A literature search was performed to identify open literature studies with relevant chemical and risk assessment information necessary to develop the HHERA, including pertinent physical and chemical properties, environmental fate and transport information, and toxicological, biological, and exposure data. A synonym list was prepared using National Library of Medicine's (NLM) ChemID; PubMed Medical Subject Headings (MeSH); and U.S. EPA's Substance Registry System (SRS). Search terms included the chemical name, synonyms, trade names, and Chemical Abstracts Service Registry Numbers (CASRNs).

The flumioxazin literature search was performed in March 2020. Information scientists accessed various bibliographic databases for the literature search, including NLM's PubMed as well as EBSCO host databases including USDA's AGRICOLA, Biological Abstracts, CAB Abstracts, Environment Complete, and Global Health. Query strings for these resources are provided in Table 3.2-1. These results were imported into the reference manager tool, Endnote.

Table 3.2-1: Bibliographic Database Literature Search Query Strings Screened in Endnote

Database	Query String
PubMed	103361-09-7[rn] OR L0PX7OGI22[rn] OR "Flumioxazin"[tw] OR "1H-Isoindole-1,3(2H)-dione, 4,5,6,7-tetrahydro-2-(7-fluoro-3,4-dihydro-3-oxo-4-(2-propynyl)-2H-1,4-benzoxazin-6-yl)-"[tw] OR "1H-Isoindole-1,3(2H)-dione, 2-(7-fluoro-3,4-dihydro-3-oxo-4-(2-propyn-1-yl)-2H-1,4-benzoxazin-6-yl)-4,5,6,7-tetrahydro-"[tw] OR "7-Fluoro-6-(3,4,5,6-tetrahydrophthalimido)-4-(2-propynyl)-1,4-benzoxazin-3(2H)-one"[tw] OR "7-fluoro-6-((3,4,5,6-tetrahydro)phthalimido)-4-(2-propynyl)-1,4-benzoxazin-3(2 H)-one"[tw] OR "Sumisoya"[tw] OR "S 53482"[tw] OR "S-53482"[tw] OR "V 53482"[tw]
EBSCO[1]	SU ("Flumioxazin" OR "1H-Isoindole-1,3(2H)-dione, 4,5,6,7-tetrahydro-2-(7-fluoro-3,4-dihydro-3-oxo-4-(2-propynyl)-2H-1,4-benzoxazin-6-yl)-" OR "1H-Isoindole-1,3(2H)-dione, 2-(7-fluoro-3,4-dihydro-3-oxo-4-(2-propyn-1-yl)-2H-1,4-benzoxazin-6-yl)-4,5,6,7-tetrahydro-" OR "7-Fluoro-6-(3,4,5,6-tetrahydrophthalimido)-4-(2-propynyl)-1,4-benzoxazin-3(2H)-one" OR "7-fluoro-6-((3,4,5,6-tetrahydro)phthalimido)-4-(2-propynyl)-1,4-benzoxazin-3(2 H)-one" OR "Sumisoya" OR "S 53482" OR "S-53482" OR "V 53482") OR TX "103361-09-7"
[1]Databases included in the search via the EBSCO interface include AGRICOLA, Biological Abstracts, CAB Abstracts, Environment Complete, and Global Health.	

To augment the bibliographic database queries various additional resources were searched to find technical reports and gray literature (i.e., unpublished studies, conference proceedings, theses, and dissertations, etc.). Table 3.2-2 provides the list of resources and URLs searched using the CASRN "103361-09-7" and/or the term "flumioxazin." These results were screened outside of Endnote and selected studies were added to Endnote, retrieved, and analyzed at full text review.

Table 3.2-2: Additional Search Resources Screened Outside of Endnote

Resource searched	URL(s)
U.S. EPA's Pesticide Chemical Search (Regulatory Action & Science tabs)	https://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:1:
NPIRS	http://npirs.ceris.purdue.edu
NTRL	https://ntrl.ntis.gov/NTRL/
ECOTOX	https://cfpub.epa.gov/ecotox/search.cfm
U.S. EPA – ChemView (including TSCATS data)	https://chemview.epa.gov/chemview
ATSDR	http://www.atsdr.cdc.gov/toxprofiles/index.asp
ECETOC publications	http://www.ecetoc.org/publications
ECHA	http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances
U.S. EPA – HPV Risk-Based Prioritization Documents (RBPs)	http://iaspub.epa.gov/oppthpv/hpv_hc_characterization.get_report?doctype=1
U.S. EPA – Robust summary/test plan	Google search CASRN and "robust summary" OR "test plan"
U.S. EPA – HPV Hazard Characterization Documents	https://iaspub.epa.gov/oppthpv/public_search.html_page
EFSA	http://www.efsa.europa.eu/
FDA	https://www.fda.gov/default.htm
HERA	http://www.heraproject.com/RiskAssessment.cfm
IARC volumes and monographs	https://monographs.iarc.fr/list-of-classifications-volumes/; https://monographs.iarc.fr/monographs-and-supplements-available-online/
INCHEM (CICADS, EHC, HSG, IARC, IPCS, JECFA, SIDS)	http://www.inchem.org/
JECDB	http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
NICNAS	http://www.nicnas.gov.au/
NIEHS (restricted to NIEHS only)	http://www.niehs.nih.gov/

Resource searched	URL(s)
NIEHS – NTP	https://ntpsearch.niehs.nih.gov/home; https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html; https://ntpsearch.niehs.nih.gov/?e=True&ContentType=Testing+Status
NITE	http://www.safe.nite.go.jp/jcheck/search.action?request_locale=en
OECD	https://www.echemportal.org/echemportal/
OECD/SIDS	https://hpvchemicals.oecd.org/UI/Search.aspx; http://webnet.oecd.org/hpv/ui/SponsoredChemicals.aspx
PubChem	https://pubchem.ncbi.nlm.nih.gov/

Abbreviations: ATSDR = Agency for Toxic Substances and Disease Registry; CICADS = Concise International Chemical Assessment Document; EFSA = European Food Safety Authority; EHC = Environmental Health Criteria; U.S. EPA = U.S. Environmental Protection Agency; FDA = Food and Drug Administration; HERA = Human and Environmental Risk Assessment; HPV = High Production Volume; HSG = Health and Safety Guidelines; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; JECDB = Japan Existing Chemical Data Base; JEFCA = Joint Expert Committee on Food Additives; NICNAS = National Industrial Chemicals Notification and Assessment Scheme; NIEHS = National Institute of Environmental Health Sciences; NITE = National Institute of Technology and Evaluation; NPIRS = National Pesticide Information Retrieval System; NTP = National Toxicology Program; NTRL = National Technical Reports Library; OECD = Organisation for Economic Cooperation and Development; SIDS = Screening Information Data Set; TSCATS = Toxic Substances Control Act Test Submissions

The National Pesticide Information Retrieval System (NPIRS) was used to locate industry studies relevant to the pesticide flumioxazin. The MRID number submitted to the U.S. EPA, and identified by NPIRS, was the primary source of data used in this assessment.

3.2.2. Data Screening and Review

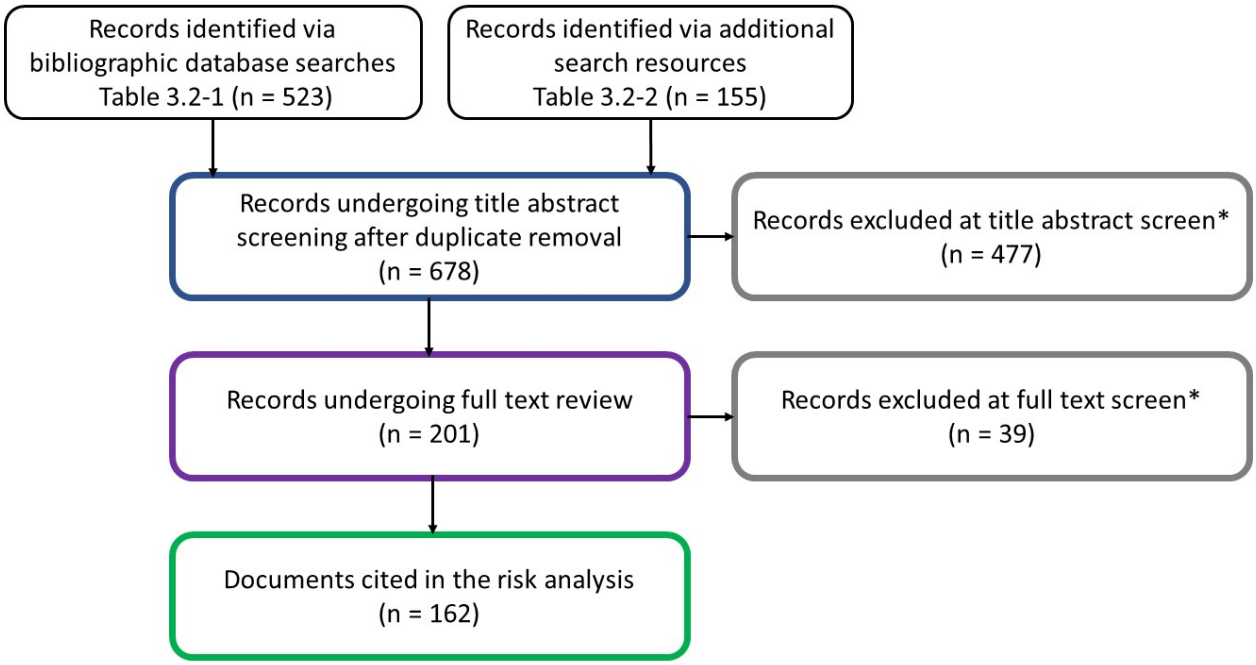
Database search results (n = 523; Table 3.2-1) were imported into Endnote for duplicate removal and were screened for relevance. Additional search results (Table 3.2-2) were screened outside of Endnote and relevant studies (n = 155) were then added to Endnote for retrieval and tracking.

A total of 678 references were identified during the literature search. The first step involved screening of the titles and abstracts to determine if the references were relevant to flumioxazin. There were 201 titles selected for full text review. Titles and abstracts were screened against the exclusion criteria to ensure that information was obtained from reliable sources and is of the quality necessary for developing the risk assessment. The exclusion criteria applied during the screening process is provided in Appendix 1. The title/abstract screen resulted in the exclusion of 477 titles.

Of the 201 references that were retrieved and screened, 162 references were selected for inclusion in the HHERA. This involved reviewing the full-text articles to determine the quality and acceptability of the references. During this stage, 39 references were excluded because they did not meet the criteria established for flumioxazin.

3.2.3. Literature Search Documentation

The literature search results are documented using a modified version of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram (Moher et al. 2009) shown in Figure 3.2-1. The PRISMA flow diagram graphically illustrates the number of studies identified, screened, excluded, and included in the risk analysis. The purpose of using the PRISMA approach is to help increase transparency and improve reporting of literature searches and systematic reviews.



*See exclusion criteria Appendix 1

Figure 3.2-1: Modified Preferred Reporting Items and Meta-Analysis (PRISMA) Flow Diagram for Documenting Literature Search Results

4. FATE AND TRANSPORT IN THE ENVIRONMENT

Environmental fate and transport of flumioxazin are critical to understanding potential exposures to both human and ecological receptors. The following sections provide an overview of the fate and transport of flumioxazin in terrestrial and aquatic environments. This is not intended to be a comprehensive analysis of fate and transport. The primary sources of information on fate and transport of flumioxazin are U.S. EPA's ecological risk assessment (U.S. EPA 2003) and Data Evaluation Records (DERs) of MRID studies submitted to U.S. EPA. Some of the fate and transport properties described in this section were used in the risk assessment to estimate exposures.

4.1. Terrestrial Environment

Flumioxazin has a mean K_{oc} of 557 L/Kg and is thus considered to have "moderate" soil mobility potential (U.S. EPA 2003). The precise value of the K_{oc} for flumioxazin is difficult to determine from batch equilibrium studies due to the rapid degradation of flumioxazin in soil and water. Flumioxazin degrades rapidly in aerobic soil (half-time [$t_{1/2}$] = 11.9 days) and very rapidly in anaerobic aquatic sediment ($t_{1/2}$ = 4.3 hours) (U.S. EPA 2003). Flumioxazin has two major degradants in the terrestrial environment, 6-amino-7-fluoro-4-(2-propynyl)-2*H*-1,4-benzoxazin-3(4*H*)-one (APF) and 3,4,5,6-tetrahydrophthalicacid (THPA). The soil mobilities of these degradants were determined and both are expected to be more mobile in the environment than flumioxazin (APF K_{oc} = 410; THPA K_{oc} = 155) (MRID 45309201; MRID 45309202). This increases the likelihood that hydrolysis products of flumioxazin will migrate to groundwater.

In two soil photolysis studies, flumioxazin degraded rapidly ($t_{1/2}$ = 3.2 and 8.4 days) (MRIDs 44295038 and 44295039). In an aerobic soil metabolism study, flumioxazin degraded with a $t_{1/2}$ of 11.9 days and produced four minor degradants: THPA; 3,4,5,6-tetrahydrophthalicanhydride (Δ-TPA); 7-fluoro-6-(3,4,5,6-tetrahydrophthalimido)-2H-1,4-benzoxazin-3(4H)-one (IMOXA); and 2-[7-fluoro-3-oxo-6-(3,4,5,6-tetrahydrophthalimido)-2H-1,4-benzoxazin-4-yl]propionicacid (482-CA) (MRID 42884009).

Based on findings in six field dissipation studies, the major routes of flumioxazin degradation in the environment are hydrolysis, photolysis, and biodegradation of the parent compound (U.S. EPA 2003). For five of the six dissipation studies, flumioxazin was broadcast in a single event at an application rate of 42.5 – 45.0 g a.i./acre (0.094-0.099 lbs a.i./acre). In the sixth study, flumioxazin was broadcast twice at a rate of 42 g a.i./acre (0.092 lbs a.i./acre) with a 30-day interval. Although these rates are one-quarter to one-half of the labeled rates of 0.188 and 0.38 lb a.i./acre, this should not affect the identities of the degradants. Calculated field dissipation $t_{1/2}$ values for flumioxazin were between 4.8 and 42 days. The large range is primarily caused by frequency of rainfall and soil pH, with more frequent rainfall and higher soil pH leading to increased soil dissipation. This is consistent with hydrolysis of flumioxazin. In one of the dissipation studies (MRID 44295047), 7-fluoro-6-[(2-carboxyl-1-cyclohexenoyl)amino]-4-(2-propynyl)-1,4-benzoxazin-3-(2*H*)-one (482-HA) and APF were detected as major degradants and 482-CA and IMOXA were detected as minor degradants. Alister et al. (2008) reported DT_{50} (time required for a 50% reduction in concentration) values of 10.6 –32.1 days and K_d values of 2.54 – 6.51 mg/L for four sites. Additionally, flumioxazin did not leach below 45 cm in any of the locations in this study (Alister et al. 2008).

4.2. Aquatic Environment

4.2.1. Surface Water and Sediments

Flumioxazin undergoes hydrolysis very rapidly, with hydrolysis rate increasing with pH ($t_{1/2}$ = 4.2 days, 23 hours, and 18.3 minutes at pH 5, 7, and 9, respectively) (MRIDs 42697501 and 42684905). At pH 5 and 7, the major degradants were APF and THPA. At pH 9, the major degradant was almost exclusively 482-HA. Degradation is accelerated by artificial sunlight (wavelength: 250 – 750 nm; 347 – 360 watts/cm^2; 12 hour light/dark cycle). In two studies, flumioxazin underwent degradation in pH 5 aqueous buffer irradiated with a xenon lamp with a $t_{1/2}$ of 20.9 – 26.3 hours in contrast to the 4.2-day $t_{1/2}$ at pH 5 observed without light. These two studies (MRIDs 44295036 and 44295037) proposed alternative photodegradation products (MRID 44295036). Shibata et al. (2011) identified these intermediate photodegradation products as N-(prop-2-ynyl)-4-[4-carboxy-3-fluoro-2-(3,4,5,6-tetrahydrophthalimido)-2-butenylidene]azetidine-2-one (Photodeg1) and its subsequent hydrolysis product 2-((4-carboxy-3-fluoro-1-(4-oxo-1-(prop-2-yn-1-yl)20zetidine-2-ylidene)but-2-en-2-yl)carbamoyl)cyclohex-1-ene-1-carboxylic acid (Photodeg2).

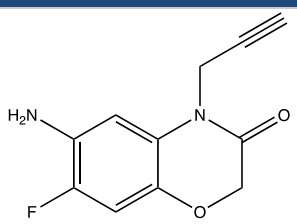
4.2.2. Aquatic Organisms

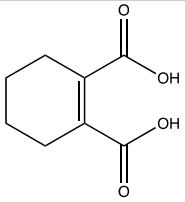
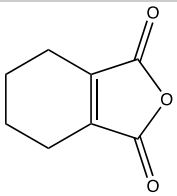
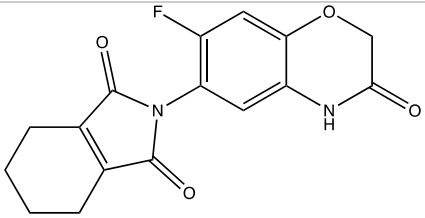
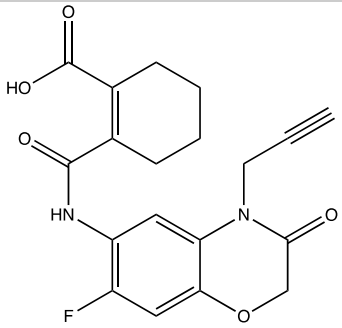
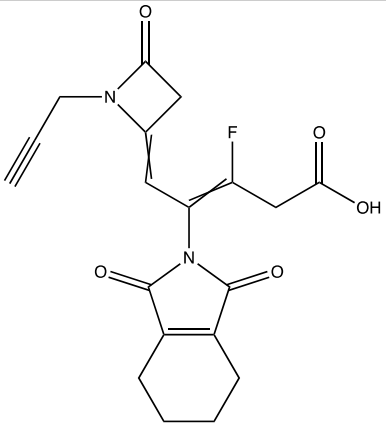
The U.S. EPA/OPP typically requires experimentally derived bioconcentration factors (BCFs) as part of the registration process for new pesticides. Since the octanol-water partition coefficient (log K_{ow}) of flumioxazin is 2.55 at 20°C and flumioxazin is rapidly hydrolyzed in aqueous solutions ($t_{1/2}$ = 4.2 days, 23 hours, and 18.3 minutes at pH 5, 7, and 9, respectively), the requirement was waived. Additionally, estimated log K_{ow} values for the three major hydrolytic degradation products, 482-HA, APF, and THPA, were lower than the parent compound (0.804, 0.127, and 0.880 respectively); therefore, the major degradation products are unlikely to partition into fatty tissue of aquatic organisms (CLH 2013). For the risk calculations, a BCF of 22.4 was estimated using the log K_{ow} of 2.55.

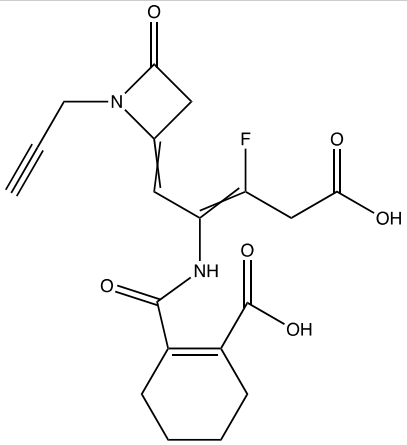
4.3. Environmental Metabolites

Flumioxazin is not persistent in the environment and its primary environmental metabolites are produced by hydrolysis and photolysis (CLH 2013). The primary known environmental metabolites of flumioxazin, 482-HA, APF, Δ-TPA, IMOXA, and THPA, are shown in Table 4.3-1 (U.S. EPA 2003). Additionally, the photodegradation products (Photodeg1 and Photodeg2) are presented in Table 4.3-1; these might be present in surface waters treated or contaminated with flumioxazin.

Table 4.3-1: Environmental Metabolites of Flumioxazin

Transformation Product/Code	Chemical Name and Formula	Chemical Structure
APF	**IUPAC Name:** 6-amino-7-fluoro-4-(2-propynyl)-2*H*-1,4-benzoxazin-3(4*H*)-one **Formula:** $C_{11}H_9FN_2O_2$	

Transformation Product/Code	Chemical Name and Formula	Chemical Structure
THPA	**IUPAC Name:** 3,4,5,6-tetrahydrophthalicacid **Formula:** $C_8H_{10}O_4$	
Δ-TPA	**IUPAC Name:** 3,4,5,6-tetrahydrophthalic-anhydride **Formula:** $C_8H_8O_3$	
IMOXA	**IUPAC Name:** 7-fluoro-6-(3,4,5,6-tetrahydro-phthalimido)-2H-1,4-benzoxazin-3(4H)-one **Formula:** $C_{16}H_{13}FN_2O_4$	
482-HA	**IUPAC Name:** 2-((7-fluoro-3-oxo-4-(prop-2-yn-1-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)carbamoyl)cyclohex-1-ene-1-carboxylic acid **Formula:** $C_{19}H_{17}FN_2O_5$	
PhotoDeg1	**IUPAC Name:** N-(prop-2-ynyl)-4-[4-carboxy-3-fluoro-2-(3,4,5,6-tetrahydrophthalimido)-2-butenylidene]azetidine-2-one **Formula:** $C_{19}H_{17}FN_2O_5$	

Transformation Product/Code	Chemical Name and Formula	Chemical Structure
Photodeg2	**IUPAC Name:** 2-((4-carboxy-3-fluoro-1-(4-oxo-1-(prop-2-yn-1-yl)22zetidine-2-ylidene)but-2-en-2-yl)carbamoyl)cyclohex-1-ene-1-carboxylic acid **Formula:** $C_{19}H_{19}FN_2O_6$	
Abbreviation: IUPAC = International Union of Pure and Applied Chemistry		

1

5. HUMAN HEALTH RISK ASSESSMENT

5.1. Hazard Identification

5.1.1. Overview

The hazard identification process involves the examination of available scientific data to determine the potential adverse health effects associated with exposure to a chemical. Information on mechanisms of action, toxicokinetics, and toxicity are reviewed in this section. Most of the available information on flumioxazin is from an extensive set of toxicity studies submitted to U.S. EPA/OPP by the registrant to support the registration of flumioxazin. As described in Section 3.3.1, each submitted study is labeled with a unique MRID number. The studies are evaluated by U.S. EPA/OPP and results are summarized in DERs. For this risk assessment, all data are taken from DERs for the MRID studies; the original submitted MRID studies were not reviewed. Only data from DERs classified as "acceptable" or "supplemental"[2] were included in this risk assessment. Relevant toxicity studies identified in the peer-reviewed literature were reviewed and summarized, providing studies were conducted using sound scientific principles.

The toxicology database for the flumioxazin human health risk assessment has a high degree of scientific quality, with animal studies for relevant human health endpoints available for acute and chronic toxicity (including carcinogenicity) and developmental, reproductive, immunologic, and neurological effects. In addition to studies on technical grade flumioxazin, studies in laboratory animals are also available for formulated products of flumioxazin for the following endpoints: acute oral, inhalation, and dermal toxicity; dermal and eye irritation; and dermal sensitization. Table 5.1-1 provides an overview of the most sensitive effects in laboratory animals. Additional details of these findings, including citations, are provided in Sections 5.1-4 – 5.1-15 and in Appendix 3. No epidemiological studies on flumioxazin were identified.

Table 5.1-1: Overview of the Most Sensitive Toxicological Effects of Technical Grade Flumioxazin in Laboratory Mammals

Exposure or Toxicity Type	Most Sensitive Effects	Toxicity Values
Acute oral exposure (via gavage)	No lethality or adverse effects	Highest dose tested: 5000 mg a.i./kg
Acute inhalation exposure	No lethality; hypoactivity	Highest concentration tested (4-hour): 3.71 mg a.i./L
Acute dermal exposure	No lethality or adverse effects	Highest dose tested: 2000 mg a.i./kg
Developmental (gestational exposure)	Fetal cardiac malformations	NOAEL: 3 mg a.i./kg/day LOAEL: 10 mg a.i./kg/day

[2] According to U.S. EPA (2019) studies classified as "acceptable" are scientifically sound and considered acceptable for use in risk assessment. Studies classified as "supplemental" are considered scientifically sound; however, they were performed under conditions that deviated substantially from recommended protocols. Results do not meet guideline requirements; however, the information may be useful in a risk assessment.

Exposure or Toxicity Type	Most Sensitive Effects	Toxicity Values
Reproduction (2-generation reproduction)	Decreased number of live pups and pup body weight	NOAEL: 6.3 mg a.i./kg/day LOAEL: 12.7 mg a.i./kg/day
Subchronic	Decreases in hematological parameters associated with anemia	NOAEL: 19.3 mg a.i./kg/day LOAEL: 65.0 mg a.i./kg/day
Chronic (non-cancer)	Nephropathy, extramedullary hematopoiesis and decreases in hematological parameters associated with anemia	NOAEL: 1.8 mg a.i./kg/day LOAEL: 18 mg a.i./kg/day
Chronic (cancer)	No evidence of carcinogenicity	Highest dose tested: 51.3 mg a.i./kg/day
Neurotoxicity (acute and subchronic)	No neurological effects	Highest dose tested (acute): 2000 mg a.i./kg/day Highest dose tested (subchronic): 358 mg a.i./kg/day
Immunotoxicity (subchronic)	No immunological effects	Highest dose tested: 375 mg a.i./kg/day
Dermal Irritation	Not irritating to slightly irritating	NA
Ocular irritation	Not irritating to minimally irritating	NA
Sensitization	Not a dermal sensitizer	NA
Abbreviations: LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level		

Note that in the following sections, discussions of toxicity studies focus on study results rather than experimental details. Experimental details for each study (e.g., number of animals per exposure group, animal weight and age, dosing vehicles, etc.) are included in the corresponding appendices. Exposures expressed in terms of mg a.i./kg and mg a.i./kg/day are to be interpreted as mg a.i./kg body weight and mg a.i./kg body weight/day, respectively.

5.1.2. Mechanism of Action

The mechanism of action refers to the specific biochemical interaction through which a substance produces an effect; in this case, the mechanism by which flumioxazin produces adverse effects. The most sensitive targets for flumioxazin toxicity are developmental, hematological, and renal effects (Table 5.1-1). As discussed in Section 2.1, the herbicidal mechanism of flumioxazin is inhibition of PPO, the enzyme responsible for converting protoporphyrinogen IX to protoporphyrin IX, a precursor of heme and chlorophyll in plants. This mechanism of action also appears to be involved in some of the toxicological effects observed in mammals. Flumioxazin-induced inhibition of PPO has been observed in laboratory animals (Kawamura et al. 1996) and is likely to be involved, at least in part, in hematological and developmental effects. Accumulation of protoporphyrinogen IX has been observed in rat embryos following gestational exposure to flumioxazin (Kawamura et al. 1996). A gestational exposure study in rats showed that peak protoporphyrinogen IX inhibition coincides with the peak period for developmental effects (Kawamura et al. 2014). It has been proposed that fetal ventricular-septal defects might be secondary to flumioxazin inhibition of PPO inhibition and heme synthesis, rather than direct cardiac effects (Kawamura et al. 1996; Kawamura et al. 2014; Kawamura et al. 2016). Proposed mechanisms for adverse renal effects were not identified;

however, as discussed below (Section 5.1.3.2), flumioxazin distributes to the kidney, and it is possible that decreased heme synthesis could contribute to renal toxicity. No additional information was identified to determine if PPO inhibition is involved in the development of any other adverse effects observed (e.g., decreased pup weight and live births) observed in mammalian toxicity studies.

5.1.3. Pharmacokinetics and Metabolism

Pharmacokinetics refers to the behavior of chemicals in the body, including absorption, distribution, metabolism, and excretion. This section focuses on the pharmacokinetic processes associated with flumioxazin exposure and provides a general discussion about absorption, distribution, metabolism, and excretion (ADME). Absorption kinetics, particularly the kinetics of dermal absorption, are important for FS risk assessments because many of the exposure scenarios involve dermal exposure as the primary exposure pathway. Rates of excretion are generally used in FS risk assessments to evaluate the likely body burdens associated with repeated exposure.

For most FS risk assessments, similarities between metabolism in humans and metabolism in experimental animals are considered, particularly in cases where human health and pharmacokinetic studies are not available. These studies encompass the toxicity of both the parent compound and any metabolites formed *in vivo*. *In vivo* metabolites refer to compounds that are formed within the animal after the chemical has been absorbed. In contrast, environmental metabolites, which are discussed in Section 4.3, refer to compounds that may be formed in the environment by a number of different biological or chemical processes such as breakdown in soil or water or breakdown by sunlight (photolysis). *In vivo* and environmental metabolites are discussed in more detail in SERA (2014a).

Although metabolism (biotransformation) is a mechanism of elimination of the parent compound, extensive *in vivo* metabolism of the parent compound does not necessarily indicate low toxicity because the metabolites might also be toxic. In addition, rapid metabolism of the parent compound might result in accumulation of toxic metabolites before they can be excreted. This risk assessment accounts for the relationship between toxicity, metabolism, and excretion of the parent compound and metabolites.

5.1.3.1. Absorption

5.1.3.1.1. Absorption from Oral Exposure

Absorption of flumioxazin following oral dosing was studied in rats (MRID 42684943). Female and male Sprague-Dawley rats received a single gavage dose (1 or 100 mg/kg of ^{14}C-flumioxazin, labeled in the phenyl ring). Based on ^{14}C recovered in urine and metabolites recovered in feces in a 7-day period following dosing, absorption was estimated as >90% following the 1 mg/kg dose and approximately 50% following the 100 mg/kg dose. Based on this study, the absorption fraction of flumioxazin in the rat appears to decrease with increasing dose, suggesting a possible capacity limitation in the absorption process.

Absorption of flumioxazin following oral dosing was studied in pregnant rats (MRID 5207106). Female Cr:CD(SD) rats were administered gavage doses of flumioxazin (in 0.5% methylcellulose) of 30 mg/kg on gestational days (GD) 6 – 19. Flumioxazin was detected in maternal plasma, with peak

concentrations estimated at one to three hours following initiation of exposure. The fraction of the oral dose that was absorbed cannot be determined from the data reported. However, as noted below, the dose-adjusted plasma area-under-the-curve (AUC) was lower in rats that received oral dosing compared to inhalation dosing, suggesting a possible capacity limitation in the absorption process.

5.1.3.1.2. Absorption from Inhalation Exposure

Absorption of flumioxazin following inhalation was studied in pregnant rats (MRID 5207106). Female Sprague-Dawley rats were exposed (nose-only) to aerosols of powdered flumioxazin (mass median aerodynamic diameter [MMAD] 2 µm; 0.003, 0.010, 0.020, or 30 mg/L) for a period of six hours/day on GD 6 – 19. Flumioxazin was detected in maternal plasma, with peak concentrations estimated to occur at 3 – 6 hours following initiation of exposure. The fraction of the inhaled dose that was absorbed cannot be determined from the data reported. However, the area under the plasma concentration-time curve (AUC) resulting from exposure to 0.02 mg/L (estimated as approximately 6.7 mg/kg/day; MRID 5207106) was similar to that achieved from daily gavage dosing at 30 mg/kg/day during the same gestational period, resulting in a higher dose-adjusted AUC in rats exposed by inhalation compared to oral dosing.

5.1.3.1.3. Absorption from Dermal Exposure

Many of the worker and general public exposure scenarios in FS risk assessments involve the dermal route of exposure. For these exposure scenarios, dermal absorption is estimated and compared to oral toxicity data, which are based on subchronic or chronic toxicity studies in animals (SERA 2014a). This approach is taken in FS risk assessments because the dermal toxicity data for most chemicals are more limited than the data from oral toxicity studies.

When assessing dermal exposures, two scenarios are taken into consideration: immersion and accidental spills. For the immersion scenario, the concentration of the chemical in contact with the surface of the skin and resulting dermal absorption rate are essentially constant (i.e., zero-order kinetics). As discussed in SERA (2014a), the rate of absorption for dermal exposure scenarios involving immersion is estimated based on a zero-order (steady state) dermal permeability rate (K_p), which is expressed in cm/hour. In exposure scenarios involving accidental spills where the chemical is deposited directly on the skin, the concentration or amount of the chemical on the surface of the skin is assumed to be the limiting factor in dermal absorption (SERA 2014a). For these scenarios, the first-order dermal absorption rate coefficient (K_a) is used, which is expressed as a proportion of the deposited dose absorbed per unit of time ($hour^{-1}$).

Information regarding dermal absorption of flumioxazin are provided below. No studies have directly measured the K_a and K_p rates for flumioxazin. For additional information on the dermal exposure scenarios and absorption rates used by the FS, see SERA (2014a).

Absorption of flumioxazin following dermal dosing was evaluated in three studies in rats (MRIDs 42684931, 42684932, and 42684944). Results of these studies suggest the absorption fraction depends on the applied dose and vehicle. Absorption fractions were higher when flumioxazin was suspended in corn oil than when an aqueous suspension of water dispersible granules was applied to the skin. The DERs for these studies provide estimates of the fraction of the dose absorbed but do not provide a basis for estimating a first order absorption rate coefficient or a dermal permeability

coefficient. The highest absorption fraction reported was 8% following 48 hours of exposure to a dermal dose of 800 mg/kg suspended in corn oil (11.8 mg/cm^2; MRID 42684932).

Male rats received a single dermal dose of ^{14}C-flumioxazin (labeled in the phenyl ring) in a mixture with water dispersible granules of flumioxazin (0.002, 0.02, or 0.1 mg/cm^2), applied to a 10 cm^2 area of dorsal skin (MRID 42684944). The estimated applied doses of flumioxazin were 0.02, 0.2, or 1 mg/rat, calculated by the FS to have been 0.084, 0.84, and 4.2 mg/kg (assuming an average body weight [bw] of 0.238 kg). Based on recovery of ^{14}C in feces, urine, and tissues, absorption following 24 hours of exposure was estimated to be 5.46% following the 0.02 mg/rat dose, 0.74% following the 0.2 mg/rat dose, and 0.47% following the 1 mg/rat dose. The declining percent absorption with increased applied dose suggests a capacity limitation in the dermal absorption process; possibly from limitations and/or kinetics of solubilization of the flumioxazin granules in the aqueous suspension applied to the skin.

Female rats received a single dermal dose of ^{14}C-flumioxazin (labeled in the phenyl ring) suspended in corn oil (200 or 800 mg/kg) applied to a 12 cm^2 area of dorsal skin (MRID 42684932). The exposures were reported as approximately 2.7 or 11.8 mg/cm^2. Based on recovery of ^{14}C in feces, urine and tissues, absorption following 48 hours of exposure was estimated to be 3.8% following the 200 mg/kg dose and 8.0% following the 800 mg/kg dose; absorption fractions were similar following 24 hours of exposure.

Pregnant female rats received a single dermal dose of ^{14}C-flumioxazin (labeled in the phenyl ring) suspended in corn oil (100 mg/kg) applied to a 12 cm^2 area of exposed skin on the back, on GD 13 (MRID 42684931). The exposure was estimated to be approximately 1.9 mg/cm^2. Based on recovery of ^{14}C in feces, urine, and tissues, absorption was estimated to be 4.3%, following 24 hours of exposure, and 5.8% following 48 hours of exposure.

5.1.3.2. Distribution

Distribution of absorbed ^{14}C-flumioxazin has been studied in rats that received oral or dermal doses of ^{14}C-flumioxazin (MRIDs 42684944 and 42684943). Results of these studies indicate that the main depots for absorbed flumioxazin and its metabolites are blood cells, liver, and kidney.

Oral Exposure of Adults. Female and male Sprague-Dawley rats received a single gavage dose (1 mg/kg) ^{14}C-flumioxazin (labeled in the phenyl ring) following 14 days of daily gavage doses of 1 mg/kg/day of unlabeled flumioxazin (MRID 42684943). At this dose, the absorption fraction was estimated to be >90% (see discussion of oral absorption in Section 5.1.3.1.1). The highest concentrations of ^{14}C were found in blood cells (approximately 50 µg/kg tissue), which were approximately twice that of whole blood. The mean concentrations of ^{14}C in heart, kidney, and liver were approximately 25 – 50% of that of the blood cell concentration and approximately 50% to 100% of whole blood. The rank order of mean concentrations in tissues were approximately as follows: blood cells > liver > kidney > thyroid > lung > spleen > testes > pancreas.

Dermal Exposure of Adults. Male rats received a single dermal dose of ^{14}C-flumioxazin (labeled in the phenyl ring) in a mixture with water dispersible granules of flumioxazin (0.002 mg/cm^2), applied to a 10 cm^2 area of exposed dorsal skin (MRID 42684944). The estimated applied dose of flumioxazin was 0.02 mg/rat, calculated by the FS as 0.084 mg/kg (assuming an average bw of 0.238 kg). At this dose,

the absorption fraction was estimated to be approximately 5% (see discussion of oral absorption in Section 5.1.3.1.1). The mean levels of ^{14}C measured after 24 hours of exposure were 0.23% of the dose in liver, 0.05% in kidney and 0.03% in blood.

Maternal-Fetal Transfer. Flumioxazin absorbed during gestation is distributed to fetal tissues following oral, dermal, and inhalation exposures (MRIDs 42884007, 42684931, and 5207106). Maternal-fetal transfer of flumioxazin following oral dosing was studied in rats and rabbits (MRID 42884007). Female Sprague-Dawley rats and JW:NIBS rabbits received a single oral dose (30 mg/kg) of ^{14}C-flumioxazin (labeled in the phenyl ring) on GD 12. The highest levels of ^{14}C in maternal tissue occurred within two to four hours of dosing. Highest levels in fetal tissues of rats and rabbits occurred four hours after dosing. The fetal tissue/maternal plasma ^{14}C concentration ratio was <0.27 in rats and <0.15 in rabbits.

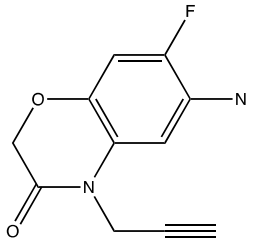
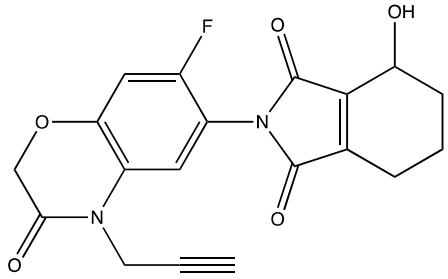
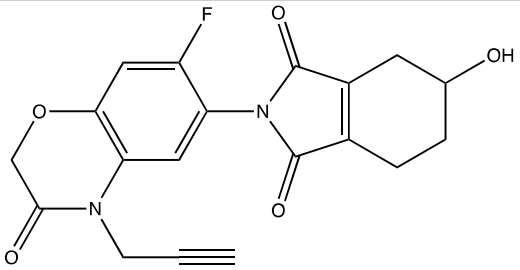
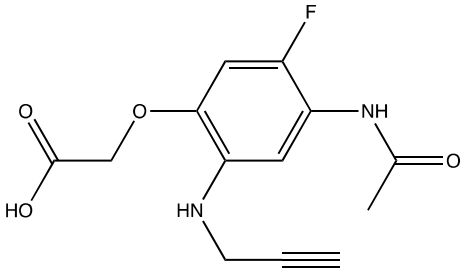
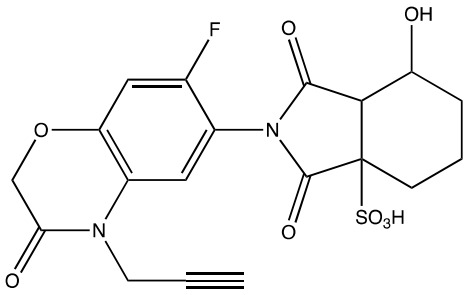
Pregnant female rats received a single dermal dose of ^{14}C-flumioxazin (labeled in the phenyl ring) suspended in corn oil (100 mg/kg) applied to a 12 cm^2 area of exposed dorsal skin, on GD 13 (MRID 42684931). The exposure was estimated to be approximately 1.9 mg/cm^2. ^{14}C was detected in fetal blood at 24- and 48-hours following dosing; at 48 hours, fetal blood ^{14}C was 0.001% of the administered dose.

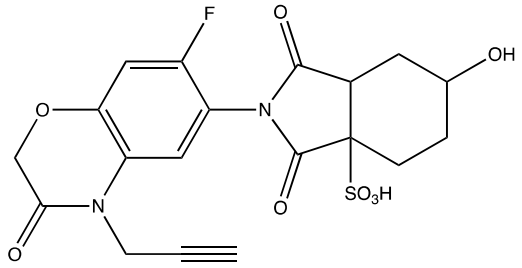
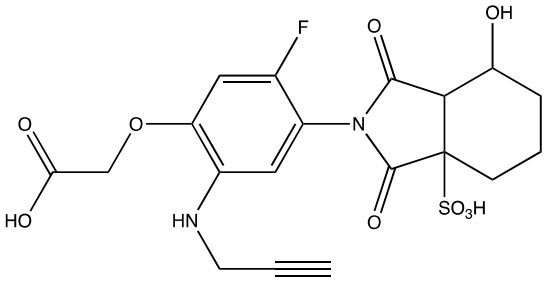
Female Sprague-Dawley rats were exposed (nose-only) to aerosols of powdered flumioxazin (MMAD 2 µm; 0.003, 0.010, 0.020, or 30 mg/L) for a period of six hours on GD 6 – 19 (MRID 50207106). Fetal plasma/maternal plasma concentration ratios of flumioxazin ranged from 0.12 to 0.31, when measured at completion of the six-hour exposure on GD 19.

5.1.3.3. Metabolism

Studies conducted in rats and rabbits have shown that flumioxazin is extensively metabolized (MRIDs 42684943 and 42884007). Following oral dosing of rats with 1 or 100 mg/kg, up to 35 metabolites were detected in urine and feces. Seven of these metabolites were identified and accounted for 37 – 46% of the administered dose following the 1 mg/kg dose and from 10% to 20% following the 100 mg/kg dose, respectively (MRID 42684943); structures of these metabolites are shown in Table 5.1-2. The major metabolite, accounting for 14% to 19% of the administered 1 mg/kg dose, was the hydroxyl sulfonic acid (3-OH-S-53482-SA, see Table 5.1-2 for structure and International Union of Pure and Applied Chemistry [IUPAC] name). Other prominent metabolites included 4-OH-S-53482-SA (5 – 7%), 3-OH-S-53482A-SA (2 – 4%), APF (2 – 7%), and Ac-APFA (4 – 6%). The metabolites 3-OH-S-53482-SA, 4-OH-S-53482-SA, APF, and Ac-APFA were also identified in maternal and fetal rat tissues following a single oral dose of 30 mg/kg ^{14}C-flumioxazin administered to rats on gestation day 12 (MRID 42884007).

1 **Table 5.1-2: Flumioxazin Metabolites Identified in Rat Studies.**

Transformation Product/Code	Chemical Name and Formula	Chemical Structure
APF	**IUPAC Name:** 6-amino-7-fluoro-4-(2-propynyl)-2*H*-1,4-benzoxazin-3(4*H*)-one **Formula:** $C_{11}H_9FN_2O_2$	
3-OH-S-53482	**IUPAC Name:** 2-(7-fluoro-3-oxo-4-(prop-2-yn-1-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)-4-hydroxy-4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione **Formula:** $C_{19}H_{15}FN_2O_5$	
4-OH-S-53482	**IUPAC Name:** 2-(7-fluoro-3-oxo-4-(prop-2-yn-1-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)-5-hydroxy-4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione **Formula:** $C_{19}H_{15}FN_2O_5$	
Ac-APFA	**IUPAC Name:** 2-(4-acetamido-5-fluoro-2-(prop-2-yn-1-ylamino) phenoxy)acetic acid **Formula:** $C_{13}H_{13}FN_2O_4$	
3-OH-S-53482-SA	**IUPAC Name:** 2-(7-fluoro-3-oxo-4-(prop-2-yn-1-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)-7-hydroxy-1,3-dioxooctahydro-3a*H*-isoindole-3a-sulfonic acid **Formula:** $C_{19}H_{17}FN_2O_8S$	

Transformation Product/Code	Chemical Name and Formula	Chemical Structure
4-OH-S-53482-SA	**IUPAC Name:** 2-(7-fluoro-3-oxo-4-(prop-2-yn-1-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)-6-hydroxy-1,3-dioxooctahydro-3a*H*-isoindole-3a-sulfonic acid **Formula:** $C_{19}H_{17}FN_2O_8S$	
3-OH-S-53482A-SA	**IUPAC Name:** 2-(5-fluoro-4-(7-hydroxy-1,3-dioxo-3a-sulfooctahydro-2*H*-isoindol-2-yl)-2-(prop-2-yn-1-ylamino)phenoxy) acetic acid **Formula:** $C_{19}H_{19}FN_2O_9S$	

Abbreviation: IUPAC = International Union of Pure and Applied Chemistry

5.1.3.4. Elimination

Elimination rates are typically not used quantitatively in FS risk assessments. However, elimination half-times can be used to infer the effect of longer-term exposures on body burden, based on the *plateau principle.* As described in SERA (2014a), this principle can be applied to a compound that is eliminated by first-order kinetics when the compound is administered repeatedly at a fixed interval (t*). Under the assumption of first-order elimination, the first-order elimination rate coefficient (*k*) is inversely related to the $t_{1/2}$ [$k = \ln(2) \div t_{1/2}$]. If a chemical with a first-order elimination rate constant of *k* is administered at fixed time interval (*t**) between doses, the body burden after the N^{th} absorbed dose ($X_{N\ Dose}$) relative to the body burden immediately following the first absorbed dose ($X_{1\ Dose}$) is:

$$\frac{X_{N\ Dose}}{X_{1\ Dose}} = \frac{(1-(e^{-kt*})^N)}{1-e^{-kt*}}$$

As the number of doses (*N*) increases, the numerator in the above equation approaches a value of 1. Over an infinite period of time, the plateau or steady-state body burden (X_{Inf}) can be calculated as:

$$\frac{X_{Inf}}{X_1} = \frac{1}{1-e^{-kt*}}$$

Whole-body half-times are most appropriate for estimating steady-state body burdens.

Elimination of flumioxazin has been studied in rats and rabbits following oral dosing and in rats following dermal dosing (MRIDs 42684931, 42684932, 42684943, 42684944, and 42884007). Collectively, these studies show that absorbed flumioxazin is extensively metabolized, and parent compound and metabolites are excreted in feces and urine (see Section 5.1.2.3 for further details on

metabolites). The urinary fraction decreases with increasing dose while the fecal fraction increases. The appearance of metabolites in feces of rats has been interpreted as evidence for biliary excretion of metabolites in the rat (MRID 50207106; U.S. EPA 1994, 2012). Direct confirmation of biliary secretion of metabolites of flumioxazin is not available. First-pass hepatic clearance of flumioxazin following oral absorption has implications for uncertainty in extrapolating reference toxicity values for oral exposure (e.g., reference doses) to other routes of exposure (e.g., dermal, inhalation) in which first pass hepatic clearance would not occur (MRID 50207106; U.S. EPA 2012).

The most informative study of elimination was conducted in rats (MRID 42684943). Sprague-Dawley rats received a single gavage dose of 1 or 100 mg/kg of ^{14}C-flumioxazin (labeled in the phenyl ring). Over a two-day period following the 1 mg/kg dose, excretion in feces and urine accounted for >96% of the administered dose. In male rats, fecal excretion was 68% of the administered dose and urinary excretion was 28% of the administered dose. In female rats, the distribution was 58% in feces and 39% in urine. Less than 1% of the ^{14}C excreted in urine was parent compound and <6% of ^{14}C in feces. The relatively small amount of parent compound in feces suggests that most of the ^{14}C in feces may have originated from metabolism of absorbed flumioxazin, although metabolism by gastrointestinal flora cannot be ruled out from these studies. The fraction of the administered dose excreted in urine was dependent on the dose level. In male rats, urinary excretion ranged from 39% to 43% following the 1 mg/kg dose and was 23% following the 100 mg/kg dose. In female rats, urinary excretion ranged from 28% to 31% following the 1 mg/kg dose and was 13% following the 100 mg/kg dose. The fraction of the dose excreted in urine as parent compound was <1% at the two dose levels; however, the fraction excreted in feces as parent compound increased from <6% following the 1 mg/kg dose to approximately 50% following the 100 mg/kg dose. The dose-dependency of the metabolite fraction in feces would be consistent with a capacity limitation in metabolism of flumioxazin, and/or biliary secretion of metabolites. Neither of these mechanisms for dose-dependency of excretion have been confirmed.

Female Sprague-Dawley rats or JW:NIBS rabbits received a single oral dose (30 mg/kg) of ^{14}C-flumioxazin (labeled in the phenyl ring) on GD 12 (MRID 42884007). During the 24-hour period following dosing of rats, 77% of the administered dose was excreted; 55% of the administered dose in feces and 22% in urine. During the 24-hour period following dosing of rabbits, 30% of the administered dose was excreted: 18% in feces and 12% in urine.

The kinetics of elimination of flumioxazin have not been studied; however, based on studies conducted in rats that showed that extensive metabolism occurs within two days of dosing (MRID 42684943) coupled with estimates of elimination kinetics of ^{14}C-flumioxazin (MRID 42684932), it is likely that the elimination half-time is less than one day. Elimination half-times were estimated in female rats following a single gavage dose of 1 or 30 mg/kg ^{14}C-flumioxazin (MRID 42684932). The half-times for ^{14}C (estimated from observations made over a 48-hour period) were similar at the two dose levels and estimates were as follows: blood, 23 – 27 hours; kidney, 12 hours; liver, 10 hours. Observations were not carried out for a sufficiently long time to reliably estimate a terminal elimination half-time.

5.1.4. Acute Oral Toxicity

Acute oral toxicity studies are used to evaluate the adverse effects of a chemical following oral administration of a single dose or multiple doses in a short duration (typically 14 days or less). The

results of acute oral toxicity studies are reported as duration-specific LD_{50} (median lethal dose) values, expressed in terms of mass of test substance per unit weight of test animal (mg/kg). The LD_{50} is the dose that can be expected to be lethal to 50% of the test population. These values are used by U.S. EPA/OPP to categorize potential risks from acute exposure. Specifically, U.S. EPA/OPP uses a toxicity category ranking system for toxicity ranging from Category I (most severe response) to Category IV (least severe response). For acute oral toxicity, Category I refers to chemicals with oral LD_{50} values of ≤50 mg/kg, while Category IV refers to chemicals with oral LD_{50} values of >5000 mg/kg. Details of the categorization system used by U.S. EPA are described in Chapter 7 of the U.S. EPA *Label Review Manual* (U.S. EPA 2018).

Two acute oral toxicity studies in rats were conducted using technical grade flumioxazin and one study was conducted using a 50% flumioxazin formulation (Table 5.1-3); all studies were classified as "Acceptable" by U.S. EPA/OPP. A single dose of flumioxazin was administered by gavage and rats were observed for 14 days following dosing. The maximum doses tested for technical grade flumioxazin were 5000 mg a.i./kg (MRID 42684911) and 2000 mg a.i./kg (MRID 50353608); for the flumioxazin product, the highest dose tested was 2500 mg a.i./kg (MRID 42684912). No mortality was observed in any study, identifying LD_{50} values as greater than the highest doses tested. In the technical grade flumioxazin studies, no adverse effects were observed. However, transient piloerection was observed during the first 24 hours after dosing in the study with the flumioxazin product. Experimental details for these studies are provided in Appendix 3, Table A3-1.

Table 5.1-3: Acute Oral Toxicity Studies for Technical Grade Flumioxazin and a Flumioxazin Product

Test Species	Results	Toxicity Category	Reference (Classification)
Technical Grade Flumioxazin			
Rat	LD_{50} >5000 mg a.i./kg *Effects:* no mortality or adverse effects	IV	MRID 42684911 (Acceptable)
Rat	LD_{50} >2000 mg a.i./kg *Effects:* no mortality or adverse effects	III	MRID 50353608 (Acceptable)
Flumioxazin Formulated Product (V-53482 50 WDG[1])			
Rat	LD_{50} >2500 mg a.i./kg *Effects:* no mortality; transient piloerection (first 24 hours only)	IV	MRID 42684912 (Acceptable)

[1]V-53482 50 WDG is a 50% a.i. formulated product of flumioxazin. The commercial name of this product was not specified.
Abbreviation: a.i. = active ingredient; LD_{50} = median lethal dose; WDG = water dispersible granule

5.1.5. Subchronic or Chronic Systemic Toxic Effects

Subchronic and chronic toxicity studies are used to describe adverse effects occurring from repeated exposure to a substance for exposure durations greater than 14 days. Typically, exposures of 15 days to < 1 year are considered subchronic and exposures of one year or longer are considered chronic. In addition, some repeated dose studies are designed to detect specific toxic endpoints, such as reproductive or neurological effects (SERA 2014a). These studies are important because they form the basis of most quantitative values used in risk assessments. Specifically, they are used to establish the highest doses at which no toxic effects were identified and the lowest doses at which toxic

effects were observed. These doses are referred to as the no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL), respectively. In some cases, the no-observed-effect level (NOEL) and lowest-observed-effect level (LOEL) may be used. For studies that provide separate NOAELs and LOAELs for males and females, the NOAELs and LOAELs are presented in this HHERA as the arithmetic average of the male and female values, with all values rounded to the nearest tenth (SERA 2014a).

Subchronic Exposure. Four subchronic toxicity studies evaluated oral exposure of rats, mice, and dogs to technical grade flumioxazin. Study results are summarized in Table 5.1-4, with experimental details provided in Appendix 3, Table A3-2. The two studies in rats (MRIDs 42684922 and 42684923) identified toxicity to the hematopoietic system as the most sensitive target for flumioxazin, with nearly identical NOAEL and LOAEL values. U.S. EPA classified MRID 42684922 as "Acceptable" and MRID 42684923 as "Supplemental" due to missing data. In the 90-day study, rats were exposed to dietary concentrations up to 3000 ppm a.i., equivalent to 196.7 and 218.4 mg a.i./kg/day for males and females, respectively (MRID 42684922). One female in the high-dose group died during week 12. Significant alterations in hematological and histologic parameters associated with anemia occurred in males and females exposed to 1000 ppm a.i., identifying male and female NOAELs of 19.3 and 22.4 mg a.i./kg/day and male and female LOAELs of 65.0 and 72.9 mg a.i./kg/day, respectively. In the 13-week study, rats were exposed to dietary concentrations of flumioxazin up to 3000 ppm a.i., equivalent to 243.5 and 229.6 mg a.i./kg/day in males and females, respectively (MRID 42684923). No mortality or clinical signs of toxicity, effects on ophthalmology, food or water consumption, or urinalysis were observed at any dose level. At 1000 ppm a.i., hematological effects consistent with anemia and altered bone marrow response were observed in males and females, identifying male and female NOAELs of 20.7 and 21.7 mg a.i./kg/day and male and female LOAELs of 69.7 and 71.5 mg a.i./kg/day, respectively. Effects on the hematopoietic system are consistent with the mechanism of action of PPO inhibition, which leads to decreased heme formation (see discussion in Section 2.1).

Table 5.1-4: Subchronic Oral Toxicity Studies for Technical Grade Flumioxazin

Species	Exposure Duration	NOAEL (mg a.i./kg/day)			LOAEL (mg a.i./kg/day)			Reference (Classification)
		M	F	Average	M	F	Average	
Rats	90 Days (dietary)	19.3	22.4	20.9	65.0	72.9	69.0	MRID 42684922 (Acceptable)
		Effects: decreased MCH, MCV, and MCHC; spleen extramedullary hematopoiesis; decreased myeloid/ erythroid ratio in bone marrow						
Rats	13 Weeks (dietary)	20.7	21.7	21.2	69.7	71.5	70.6	MRID 42684923 (Supplemental)
		Effects: decreased MCV and platelet count						
Mice	4 Weeks (dietary)	180	200	190	540	590	565	MRID 44307301 (Acceptable/ Guideline)
		Effects: increased relative liver weight						

Species	Exposure Duration	NOAEL (mg a.i./kg/day)			LOAEL (mg a.i./kg/day)			Reference (Classification)
		M	F	Average	M	F	Average	
Dogs	13 Weeks (capsule)	100	100	100	1000	1000	1000	MRID 42684924 (Supplemental)
		Effects: Decreased body weight; increased total cholesterol; histopathological lesions in the liver						

Abbreviations: a.i. = active ingredient; F = female; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; M= male; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; mg = milligram; NOAEL = no-observed-adverse-effect level

The studies in mice and dogs identified the liver as the most sensitive target of subchronic exposure to flumioxazin. A four-week guideline study exposed mice to dietary concentrations of flumioxazin up to 10,000 ppm a.i., equivalent to 1800 and 2000 mg a.i./kg/day for males and females, respectively (MRID 44307301); U.S. EPA classified this study as "Acceptable." No mortality was observed. Increased relative liver weight in males and females compared to controls occurred at 3000 ppm a.i., identifying male and female NOAELs of 180 and 200 mg a.i./kg/day and male and female LOAELs of 540 and 590 mg a.i./kg/day, respectively. The 13-week study in dogs administered flumioxazin in gelatin capsules at doses up to 1000 mg a.i./kg/day (MRID 42684924). No mortality or treatment-related clinical signs or effects on food consumption, ophthalmology, or urinalysis were observed at any dose. At 1000 mg a.i./kg/day, significant increases in total cholesterol and alkaline phosphatase activity in blood and hepatic lesions (including chronic focal inflammation) were observed in all treated males. Study authors identified NOAEL and LOAEL values of 100 and 1000 mg a.i./kg/day, respectively. U.S. EPA/OPP classified this study "Supplemental" because data on flumioxazin stability in gelatin capsules were not reported.

Based on the subchronic toxicity values summarized in Table 5.1-4, rats appear to be more sensitive to flumioxazin than mice and dogs. For example, based on LOAEL values, rats appear more sensitive than mice by a factor of 8 (565 mg a.i./kg/day ÷ 70 mg a.i./kg/day ≈ 8.1).

Chronic Exposure. One chronic oral exposure study of technical grade flumioxazin was submitted to U.S. EPA (MRID 44295017); this guideline study was classified as "Acceptable" by U.S. EPA/OPP. Study results are summarized in Table 5.1-5, with experimental details provided in Appendix 3, Table A3-2. Beagle dogs were administered technical grade flumioxazin at doses up to 1000 mg a.i./kg/day in a gelatin capsule for 1 year. No mortality was observed at any dose, and no toxicologically significant sublethal effects were noted below 1000 mg a.i./kg/day. At 1000 mg a.i./kg/day, several adverse effects were observed including increased cholesterol, phospholipids, and alkaline phosphatase in blood, bile duct proliferation, liver congestion with inflammatory cell infiltrate, and extramedullary hematopoiesis, identifying NOAEL and LOAEL values of 100 and 1000 mg a.i./kg/day, respectively. Hemosiderosis of the spleen is consistent with inhibition of PPO. In addition to this study, two carcinogenicity studies in rats (MRID 44295028; MRID 42684937) and one carcinogenicity study in mice (MRID 44295018) evaluated non-cancer effects. Studies are reviewed in Section 5.1.10). Studies in rats reported chronic nephropathy, extramedullary hematopoiesis, and decreased hematopoietic parameters consistent with anemia, with the lowest NOAEL and LOAEL values of 1.8 and 18 mg/kg/day, respectively, in male rats (MRID 44295028). No adverse effects were observed in mice at the highest dose tested of 859.1 mg/kg/day (MRID 44295018).

Table 5.1-5: Chronic Oral Toxicity of Technical Grade Flumioxazin

Species	Exposure Duration	NOAEL (mg a.i./kg/day)			LOAEL (mg a.i./kg/day)			Reference (Classification)
		M	F	Average	M	F	Average	
Dog	12 Months	100	100	100	1000	1000	1000	MRID 44295017 (Acceptable/ guideline)
		Effects: increased cholesterol, phospholipids, α_2-globulin, and alkaline phosphatase; hyperplasia of connective tissue adjacent to the gall bladder; bile duct proliferation; liver congestion and mononuclear and inflammatory cell infiltrate; extramedullary hematopoiesis and hemosiderin pigment associated with the spleen						

Abbreviations; a.i. = active ingredient; F = female; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; M= male; mg = milligram; NOAEL = no-observed-adverse-effect level

5.1.6. Effects on the Nervous System

Exposure to any chemical might cause gross signs of toxicity that might be attributed to neurotoxicity, including incoordination, tremors, or convulsions. A direct neurotoxicant, however, is defined as a chemical that interferes with the function of nerves, either by interacting with nerves directly or with supporting cells (SERA 2014a). This definition of a direct neurotoxicant distinguishes chemicals that act directly on the nervous system (direct neurotoxicants) from those that might produce neurological effects secondary to other forms of toxicity (indirect neurotoxicants).

Two neurotoxicity studies of technical grade flumioxazin in rats were submitted to U.S. EPA/OPP by registrants and were classified as "Acceptable/Guideline" studies. One of these is an acute neurotoxicity screening battery and one is a subchronic study that evaluated both neurotoxicity and systemic toxicity. No chronic neurotoxicity studies were identified.

5.1.6.1. Acute Screening Battery

One acute neurotoxicity test in rats was submitted to U.S. EPA (MRID 48402405); results are summarized in Table 5.1-6. This study was classified as "Acceptable/Guideline" by U.S. EPA. Rats were administered a single gavage dose of flumioxazin up to 2000 mg a.i./kg and observed for 14 days. Neurobehavioral assessments (functional observational battery [FOB] testing and locomotor activity testing) were conducted on study days 7 and 14. No mortality, clinical signs of toxicity, or changes in body weight were observed in any dose group. No effects on FOB testing, locomotor activity, gross pathology, or histopathological evaluation of central and peripheral nervous system tissue was observed between treated and control groups. Based on these observations, the NOAEL and LOAEL values were identified as 2000 and >2000 mg a.i./kg, respectively. Details of this study are provided in Appendix 3, Table A3-3.

Table 5.1-6: Acute Neurotoxicity of Technical Grade Flumioxazin in Rats

Exposure Duration	NOAEL (mg a.i./kg/day)			LOAEL (mg a.i./kg/day)			Reference (Classification)
	M	F	Average	M	F	Average	
14 Days	2000	2000	2000	>2000	>2000	>2000	MRID 48402405 (Acceptable/ Guideline)
	Effects: no effects were observed for FOB, locomotor testing, or histopathology of central and peripheral tissues						

Abbreviations: a.i. = active ingredient; F = female; FOB = functional observational battery; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; M= male; mg= milligram; NOAEL = no-observed-adverse-effect level

5.1.6.2. Subchronic Screening Battery

A subchronic neurotoxicity screening battery was conducted on rats (MRID 48651401); U.S. EPA classified this study as "Acceptable/Guideline;" study results are summarized in Table 5.1-7, with experimental details provided in Appendix 3, Table A3-3. Rats were exposed to dietary concentrations of flumioxazin up to 4500 ppm a.i., equivalent to 323 and 358 mg a.i./kg/day in males and females, respectively, for 90 days. Neurobehavioral assessments (FOB and locomotor activity testing) were conducted in study weeks 3, 7, and 12. No treatment-related effects on FOB testing, motor activity, brain weight or size, or microscopic neurohistopathology were observed, identifying a NOAEL and LOAEL of 323 and >323 mg a.i./kg/day, respectively, for males and a NOAEL and LOAEL of 358 and >358 mg a.i./kg/day, respectively, for females. Significant signs of anemia were observed in males and females at 1500 ppm a.i.; no treatment-related mortality or effects on clinical signs of toxicity, body weight, body weight gain, food consumption, ophthalmology, or gross pathology were observed. For systemic toxicity, a NOAEL and LOAEL of 37 and 110 mg a.i./kg/day, respectively, were identified for males, and a NOAEL and LOAEL of 41 and 124 mg a.i./kg/day, respectively, were identified for females.

Table 5.1-7: Subchronic Neurotoxicity of Technical Grade Flumioxazin in Rats

Exposure Duration	Effect	NOAEL (mg a.i./kg/day)			LOAEL (mg a.i./kg/day)			Reference (Classification)
		M	F	Average	M	F	Average	
90 Days	Neuro	323	358	340.5	>323	>358	>340.5	MRID 48651401 (Acceptable/ Guideline)
		Effects: No effects were observed for FOB, locomotor testing, or histopathology of nervous system tissues						
	Sys	37	41	39	110	124	39	
		Effects: Decreased hemoglobin, hematocrit, MCV, MCH, MCHC						

Abbreviations: a.i. = active ingredient; F = female; FOB = functional observational battery; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; M= male; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; mg = milligram; Neuro = neurological toxicity; NOAEL = no-observed-adverse-effect level; Sys = systemic toxicity

5.1.7. Effects on the Immune System

A subchronic immunotoxicity study was conducted in female rats (MRID 48402408); U.S. EPA classified this study as "Acceptable/Guideline." Results of this study are presented in Table 5.1-8 and experimental details are summarized in Appendix 3, Table A3-4. Two groups of female rats, a T-cell dependent antibody response (TDAR) group and a hematology group, were exposed to dietary technical grade flumioxazin for 28 days. Animals were exposed to dietary concentrations up to

4500 ppm a.i.; this is equivalent to 375 mg a.i./kg/day for the TDAR rats and 371 mg a.i./kg/day for the hematology rats. On day 24 of exposure, TDAR rats were injected with a suspension of sheep red blood cells and rats were evaluated for immunotoxicity using a splenic IgM antibody plaque-forming cell (PFC) assay, and spleen and thymus weights at necropsy. No treatment-related effects on thymus weight, antibody forming cell (AFC) response, or histopathology in immunological tissues were observed in any flumioxazin group. An increase in mean relative spleen weight was observed in the high-dose group; however, this response is most likely a compensatory response to anemia as no effects were observed on the AFC assay response in the spleen. In the hematology group, significantly decreased mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were observed compared to controls, identifying a systemic NOAEL and LOAEL of 42 and 126 mg a.i./kg/day, respectively.

Table 5.1-8: Subchronic Immunotoxicity of Technical Grade Flumioxazin in Female Rats

Exposure Duration	Effect	NOAEL (mg a.i./kg/day)	LOAEL (mg a.i./kg/day)	Reference (Classification)
28 Days	Immune	375	<375	MRID 48651401 (Acceptable/ Guideline)
		Effects: no effects PFC or AFC assays or thymus weight		
	Systemic	42	126	
		Effects: decreased MCV and MCH		

Abbreviations: a.i. = active ingredient; AFC = antibody forming cell; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; mg = milligram; NOAEL = no-observed-adverse-effect level; PFC = plaque-forming cell

5.1.8. Effects on the Endocrine System

Endocrine effects can occur through endocrine disruption due to interactions of chemicals with endogenous endocrine receptors or by direct toxic effects on endocrine organs (SERA 2014a). U.S. EPA has developed the Endocrine Disruptor Screening Program (EDSP) to identify if certain substances, including pesticides, are capable of producing adverse effects in humans or wildlife similar to effects associated with a naturally occurring estrogen. The EDSP uses a tiered approach to determine if a given chemical is capable of endocrine disruption. Tier 1 consists of screening assays to identify if a chemical interacts with estrogen, androgen, or thyroid hormonal systems. Tier 2 consists of testing designed to identity any adverse endocrine related effects caused by the given chemical and to establish a dose-response relationship for the effect on estrogen, androgen, or thyroid hormonal systems. If during Tier 1 screening a chemical is found to interact with one of the hormonal systems, it then proceeds to Tier 2 of the EDSP in which U.S. EPA determines which (if any) of the Tier 2 tests are applicable based on the available data.

Between October 2009 and February 2010, U.S. EPA issued test orders/data call-ins for the first group of 67 chemicals, which included 58 pesticide active ingredients and nine inert ingredients. A second list of chemicals was published on June 26, 2014 and consisted of 109 chemicals, 41 which are pesticide active ingredients (U.S. EPA 2014). Flumioxazin was not among the group of pesticide active ingredients on the screening list for endocrine disruption. As a result, this risk assessment does not specifically address the potential for adverse effects on endocrine function.

Available toxicity studies on flumioxazin in laboratory animals did not identify effects to the endocrine system.

5.1.9. Developmental and Reproductive Effects

5.1.9.1. Developmental Effects

Several studies have investigated the developmental effects of gestational exposure to technical grade flumioxazin. Studies have evaluated effects of oral (MRIDs 42684925, 42684926, 49615801, and 42684928), dermal (Kawamura et al. 2014), and inhalation (MRIDs 50207105 and 50207106/50207108) exposure to flumioxazin administered over several days during gestation in rats and rabbits. In addition, three studies evaluated the effects of oral flumioxazin administered on a single day of gestation to determine the most sensitive developmental stage for fetal toxicity (MRIDs 44295020 and 4288400). Study results are summarized in Table 5.1-9, with experimental details described in Appendix 3, Table A3-5.

Table 5.1-9: Developmental and Maternal Toxicity Studies for Technical Grade Flumioxazin

Species	Exposure Duration	Effect	NOAEL (mg a.i./kg/day)	LOAEL (mg a.i./kg/day)	Reference (Classification)
Oral Exposure					
Rats	GD 6 – 15	Dev	3[1]	10	MRID 42684925 (Supplemental)
			Effects: cardiac malformations (atrioventricular canal and ventricular septal defect)		
		Mat	30	>30	
			Effects: no mortality or adverse effects		
Rats	GD 6 – 15	Dev	30	100	MRID 42684926 (Supplemental)
			Effects: cardiac abnormalities		
		Mat	300	>300	
			Effects: no mortality of adverse effects		
Rats	GD 6 – 15	Dev	15	30	MRID 49615801 (Acceptable/ Non-guideline)
			Effects: cardiac malformations		
		Mat	30	60	
			Effects: decreased body weight and body weight gain; clinical signs of toxicity		
Rats	GD 12	Dev	<1000	1000	MRID 44295020 (Acceptable/ Non-guideline)
			Effects: cardiovascular malformations, histopathological changes in erythroblasts and hepatocytes; sinusoidal vessel dilation and hepatocytic necrosis		
Rats	GD 11, 12, 13, 14, or 15	Dev	<400	400	MRID 42884006 (Supplemental)
			Effects: most sensitive developmental stage was GD 12; fetal effects included fetal death, decreased fetal weight, and cardiac malformations		

Species	Exposure Duration	Effect	NOAEL (mg a.i./kg/day)	LOAEL (mg a.i./kg/day)	Reference (Classification)
Rabbits	GD 7 – 19	Dev	3000	>3000	MRID 42684928 (Acceptable/ Guideline)
			Effects: no resorptions, fetal mortality, or malformations/variations		
		Mat	1000	3000	
			Effects: decreased body weight gain		
Rabbits	GD 12	Dev	1000	>1000	MRID 44295020 (Acceptable/ Non-guideline)
			Effects: no mortality or external malformations or variations		
Dermal Exposure					
Rats	GD 6 – 15	Dev	100	300	Kawamura et al. (2014)
			Effects: increased embryo mortality; decreased number of live fetuses; decreased fetal body weight; ventricular septal defect and wavy ribs		
		Mat	300	>300	
			Effects: no mortality or adverse effects		
Inhalation Exposure					
Rats	GD 6 – 19	Dev	0.010 mg a.i./L (10 mg a.i./m^3)	0.030 mg a.i./L (30 mg a.i./m^3)	MRID 50207105 (Acceptable/ Guideline)
			Effects: decreased fetal body weights; ventricular septal defect		
		Mat	0.010 mg a.i./L (10 mg a.i./m^3)	0.030 mg a.i./L (30 mg a.i./m^3)	
			Effects: decreased body weight gain and gravid uterus weight; increased resorptions and post-implantation loss		
Rats	GD 6 – 19	Dev	0.010 mg a.i./L (20 mg a.i./m^3)	0.020 mg a.i./L (20 mg a.i./m^3)	MRID 50207106 MRID 50207108 (Acceptable/ Guideline)
			Effects: malformations include ventricular septal defect, bent ribs, bent scapula, and decreased ossification of vertebral arches and skull		
		Mat	0.010 mg a.i./L (10 mg a.i./m^3)	0.020 mg a.i./L (20 mg a.i./m^3)	
			Effects: decreased body weight, gravid uterus weight, and body weight gain; increased absolute reticulocyte counts		

[1]Value used to assess human health risks associated with acute exposure to flumioxazin to females of childbearing potential.
Abbreviations: a.i. = active ingredient; Dev = developmental; GD = gestational day; kg = kilogram; L = liter; LOAEL = lowest-observed-adverse-effect level; m^3 = cubic meter; Mat = maternal; mg = milligram; NOAEL = no-observed-adverse-effect level

1

Results of developmental studies in rats consistently show that flumioxazin induces fetal cardiac malformations for all routes of exposure. Studies exposing dams to oral flumioxazin on GD 6 – 15 reported LOAEL values of 10, 30, and 100 mg a.i./kg/day for cardiac malformations (atrioventricular canal and ventricular septal defect) (MRIDs 42684925, 42684926, and 49615801). Dermal exposure of rats on GD 6 – 15 also induced fetal ventricular septal defects, with NOAEL and LOAEL values of 100 and 300 mg a.i./kg/day, respectively. Other developmental effects observed at 300 mg a.i./kg/day included increased embryo mortality, decreased number of live fetuses, decreased fetal body weight, and wavy ribs. Cardiac malformations were also observed following inhalation exposure of rats on GD 6 – 19, with LOAEL values of 0.020 mg a.i./L (20 mg a.i./m^3) (MRID 50207106/50207108) and 0.030 mg a.i./L (30 mg a.i./m^3) (MRID 50207105). Other developmental effects observed in inhalation studies include decreased fetal body weight (MRID 50207105) and bent ribs, bent scapula, and decreased ossification of vertebral arches and skull (MRID 50207106/50207108). Studies in which rats were exposed to flumioxazin on a single day of gestation (GD 11, 12, 13, 14, or 15) indicate that the most sensitive developmental stage for cardiac malformations occurs on GD 12 (MRIDs 44295020 and 42884006). In contrast to studies in rats, no cardiac malformations or any other developmental effects were observed in rabbits exposed to flumioxazin on GD 7 – 19 or on GD 12 at the highest doses tested, with NOAEL values of 1000 and 3000 mg a.i./kg/day, respectively (MRIDs 42684928 and 44295020).

Collectively, these results suggest that rats are more sensitive than rabbits to the developmental effects of flumioxazin. As discussed in Section 5.1.2, inhibition of PPO may be the underlying mechanisms for cardiac malformations. Accumulation of protoporphyrinogen IX has been observed in rat embryos following gestational exposure to flumioxazin (Kawamura et al. 1996), with highest peak protoporphyrinogen IX inhibition coinciding with the sensitive gestational period for developmental effects (Kawamura et al. 2014).

5.1.9.2. Reproductive Effects

A 2-generation reproduction study in rats examined effects of technical grade flumioxazin (MRID 42684935) at dietary concentrations up to 300 ppm a.i. (equivalent to 18.9 and 22.7 mg a.i./kg/day in males and females, respectively). Results are summarized in Table 5.1-10, with experimental details described in Appendix 3, Table A3-5. In parental animals of F0 and F1 generations, treatment-related effects were seen in the highest dose group; effects included increased mortality in females (likely related to hepatotoxicity), decreased growth, centrilobular necrosis of the liver and bile stasis. Reproductive effects included decreased number of live pups/litter and decreased pup body weight at dietary concentrations ≥200 ppm. The sex-averaged NOAEL and LOAEL for parental systemic toxicity were identified as 13.9 and 20.8 mg a.i./kg/day, respectively, and the average NOAEL and LOAEL for reproductive toxicity were identified as 7.0 and 13.9 mg a.i./kg/day, respectively. Histopathological examination of the testes showed testicular atrophy in F1 males at the highest dose tested (18.9 mg/kg/day); however, testes were only examined microscopically in the control, low-dose (3.2 mg/kg/day), and high-dose groups and not in the (6.3 and 12.7 mg/kg/day) groups. Note that the incidence of testicular atrophy in the high dose groups was 3/30 rats, compared to 2/30 rats in the control group. The NOAEL value of 6.3 mg/kg/day for decreased pup weight and number of live pups was used to derive a surrogate acute reference dose (RfD) to assess the human health risks associated with acute exposure to flumioxazin to the general population.

Table 5.1-10: Reproductive Toxicity of Technical Grade Flumioxazin

Test Species	Effect	NOAEL (mg a.i./kg/day)			LOAEL (mg a.i./kg/day)			Reference (Classification)
		M	F	Average	M	F	Average	
Rat	Parental lethal and sublethal	12.7	15.1	13.9	18.9	22.7	20.8	MRID 42684935 (Acceptable/Guideline)
		Effects: mortality; clinical signs of toxicity; decreased body weight/weight gain and food consumption; liver pathology						
	Reproductive	**6.3**[1]	7.6	7.0	12.7	15.1	13.9	
		Effects: significant decrease in number of liveborn pups; decreased pup body weight						

[1]Value used to assess human health risks associated with acute exposure to flumioxazin to the general population.
Abbreviations: a.i. = active ingredient; F= female; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; M = male; mg = milligram; NOAEL = no-observed-adverse-effect level

5.1.10. Carcinogenicity and Mutagenicity

As discussed in SERA (2014a), three types of data are commonly used to assess potential carcinogenic hazard: epidemiology studies; tests for genetic toxicity, including mutagenicity; and cancer bioassays on mammals. When applicable, quantitative estimates of carcinogenic potency are typically based on mammalian bioassays.

Carcinogenicity. No epidemiological studies specific to flumioxazin were identified. Two "Acceptable/Guideline" carcinogenicity bioassays and one supplemental non-guideline carcinogenicity bioassay for technical grade flumioxazin were submitted by the registrants to U.S. EPA/OPP. No evidence of carcinogenicity was observed in any study. Therefore, the following discussion focuses on non-cancer effects observed in these studies. Results of these studies are summarized in Table 5.1-11 and experimental details are provided in Appendix 3, Table A3-6.

Table 5.1-11: Carcinogenicity Studies for Flumioxazin

Test Species	Exposure Duration	NOAEL (mg a.i./kg/day)			LOAEL (mg a.i./kg/day)			Reference (Classification)
		M	F	Average	M	F	Average	
Rats	24 Months	**1.8**[1]	2.2	2	18.0	21.8	19.9	MRID 44295028 (Acceptable/ Guideline)
		Effects: chronic nephropathy and extramedullary hematopoiesis (M); decreased MCV and MCH (F) *Carcinogenicity:* no evidence of carcinogenicity						
Rats	24 months	20.8	25.3	23.1	42.1	51.3	46.7	MRID 42684937 (Supplemental/ Non-guideline)
		Effects: decreased MCV, MCH, MCHC, and hematocrit, increased reticulocytes and erythroblasts *Carcinogenicity:* no evidence of carcinogenicity						

Test Species	Exposure Duration	NOAEL (mg a.i./kg/day)			LOAEL (mg a.i./kg/day)			Reference (Classification)
		M	F	Average	M	F	Average	
Mice	78 Weeks	754.1	859.1	806.6	>754.1	>859.1	>806.6	MRID 44295018 (Acceptable/ Guideline)
		Effects: no mortality, clinical signs of toxicity, body weight, food consumption, hematological parameters, organ weights, or gross pathology *Carcinogenicity:* no evidence of carcinogenicity						

[1]Value used to assess human health risks associated with chronic exposure to flumioxazin.
Abbreviations: a.i. = active ingredient; F = female; LOAEL = lowest-observed-adverse-effect level; kg = kilogram; M= male; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; mg = milligram; NOAEL = no-observed-adverse-effect level

In an "Acceptable/Guideline" study (MRID 44295028), rats were exposed to dietary concentrations of flumioxazin up to 1000 ppm a.i. (equivalent to 36.5 and 43.6 mg a.i./kg/day for males and females, respectively) for two years. At 500 and 1000 ppm, increased incidence of chronic nephropathy and hematological effects were observed in males and females. Male NOAEL and LOAEL values were 1.8 and 18.0 mg a.i./kg/day, respectively, and female NOAEL and LOAEL values were 2.2 and 21.8 mg a.i./kg/day, respectively. The NOAEL value of 1.8 mg a.i./kg /day in male rats is used to derive a chronic RfD in this risk assessment to assess chronic risks to humans from exposure to flumioxazin. In a non-guideline supplemental study (MRID 42684937), rats were exposed to dietary concentrations of flumioxazin up to 1000 ppm a.i. (equivalent to 42.1 and 51.3 mg a.i./kg/day for males and females, respectively) for two years. No toxicologically significant treatment-related effects were observed in the two lower dose groups. At 1000 ppm a.i., significant hematological effects consistent with anemia were observed in males and females (decreased MCV, MCH, mean corpuscular hemoglobin concentration [MCHC], and hematocrit; increased reticulocytes and erythroblasts). The sex-averaged NOAEL and LOAEL values were 23.1 and 46.7 mg a.i./kg/day, respectively. In mice exposed to dietary concentrations up to 7000 ppm a.i. (equivalent to 754.1 and 859.1 mg a.i./kg/day in males and females, respectively), no lethal or sublethal effects were noted at any concentration (MRID 44295018). Male and female NOAELs were 754.1 and 859.1 mg a.i./kg/day, respectively.

Five genotoxicity studies, two gene mutation studies, and three cytogenetics studies were conducted on technical grade flumioxazin, as detailed in Appendix 3, Table A3-6. Results of a bacterial reverse gene mutation assay in *Salmonella typhimurium* and *Escherichia coli* were equivocal (MRID 42684938), and flumioxazin was negative for inducing unscheduled DNA synthesis in rat hepatocytes (MRID 42684941). An *in vitro* chromosomal aberration test in Chinese Hamster ovary cells was negative without S9 activation, but positive with S9 activation (MRID 42684939). An *in vivo* study in which rats were administered a single oral dose of 5000 a.i./kg was also negative for chromosome aberrations in bone marrow cells (MRID 42684940). Results of a micronuclei test in rats was negative for exposure to intraperitoneal doses of flumioxazin up to 5000 mg a.i./kg (MRID 42684942).

5.1.11. Irritation and Sensitization (Effects on the Skin and Eyes)

U.S. EPA/OPP requires acute assays for eye irritation, skin irritation, and skin sensitization. As with acute oral toxicity, U.S. EPA uses a ranking system for responses ranging from Category I (most severe response) to Category IV (mild or minimal response) for eye and skin irritation. Skin

sensitization is classified simply as occurring or not occurring. Details of the categorization system used by U.S. EPA is described in Chapter 7 of the U.S. EPA *Label Review Manual* (U.S. EPA 2018). Table 5.1-12 summarizes results of irritation and sensitization tests. Additional information is provided in Appendix 3, Table A3-7. In addition to these studies, results of irritation and sensitization studies for flumioxazin formulated products are listed in product SDSs. For the products listed in Section 2.1 (Table 2.1-2), results of these studies are provided in Appendix 2, Table A2-1.

Table 5.1-12: Acute Eye Irritation, Skin Irritation, and Skin Sensitization Toxicity Studies for Technical Grade Flumioxazin and a Flumioxazin Product

Test Species	Study Type	Test Substance	Result	Toxicity Category	Reference (Classification)
Rabbit	Acute eye irritation	TG	Minimally irritating	III	MRID 42684917 (Acceptable/ Guideline)
Rabbit	Acute eye irritation	TG	Non-irritant	IV	MRID 50353611 (Acceptable)
Rabbit	Acute eye irritation	V-53482 50 WDG[1]	Non-irritant	IV	MRID 42684918 (Acceptable/ Guideline)
Rabbit	Acute dermal irritation	TG	Non-irritant	IV	MRID 50353612 (Acceptable)
Rabbit	Acute dermal irritation	TG	Non-irritant	IV	MRID 42684917 (Acceptable/ Guideline)
Rabbit	Acute dermal irritation	V-53482 50 WDG[1]	Slightly irritating	IV	MRID 42684919 (Acceptable/ Guideline)
Guinea pig	Skin sensitization (Guinea Pig Maximization Test)	TG	Not a dermal sensitizer	NA	MRID 42684921 (Acceptable/ Guideline)
Guinea pig	Skin sensitization (Buehler Method)	TG	Not a dermal sensitizer	NA	MRID 50353613 (Acceptable)
Guinea pig	Skin sensitization (Guinea Pig Maximization Test)	V-53482 50 WDG[1]	Not a dermal sensitizer	NA	MRID 42684920 (Acceptable/ Guideline)

[1]V-53482 50 WDG is a 50% a.i. formulated product of flumioxazin. The commercial name of this product was not specified.
Abbreviations: NA = not applicable; TG = technical grade

5.1.11.1. Eye Irritation

Eye irritation studies have evaluated technical grade flumioxazin (MRID 42684917; MRID 50353611) and a flumioxazin formulated product (MRID 42684918) in rabbits (Table 5.1-12). Experimental details for these studies are summarized in Appendix 3, Table A3-7. The two studies on technical

grade flumioxazin found slightly different results, with one study showing minimal irritation (MRID 42684917) and one study showing no irritation (MRID 50353611). For the study showing minimal irritation, 100 mg a.i. was instilled into the eye. Effects, which resolved within 48 hours, included iritis, conjunctival redness, and/or chemosis; no corneal opacity was observed (MRID 42684917). Based on results of this study, flumioxazin is classified as "minimally irritating." For the study reporting no irritation, 72 mg a.i. was instilled into the eye; minimal conjunctival redness resolved within 24 hours (MRID 50353611). Differences in the findings of these two studies might be related to the dose of flumioxazin that was instilled in the eye. In the study on a formulated flumioxazin product, 25 mg a.i. was instilled into the eye; slight conjunctival redness, chemosis, and discharge were observed (MRID 42684918). U.S. EPA rated this flumioxazin product as a non-irritant.

In addition to these studies, SDSs for formulated flumioxazin products report classifications for eye irritation; classifications are summarized in Appendix 2, Table A2-1. The eye irritation classifications for formulated flumioxazin products as reported in SDSs are non-irritating, mildly irritating, and/or brief and/or minor irritation. As noted in Table A2-1, for most products, SDSs did not specify the test substance; information on eye irritation could be from studies on the specific product, a substantially similar product, a formulation containing 50% a.i., or technical grade material.

5.1.11.2. Skin Irritation

Skin irritation studies have evaluated technical grade flumioxazin and a flumioxazin formulated product in rabbits (see Table 5.1-12). Experimental details for these studies are summarized in Appendix 3, Table A3-7. No dermal irritation was observed in studies on technical grade flumioxazin (MRIDs 50353612 and 42684917). The study on the flumioxazin formulated product reported very slight erythema and/or very slight edema, though both effects were resolved by 96 hours and 72 hours, respectively (MRID 42684919). Based on these findings, the flumioxazin product was classified as "slightly irritating" to skin. Acute dermal toxicity studies did not observe skin irritation (see Section 5.1.12.1). However, these studies were designed to assess systemic toxicity and not to classify skin irritation.

In addition to these studies, SDSs for formulated flumioxazin products report classifications for skin irritation; classifications are summarized in Appendix 2, Table A2-1. Skin irritation is listed as slightly irritating, and brief and/or minor irritation. As noted in Table A2-1, information on skin irritation might be from studies on the specific product, a substantially similar product, a formulation containing 50% a.i., or technical grade material.

5.1.11.3. Skin Sensitization

Three studies evaluated skin sensitization on flumioxazin: two studies on technical grade flumioxazin (MRIDs 42684921 and 50353613) and one study on a formulated product (MRID 42684920). Experimental details for these studies are summarized in Appendix 3, Table A3-7. Results of these studies indicate that flumioxazin is not a dermal sensitizer. Tests used to evaluate sensitization effects of technical grade product are the guinea pig maximization test (test material is applied with an adjuvant) and the Buehler method (test material is applied without an adjuvant). The Buehler method was also used to evaluate skin sensitization for the formulated product.

As noted above for eye and skin irritation studies, SDSs for formulated flumioxazin products list results of skin sensitization studies (Appendix 2, Table A2-1). Product SDSs list skin sensitizing effects

as follows: not a sensitizer; not expected to cause allergic skin reactions; probably non-sensitizer; and non-sensitizer.

5.1.12. Systematic Toxic Effects from Dermal Exposure

5.1.12.1. Acute Dermal Toxicity

Three studies of the acute dermal toxicity of flumioxazin to rats were available for review: two studies on technical grade flumioxazin (MRIDs 42684913; MRID 50353609) and one study on a formulated flumioxazin product (MRID 42684914). The same protocol was used in all studies. The test substance was applied to the shaved dorsal skin of the animals in a single application; following 24 hours of exposure, the treated skin was washed and animals were observed for 14 days. No lethal or sublethal effects were observed in any animals tested. All studies were considered acceptable by U.S. EPA/OPP, and all classified flumioxazin as "slightly irritating" for acute dermal toxicity to rats. LD_{50} values are summarized in Table 5.1-13, and study details are provided in Appendix 3, Table A3-8.

Table 5.1-13: Acute Dermal Toxicity of Technical Grade Flumioxazin and a Flumioxazin Product

Test Species	Results	Toxicity Category	Reference (Classification)
Technical Grade Flumioxazin			
Rat	LD_{50} >2000 mg a.i./kg *Effects:* no mortality, clinical signs of toxicity, dermal irritation, changes in body weight, or gross pathological changes	III	MRID 42684913 (Acceptable/Guideline)
Rat	LD_{50} >2000 mg a.i./kg *Effects:* no mortality, clinical signs of toxicity, dermal irritation, changes in body weight, or gross pathological changes	III	MRID 50353609 (Acceptable)
Flumioxazin Formulated Product (V-53482 50 WDG[1])			
Rat	LD_{50} >1000 mg a.i./kg *Effects:* no mortality, clinical signs of toxicity, dermal irritation, changes in body weight, or gross pathological changes	III	MRID 42584914 (Acceptable/Guideline)

[1]V-53482 50 WDG is a 50% a.i. formulated product of flumioxazin. The commercial name of this product was not specified.
Abbreviations: a.i. = active ingredient; LD_{50} = median lethal dose; WDG = water dispersible granule

5.1.12.2. Subchronic Dermal Toxicity

One study of subchronic dermal toxicity of flumioxazin was available, as summarized in Table 5.1-14 below. Rats were exposed to technical grade flumioxazin at doses up to 1000 mg a.i./kg/day to the skin for six hours/day for 21 days (MRID 44295016). Treatment sites (shaved) were covered for six hours after each daily application and then cleaned daily. No mortality or significant sublethal effects were observed at any dose level. Although small decreases in hemoglobin (7%) and hematocrit (6%) in high-dose females were statistically significant compared to controls, the DER

reviewer did not consider these effects to be toxicologically significant. Additional experimental details are provided in Appendix 3, Table A3-9.

Table 5.1-14: Subchronic Dermal Toxicity of Technical Grade Flumioxazin

Test Species	Exposure Duration	NOAEL (mg a.i./kg/day)	LOAEL (mg a.i./kg/day)	Reference (Classification)
Rat	21 Days	1000	>1000	MRID 44295016 (Acceptable/Guideline)
		Effects: no mortality, clinical signs of toxicity, effects on body weight, body weight gain, food consumption, clinical chemistry, organ weights, gross pathology, or histopathology		

Abbreviations: a.i. = active ingredient; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; mg = milligram; NOAEL = no-observed-adverse-effect level

5.1.13. Inhalation Exposures

Studies on the acute inhalation toxicity were submitted to U.S. EPA for technical grade flumioxazin (MRIDs 42684915 and 50353610) and a formulated flumioxazin product (MRID 42684916). Of these studies, only one study (MRID 50353610) was classified as "Acceptable" by U.S. EPA. Study MRID 42684915 was classified as supplemental because particle size was not reported. Study MRID 42684916 was classified as supplemental because only one concentration was tested. Study results are summarized in Table 5.1-15, with experimental details provided in Appendix 3, Table A3-10.

Table 5.1-15: Acute Inhalation Toxicity of Technical Grade Flumioxazin and a Flumioxazin Product

Test Species	Results	Toxicity Category	Reference (Classification)
Technical Grade Flumioxazin			
Rats	4-hour LC_{50} not defined due to lack of particle size data *Effects:* no mortality; bradypnea and decreased spontaneous activity at 1.55 and 3.98 mg a.i./L	ND	MRID 42684915 (Core Supplemental)
Rats	4-hour LC_{50} >3.71 mg a.i./L *Effects:* no mortality; hypoactivity and ruffled fur from the 4th hour of exposure (recovered by day 2)	IV	MRID 50353610 (Acceptable)
Flumioxazin Formulated Product (V-53482 50 WDG[1])			
Rats	4-hour LC_{50} >0.094 mg a.i./L *Effects:* no mortality; focal degeneration of the ventral cartilage of the larynx	I	MRID 42684916 (Core Supplemental)

[1]V-53482 50 WDG is a 50% a.i. formulated product of flumioxazin. The commercial name of this product was not specified.
Abbreviations: a.i. = active ingredient; L = liter; LC_{50} = median lethal concentration; ND = not defined; WDG = water dispersible granule

The acceptable study on technical grade flumioxazin exposed rats to an aerosolized flumioxazin of 3.71 mg a.i./L (MRID 50353610); no mortality or treatment-related effects on body weight were

observed. All exposed animals exhibited clinical signs of toxicity starting 4 hours after exposure which resolved by observation day 2. A lethal concentration (LC_{50}) >3.71 mg a.i./L was identified, and flumioxazin was classified as "practically non-toxic" based on these results. The supplemental study on technical grade flumioxazin exposed rats to 1.55 and 3.93 mg a.i./L (MRID 42684915). No mortality was observed but an LC_{50} was not identified by U.S. EPA due to lack of particle size data; it is not possible to determine if the particle size was in the respirable range. All treated animals exhibited bradypnea and decreased spontaneous activity at both concentrations during exposure. For the study on the flumioxazin product, no mortality was observed, identifying an LC_{50} >0.094 mg a.i./L. However, because focal degeneration of ventral cartilage in the larynx (considered a serious acute effect) was observed in most animals exposed to the flumioxazin product, U.S. EPA/OPP assigned a temporary toxicity classification of "highly toxic" to flumioxazin.

5.1.14. Adjuvants and Other Ingredients

5.1.14.1. Adjuvants

U.S. EPA is responsible for the regulation of adjuvants and other ingredients in pesticide formulations. While most FS risk assessments do not assess the risk of using adjuvants, some adjuvants may be evaluated if there is information to suggest that the risks might be substantial. For example, some adjuvants used in glyphosate formulations might be as toxic as or more toxic than glyphosate itself, based on the FS risk assessment on glyphosate (SERA 2011).

5.1.14.2. Other Ingredients

Pesticide products may contain both active ingredients and *inert* ingredients, which are also referred to as *other ingredients*. An inert ingredient is any substance other than an active ingredient and consists of a broad range of compounds, including emulsifiers, solvents, carriers, aerosol propellants, fragrances, and dyes (USDA/FS 2019). U.S. EPA/OPP is responsible for regulating both the active ingredients in pesticide formulations as well as any other chemicals that may be added to the formulation. As implemented, these regulations affect only pesticide labeling and testing requirements. While the term inert as used in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) might suggest non-toxicity, some inerts are toxic, and the U.S. EPA/OPP now uses the term other ingredients rather than inerts (USDA/FS 2019). For purposes of this report, the discussion below uses the term *other ingredients* to refer to any substance other than the active ingredient.

Labels and SDSs for flumioxazin formulated products do not identify other ingredients in the formulation other than common ingredients such as kaolin clay, propylene glycol, aluminum oxide, and sodium lauryl sulfate. The identities of other ingredients in pesticide formulations are generally considered trade secrets and are not required to be disclosed to the general public, unless the compound is classified by U.S. EPA as toxic or potentially toxic compound and it is present at a level of 1% or greater in the formulation. Nonetheless, all other ingredients as well as the amounts of such in the pesticide formulations are disclosed to and reviewed by the U.S. EPA/OPP as part of the registration process.

5.1.15. Impurities

Impurities are not discussed in the open literature or the recent risk assessments by U.S. EPA (U.S. EPA 2003, 2012). However, the U.S. EPA requires registrants to submit information on impurities as a

condition for registration. This information is reviewed by U.S. EPA/OPP, but it is not disclosed to the general public because it is considered to be Confidential Business Information. Thus, information on impurities was not obtainable for the current FS risk assessment.

5.1.16. Toxicological Interactions

Data regarding the possible interactions of flumioxazin with other compounds were not identified in the available studies submitted to U.S. EPA/OPP or the open literature. Consequently, there is no basis for inferring toxicological interactions of flumioxazin with other chemicals.

5.2. Exposure Assessment

Exposure assessment is a process in risk assessment that identifies potential receptors of contamination or chemical releases, exposure routes, and exposure point concentrations for environmental media to which the receptor may be exposed. These three elements (receptor, exposure route, exposure medium) comprise what is described as an exposure scenario. In this risk assessment, exposure assessments are presented for both workers and members of the general public, which is consistent with previous FS risk assessments. When assessing exposures for workers and the general public, two types of exposure scenarios are taken into consideration, which include general exposures and accidental/incidental exposures. The term general exposures refers to human exposures resulting from the normal handling and application of the compound (SERA 2014a). The accidental/incidental exposure scenarios involve specific events that might occur during any type of application.

The following subsections describe the exposure scenarios and associated doses for workers and the general public. Exposures for flumioxazin were assessed using an Excel workbook that includes detailed calculations for quantitative exposures and risks for various receptors. The Excel workbooks were generated using the FS risk assessment tool called Worksheet Maker and are included in Attachment 1. Three different commercially available formulations were evaluated as proxies for the flumioxazin products for modeling purposes: SureGuard™ Herbicide (51% a.i.), PondKlear Aquatic Herbicide (44% a.i.) and Broadstar™ Herbicide (0.25% a.i.). SureGuard is used in spray applications as a liquid. PondKlear is used to manage aquatic vegetation and Broadstar is dispensed as a granule onto the soil. The Excel workbooks are important in providing an exposure dose for each exposure scenario, which is then compared to toxicity values to calculate HQs. In FS HHERAs, the methodology and results of calculations of HQs are provided in the Excel workbooks (Attachments 1 – 6).

Calculations of exposure are based on the maximum application rates for each application method (Attachments 1 – 6), which introduces a health prospective (conservative) bias into the resulting HQs. The maximum recommended labeled rate for formulations of flumioxazin in single aerial terrestrial applications relevant to FS activities is 0.38 lb a.i./acre. For spray application to the surface of water bodies, the maximum application rate is also 0.38 lb a.i./acre, and for subsurface applications, the recommended maximum application concentration is 400 ppb. The maximum application rate of the granular product is 0.38 lb a.i./acre. Only a single application rate is considered in the exposure assessment as flumioxazin is not persistent in the environment due to rapid degradation; however, as discussed in Section 2.3, different formulations have different recommended re-application frequencies. The Excel workbooks for the six application methods are

provided in Attachments 1 – 6 for spray backpack, spray boom, spray aerial, application to surface of water bodies, subsurface application to water bodies, and granular application, respectively.

5.2.1. Workers

Worker exposures were evaluated for the three general application methods described in Section 2.2: spray of liquid by backpack, boom, or aerial application; direct water application (surface and subsurface); and ground application of a granular product. Dermal exposure is the predominant route of exposure for pesticide applicators (SERA 2014a). As described in SERA 2014a, dermal exposures for workers are evaluated quantitatively in FS HHERAs and include direct contact with a pesticide solution and accidental spills of the pesticide onto the surface of the skin.

5.2.1.1. General Worker Exposures

Absorbed dose rates for the general worker exposure scenario are functions of the application rate (e.g., lb/acre), acreage treated, and generic worker exposure (i.e., absorption) rates for specific application methods (mg absorbed/kg bw per lb handled/day). Generic absorption rates for reference pesticides and application rates have been derived from biomonitoring studies of workers (SERA 2014b) and must be extrapolated to the chemical of interest. The generic worker exposure rates for standard terrestrial application methods are shown on Table 2 of SERA (2014b). These rates were used for estimating worker absorbed dose rates for flumioxazin and were derived by incorporating the approach described in the *Reassessment of Worker Exposure Rates* guidance document developed by SERA (SERA 2014b).

In addition to worker exposure rates, the estimated number of acres per day that a worker will treat are used in estimating the amount of pesticide that a worker will handle, based on the maximum labeled application rate for a single application (0.38 lb a.i./acre). These values are presented in Worksheets C01 (Attachments 1 – 6) and are based on general estimates from the FS. The number of hours worked per day is expressed as a range, with the lower end based on working six hours per day with one hour at each end of the eight-hour work day spent in activities that do not involve herbicide exposure. The upper end of the range, eight hours per day, is based on an extended (10-hour) work day, allowing for one hour at each end of the work day to be spent in activities that do not involve herbicide exposure (SERA 2014a). As shown in Table 5.2-1, worker exposure doses are estimated for each exposure scenario (central estimate and lower and upper bound 95% confidence estimates) associated with the three different types of application methods.

Table 5.2-1: General Worker Exposure Doses (mg a.i./kg bw/day or mg a.i./kg bw/event)

Scenario	Lower Dose	Central Dose	Upper Dose	Attachment and Worksheet
Spray - Backpack Application (Directed Foliar)	1.82E-01	1.68E00	1.22E01	Attachment 1 C01
Spray – Boom Ground Application	8.21E-05	7.45E-03	6.08E-01	Attachment 2 C01
Spray – Aircraft Aerial Application	8.21E-05	7.45E-03	6.08E-01	Attachment 3 C01
Direct Water Application - Surface	1.50E-03	7.53E-03	3.38E-02	Attachment 4 C01
Direct Water Application - Subsurface	2.12E-03	1.06E-02	5.29E-02	Attachment 5 C01
Ground Application - Broadcast Granule	9.90E-05	8.40E-03	5.67E-01	Attachment 6 C01

Note: The lower and upper dose represent the 95% confidence interval.

5.2.1.2. Accidental/Incidental Worker Exposures

Dermal exposure is the predominant route of exposure for pesticide applicators (SERA 2014a). As described in SERA 2014a, dermal exposures for workers are evaluated quantitatively in FS HHERAs and include direct contact with a pesticide solution and accidental spills of the pesticide onto the surface of the skin. Four accidental/incidental exposure scenarios evaluated for dermal exposure for workers to flumioxazin include the following:

- Direct Contact to Surface Area of Hands for One Minute (All Attachments, Worksheet C02a)
- Direct Contact to Surface Area of Hands for One Hour (All Attachments, Worksheet C02b)
- Accidental Spill on Hands for One Hour (All Attachments except 6 [granules], Worksheet C03a)
- Accidental Spill on Lower Legs for One Hour (All Attachments except 6 [granules], Worksheet C03b)

For the first two exposure scenarios involving direct contact with flumioxazin, the scenarios evaluated include either immersion of the hands in a field solution for 1 minute or wearing pesticide contaminated gloves for one hour. As discussed in SERA 2014a, it may seem unreasonable to assume that the hands or any other part of a worker's body will be immersed in a chemical solution for a prolonged period of time. However, it is possible that the gloves or clothing worn by a worker might become contaminated with the pesticide being handled. Therefore, the key assumption for these exposure scenarios is that wearing gloves contaminated with a pesticide is equivalent to immersing the bare hands in the solution. In both cases, the chemical concentration in contact with the skin and the resulting dermal absorption rate are essentially constant. The rate of absorption is estimated based on a zero-order dermal permeability rate (K_p), which is calculated in Worksheet B03a. The amount of the pesticide absorbed per unit time depends directly on the concentration of the chemical in solution, which varies depending on the application method and dilution volume. At an application rate of 0.38 lb a.i./acre, the estimated concentrations in a field solution is 0.52 mg/mL for backpack application, 3 mg/mL for boom broadcast application, 4.6 mg/mL for aerial application, 2.8 mg/L for surface aquatic application, and 130 mg/mL for subsurface aquatic application (Worksheet A01). Note that the maximum application rate for the direct water subsurface scenario is 400 ppb. Section 2.1, Table 2.1-2 lists additional information on flumioxazin formulations and application rates.

The accidental dermal exposure scenarios for workers consist of spilling flumioxazin onto the hands (Worksheet C03a) and spilling a solution of flumioxazin onto the lower legs for one hour (Worksheet C03b). These dermal exposures are described as "second order" in that some (but not all) of the flumioxazin solution adheres to the skin. The absorbed dose is then calculated as the product of the amount of flumioxazin on the skin surface, the first-order absorption rate coefficient, and the duration of exposure. The calculations used to derive the first-order absorption rate coefficient are shown in Worksheet B03b.

The direct contact and accidental spill scenarios are detailed in Worksheets C02a (contaminated gloves, one-minute exposure), C02b (contaminated gloves, one-hour exposure), C03a (spill on hands, one-hour exposure), and C03b (spill on lower legs, one-hour exposure). The calculated exposure doses for workers to flumioxazin (central, lower, and upper estimates) associated with accidental/incidental exposure scenarios are reported in Table 5.2-2 and Worksheet E01.

Table 5.2-2: Accidental/Incidental Worker Exposure Doses (mg a.i./kg/day or mg a.i./kg/event)

Scenario	Lower Dose	Central Dose	Upper Dose	Worksheet
Spray: Backpack Application (Attachment 1)				
Direct Contact to Surface Area of Hands for 1 Minute	5.38E-05	8.51E-05	1.35E-04	C02a
Direct Contact to Surface Area of Hands for 1 Hour	3.23E-03	5.10E-03	8.09E-03	C02b
Accidental Spill on Hands for 1 Hour	2.72E-05	6.41E-05	1.52E-04	C03a
Accidental Spill on Lower Legs for 1 Hour	6.82E-05	1.61E-04	3.81E-04	C03b
Spray: Boom Ground Application (Attachment 2)				
Direct Contact to Surface Area of Hands for 1 Minute	3.10E-04	4.91E-04	7.78E-04	C02a
Direct Contact to Surface Area of Hands for 1 Hour	1.86E-02	2.945E-02	4.67E-02	C02b
Accidental Spill on Hands for 1 Hour	1.57E-04	3.70E-03	8.77E-04	C03a
Accidental Spill on Lower Legs for 1 Hour	3.93E-04	9.27E-04	2.19E-03	C03b
Spray: Aircraft Aerial Application (Attachment 3)				
Direct Contact to Surface Area of Hands for 1 Minute	4.75E-04	7.53E-04	1.19E-03	C02a
Direct Contact to Surface Area of Hands for 1 Hour	2.86E-02	4.52E-02	7.15E-02	C02b
Accidental Spill on Hands for 1 Hour	2.40E-04	5.673E-04	1.34E-03	C03a
Accidental Spill on Lower Legs for 1 Hour	6.03E-04	1.42E-03	3.37E-03	C03b
Direct Water Application - Surface (Attachment 4)				
Direct Contact to Surface Area of Hands for 1 Minute	2.89E-04	4.58E-04	7.26E-04	C02a
Direct Contact to Surface Area of Hands for 1 Hour	1.74E-02	2.75E-02	4.35E-02	C02b
Accidental Spill on Hands for 1 Hour	1.46E-04	3.45E-04	8.18E-04	C03a
Accidental Spill on Lower Legs for 1 Hour	3.67E-04	8.65E-04	2.05E-03	C03b
Direct Water Application - Subsurface (Attachment 5)				
Direct Contact to Surface Area of Hands for 1 Minute	1.35E-02	2.13E-02	3.37E-02	C02a
Direct Contact to Surface Area of Hands for 1 Hour	8.07E-01	1.27E+00	2.02E+00	C02b
Accidental Spill on Hands for 1 Hour	6.80E-03	1.60E-02	3.79E-02	C03a
Accidental Spill on Lower Legs for 1 Hour	1.70E-02	4.02E-02	9.51E-02	C03b

Scenario	Lower Dose	Central Dose	Upper Dose	Worksheet
Ground Application - Granule (Attachment 6)				
Direct Contact to Surface Area of Hands for 1 Minute	1.86E-07	2.94E-07	4.66E-07	C02a
Direct Contact to Surface Area of Hands for 1 Hour	1.12E-05	1.77E-05	2.79E-05	C02b

Note: The lower and upper dose represent the 95% confidence interval.
Ground application – granules does not include accidental spill scenarios.

5.2.2. General Public

5.2.2.1. General Considerations

The likelihood that individuals from the general public will be exposed to flumioxazin depends on the application method and where the pesticide is applied. The FS might use flumioxazin for control of aquatic vegetation; terrestrial weeds and invasive plants, such as managing forest vegetation in roadsides, utility corridors, hardscapes, and conifer and hardwood production areas; as well as release or restoration of desirable vegetation in wildlife management areas, recreational areas, fire rehabilitation areas, natural areas, prairies, and fire breaks. Although some of these applications might be made at locations remote from the general public, exposures to members of the general public cannot be excluded. The exposure scenarios developed for the general public are summarized in Worksheet E03 of Attachments 1 – 6. In addition, details about the assumptions and calculations for the general public exposure scenarios are provided in Worksheets D01 through D10. The general public exposure scenarios include accidental acute exposures, non-accidental acute exposures, and longer-term or chronic exposures. Unlike worker exposures which focus on dermal exposure, scenarios for exposure of the general population include both dermal and oral exposure.

FS risk assessments are based on *Extreme Values* rather than a single value (SERA 2014a). Extreme Values are used to assess the most plausible estimate of exposure (referred to statistically as the central or maximum likelihood estimate) with extreme lower and upper bounds of plausible exposures. This approach is drawn on the concept of the *Most Exposed Individual*, which may also be referred to as the *Maximum Exposed Individual* (MEI). The MEI is estimated as the extreme but plausible upper bound of the distribution of individual exposures. This estimate involves many conservative assumptions and is used by U.S. EPA and other government agencies.

For FS risk assessments, the upper bounds on exposure estimates are based on the MEI. The central and lower estimates of exposure are also provided and are used to assess the feasibility of mitigation such as protective measures to limit exposure. If the lower bound exposure estimates exceed a level of concern (LOC), this is a strong indication that the pesticide cannot be used in a manner that will lead to acceptable risk (SERA 2014a).

The accidental exposure scenarios for the general public assume that an individual is exposed to flumioxazin during or shortly after direct spray application or an accidental spill. Non-accidental exposures involve dermal contact with treated or contaminated vegetation and the consumption of treated or contaminated fruit, vegetation, water, or fish. Potential risks associated with swimming in treated or contaminated water are also assessed in the non-accidental exposures. The longer term

or chronic exposure scenarios are the same as the acute exposure scenarios for the consumption of contaminated fruit, water, or fish.

Accidental and non-accidental exposure scenarios for the general public are described in the following subsections. The nature of the acute accidental exposure scenarios is intentionally extreme. In contrast, the acute non-accidental exposure scenarios are intended to be conservative but plausible. For longer-term or chronic exposures, it is assumed that an individual will consume either treated or contaminated vegetation, fruits, or water from a treated area every day over a prolonged period of time. While this type of exposure cannot be completely ruled out, the likelihood of such exposures is low.

5.2.2.2. Dermal Exposure from Direct Spray

Two direct spray scenarios were evaluated: one for a child (body weight 11 kg) and one for an adult female of child-bearing age (body weight 69 kg). The scenarios are modeled in a manner similar to accidental spills for workers in that it is assumed that the individual is sprayed with a flumioxazin solution and the amount of solution remaining on the skin is absorbed by first-order kinetics (SERA 2014a). For the child scenario, it is assumed that a child is sprayed directly (backpack, boom, and aerial applications) and that 100% of the body surface area is exposed. This scenario is intentionally extreme, and the upper limits of this exposure scenario are intended to represent the Extreme Value upper limits of exposure for the MEI (SERA 2014a).

The exposure scenario for an adult woman sprayed accidentally with flumioxazin is less extreme compared to the child. In this scenario, it is assumed that the lower legs and feet are accidentally sprayed with flumioxazin. A female, rather than a male, is used in this risk assessment to be conservative given that, at the same exposure rate, a female would typically be subject to a higher dose per kg of body weight. The assumptions and calculation of doses associated with these exposure scenarios are reported in Worksheets D01a (child) and D01b (adult female) for the ground spray application methods (backpack, boom) and spray aerial application method. These exposure scenarios are not applicable to the direct water application methods or the ground application of granules. Table 5.2-3 shows the central absorbed doses for the child and adult for the three spray application methods. Aerial application results in the highest central absorbed dose from the three application methods for this accidental acute exposure. Lower and upper doses can be found on worksheets D01a and D01b in Attachment 1 for backpack application, Attachment 2 for boom application, and Attachment 3 for aerial application.

Table 5.2-3: Accidental Acute Direct Spray Dermal Exposure Central Doses (mg a.i./kg bw)

Scenario	Receptor	Spray - Backpack	Spray - Boom	Spray - Aircraft
Direct spray of child, whole body	Child	2.82E-03	1.63E-02	2.50E-02
Direct spray of female, feet and lower legs	Adult Female	2.60E-04	1.53E-03	2.34E-03

5.2.2.3. Dermal Exposure from Treated or Contaminated Vegetation

Dermal exposure from treated or contaminated vegetation applies to spray application methods only (backpack, boom and aerial); exposure from treated or contaminated vegetation is not

applicable for the ground application using granules or the direct water application methods. For this exposure scenario**,** it is assumed that flumioxazin is sprayed onto vegetation and that an adult female contacts the vegetation at some period after the spray operation. In order to estimate this scenario, the dislodgeable residue (a measure of the amount of the flumioxazin that could be freed from the vegetation) and the rate of transfer of the herbicide from the vegetation to the surface of the skin must be provided.

Data are not available on the dislodgeable residue or dermal transfer rates for flumioxazin. However, because dermal transfer rates are reasonably consistent for numerous pesticides (SERA 2014a), the dermal transfer rates are used as defined in Worksheets D02 for spray application methods (backpack, boom, and aerial).

For spray scenarios, a default dislodgeable residue rate of 0.1 of the flumioxazin application rate is assumed, which is based on liquid applications (SERA 2014a). The exposure scenario also assumes a contact period between skin and vegetation of one hour and that the herbicide is not effectively removed by washing for 24 hours. The assumptions and calculations of doses associated with these exposure scenarios are reported in Worksheet D02 and the resulting central dose is 1.28E-03 mg/kg-bw for the backpack, boom, and aerial application methods.

5.2.2.4. Contaminated Water

To estimate exposure of human receptors to flumioxazin, it is necessary to estimate flumioxazin levels in environmental media. Contamination of environmental media might result from spray applications, accidental spills, and other chronic exposures. The following subsections describe how flumioxazin exposures are estimated for surface water in a small pond after an accidental spill, accidental direct spray, or incidental spray drift to a small stream and pond, and contamination to non-target fields or bodies of water at peak and longer-term concentrations.

5.2.2.4.1. Concentrations in Small Pond After Accidental Spill

Flumioxazin concentrations in the surface water of a small pond were estimated for accidental spill exposure scenarios (Worksheet D05). In this scenario, it is assumed that a child consumes contaminated water shortly after an accidental spill of flumioxazin into a small pond. Given that the scenario is based on the assumption that exposure occurs shortly after the spill, no environmental degradation of the pesticide is assumed, and the pesticide is considered to be uniformly dispersed in the pond. It is also assumed that the small pond has a surface area of one-quarter of an acre (1000 m^2) and a depth of one meter, resulting in a pond volume of 1000 m^3 or 1,000,000 liters. This is a standard assumption in FS risk assessments (SERA 2014a).

For applications involving liquid formulations, a spill volume of the mixed application solution with a central tendency of 100 gallons is assumed, ranging from 20 to 200 gallons to reflect plausible spill events. As summarized in Worksheet B04b, the estimated concentration of flumioxazin in the hypothetical small pond are dependent on the application method:

- Spray Backpack Application – pond water concentrations range from 0.039 to 0.39 mg/L, with a central estimate of approximately 0.19 mg/L (Attachment 1, B04b)
- Spray Boom Application – pond water concentrations range from 0.2271 to 2.271 mg/L, with central estimate of approximately 1.135 mg/L (Attachment 2, B04b)

- Spray Aerial Application – pond water concentrations range from 0.3482 to 3.4822 mg/L, with central estimate of approximately 1.7411 mg/L (Attachment 3, B04b)
- Direct Water Surface Application – pond water concentrations range from 0.21196 to 2.1196 mg/L, with a central estimate of approximately 1.0598 mg/L (Attachment 4, B04b)
- Direct Water Subsurface Application – pond water concentrations range from 9.841 to 98.41 mg/L, with a central estimate of approximately 49.205 mg/L, which is significantly higher than the application rate concentrations of 0.2 to 0.4 mg/L (Attachment 5, B04b)
- Granule Ground Application – pond water concentrations range from 7.257 to 36.288 mg/L, with central estimate of approximately 18.144 mg/L (Attachment 6, B04b)

5.2.2.4.2. Concentrations in Small Pond or Stream After Accidental Direct Spray/Incidental Spray Drift

These scenarios involve the accidental direct spray or incidental spray drift to a small pond (Worksheet B04c) and a small stream (Worksheet B04d) for the spray backpack, boom, and aerial application methods. The concentrations of flumioxazin in a pond and stream are based on the estimates of drift adapted from AgDRIFT (aerial spray prediction model from ground boom and air-blast applications). AgDRIFT permits very detailed modeling of drift based on the chemical and physical properties of the applied product, the configuration of the aircraft, wind speed, and temperature for aerial applications. While the drift estimates used in this risk assessment are intended to be conservative, estimates can be refined for site-specific application.

5.2.2.4.3. Concentrations in Non-Target Fields or Bodies of Water After Treatment (GLEAMS-Driver Modeling)

GLEAMS-Driver was used in this risk assessment to model peak and longer-term (non-accidental) flumioxazin concentrations in surface water. GLEAMS-Driver was developed to support FS risk assessments and serves as a preprocessor and postprocessor for GLEAMS (Groundwater Loading Effects of Agricultural Management Systems). GLEAMS is a field-scale model developed by the USDA/Agricultural Research Station (ARS), which the FS and other USDA agencies use to provide direct estimates of concentrations and/or amounts of pesticides in and losses of pesticides from treated fields. This output may then be used to estimate concentrations of pesticides in either non-target fields or bodies of water (pond or stream) that are immediately adjacent to the treated field. Additional information on GLEAMS-Driver is provided in the *GLEAMS-Driver User Guide* (SERA 2007).

GLEAMS-Driver allows users to derive exposure estimates using a number of site-specific conditions, including weather patterns; soil types; physical characteristics of the treated field, as well as the non-target field and bodies of water; and chemical properties.

Site-specific weather data are generated using WEPP (Watershed Erosion Prediction Project), which is a climate simulation generator developed and maintained by the USDA/ARS (USDA/NSERL 2019). WEPP was utilized to generate 1000-year climate simulations that were incorporated into the GLEAMS-Driver. As summarized in Table 5.2-4, nine standard site conditions are used in the GLEAMS-Driver simulations that represent combinations of precipitation (dry, average, and wet) and temperature (hot, temperate, and cool). These nine locations are the standard sites used for generic FS risk assessments (SERA 2014a, 2007).

Table 5.2-4: Precipitation, Temperature and Classifications for Standard Test Sites

Location	Precipitation	Temperature	Average Annual Rainfall (inches)	Average Annual Temperature (◦F)
HI, Hilo	Wet	Warm	126.06	73.68
WA, Quillayute	Wet	Temperate	95.01	49.14
NH, Mt. Washington	Wet	Cool	98.49	27.12
FL, Key West	Average	Warm	37.68	77.81
IL, Springfield	Average	Temperate	34.09	52.79
MI, Sault Ste. Marie	Average	Cool	32.94	40.07
AR, Yuma Test Station	Dry	Warm	3.83	73.58
CA, Bishop	Dry	Temperate	5.34	56.02
AK, Barrow	Dry	Cool	4.49	11.81

Note: WA, Quillayute based on composite estimation in WEPP using a latitude of 47.94 N and a longitude of -124.54 W.

The soil types and physical characteristics of the fields and bodies of water selected in GLEAMS-Driver are summarized in Table 5.2-5. For each location, simulations were conducted using clay (high runoff, low leaching potential), loam (moderate runoff, moderate leaching potential), and sand (low runoff, high leaching potential) soil textures. In addition, for each combination of location and soil, GLEAMS-Driver was used to simulate flumioxazin losses to surface water from 100 modeled applications at a unit application rate of 1 lb a.i./acre, with simulations followed 1.5 years post application. While the application rate of 1 lb a.i./acre is used as a convention in FS risk assessments in order to avoid rounding limitations in the GLEAMS-Driver outputs, all exposure concentrations discussed are based on the maximum single application rate of 0.38 lb a.i./acre. Multiple applications are not considered in this assessment because flumioxazin is not persistent in the environment due to rapid degradation. This adjustment is shown in Worksheet B04a, where the application rate is multiplied by the water contamination rates (mg/L per lb/acre) to estimate the expected concentrations of flumioxazin.

Table 5.2-5: Input Parameters for Fields and Water Bodies Used in GLEAMS-Driver Modeling

Field Characteristics	Description	Pond Characteristics	Description
Type of site and surface (FOREST)	Field (0)	Surface area	1 acre
Treated and total field areas	10 acres	Drainage area	10 acres
Field width	660 feet	Initial depth	2 meters
Slope	0.1 (loam and clay) 0.05 (sand)	Minimum depth	1 meter
Depth of root zone	36 inches	Maximum depth	3 meters
Cover factor	0.15	Relative sediment depth	0.01
Type of clay	Mixed		
Surface cover	No surface depressions		

Stream Characteristics	Value
Width	2 meters
Flow Velocity	6900 meters/day
Initial Flow Rate	710,000 liters/day

GLEAMS Crop Cover Parameters	Description	Value
ICROP	Weeds	78
CRPHTX	Maximum height in feet	3
BEGGRO	Julian day for starting growth	32
ENDGRO	Julian day for ending growth	334

Application, Field, and Soil Specific Factors	Code	Clay	Loam	Sand
Percent clay (w/w/)	CLAY	50%	20%	5%
Percent silt (w/w/)	SILT	30%	35%	5%
Percent sand (w/w/)	NA	20%	45%	90%
Percent Organic Matter	OM	3.7%	2.9%	1.2%
Bulk density of soil (g/cc)	BD	1.4	1.6	1.6
Soil porosity (cc/cc)	POR	0.47	0.4	0.4
Soil erodibility factor (tons/acre)	KSOIL	0.24	0.3	0.02
SCS Runoff Curve Number [2]	CN2	83	70	59
Evaporation constant (mm/d)	CONA	3.5	4.5	3.3
Saturated conductivity below root zone (in/hr)	RC	0.087	0.212	0.387
Saturated conductivity in root zone (in/hr)	SATK	0.087	0.212	0.387
Wilting point (cm/cm)	BR15	0.28	0.11	0.03
Field capacity (cm/cm)	FC	0.39	0.26	0.16

Note: Application, field and soil specific factors from Knisel and Davis 2000 (Table H-4), *Clay*: Group D, Dirt, upper bound; *Loam*: Group C, woods, fair condition, central estimate; *Sand*: Group A, meadow, good condition, central estimate. Codes used in documentation for GLEAMS (Knisel and Davis 2000) and GLEAMS-Driver (SERA 2007).

The chemical-specific inputs that were used in GLEAMS-Driver are provided in Table 5.2-6. The inputs are based on the environmental fate studies submitted to U.S. EPA by the registrant and the standard values for GLEAMS modeling recommended by Knisel and Davis (2000). These inputs are shown as ranges or confidence intervals.

Table 5.2-6: Chemical-Specific Parameters Used in GLEAMS-Driver Modeling

Parameter	Values	Note
Aquatic Sediment Half-Life (days)	0.54	U.S. EPA 2009
Foliar Half-Life (days)	20	U.S. EPA 2003
Soil Half-Life (days)	23.4	U.S. EPA 2009
Water Half-Life (days)	0.96	Value used by U.S. EPA/OPP (U.S. EPA/OPP 2003).
Soil Koc (L/kg)	670	U.S. EPA 2009
Sediment Kd (L/kg)	4.53	U.S. EPA 2009
Water Solubility (mg/L)	1.8	U.S. EPA 2003
Foliar Washoff Fraction (unitless)	0.40	Knisel and Davis 2000

Parameter	Values	Note
Fraction Applied to Foliage (unitless)	0.5	A foliar fraction of 0.5 is used in GLEAMS-driver by default for liquid formulations. (0.0 for broadcast soil).
Coefficient of Transformation (unitless)	1	A default value of 1 is used when metabolites are not being modelled.
Coefficient of Uptake (unitless)	1	A default value of 1 is used for pesticides absorbed by plants.
Depth to Soil Incorporation (cm)	1	Standard assumption
Irrigation after Application	None	NA

The results of the modeled concentrations of flumioxazin in surface water are summarized in Table 5.2-7 and include an average of central values, a lower bound (30th percentile of lower bounds), and an upper bound (maximum value). In addition, the outputs of the GLEAMS-Driver simulations are provided in Appendix 10: Flumioxazin Arial Broadcast Foliar GLEAMS-Driver Modeling Results, which include the off-site application rate, flumioxazin concentrations in the top 12 and 36 inches of soil, maximum penetration into the soil column, and peak and longer-term flumioxazin concentrations in a small pond and stream. As shown in Appendix 10, GLEAMS was run for broadcast application of 50% foliar and 50% soil (Appendix Table A10-1) and 100% soil for the granular application (Appendix 10-2).

The results of the small stream simulations provide the highest estimates of flumioxazin in surface water. The specific concentrations of flumioxazin in surface water used in the exposure assessment are discussed in Section 5.2.2.4.5.

Table 5.2-7: Summary of Modeled Concentrations in Surface Water

Scenario/Source	Peak Concentrations (ppb a.i. or µg a.i./L per lb a.i./acre)		Long-Term Average Concentrations (ppb a.i. or µg a.i./L per lb a.i./acre)	
	Soil Type	Concentration	Soil Type	Concentration
Pond (See Appendix 10: Flumioxazin Arial Broadcast Foliar GLEAMS-Driver Modeling Results, Tables 7 and 8)	Clay	5.93 (0.20 – 44.80)	Clay	0.27 (0.01 – 8.05)
	Loam	2.17 (0.0 – 20.70)	Loam	0.04 (0.0 – 0.28)
	Sand	1.58 (0.0 – 22.90)	Sand	0.02 (0.0 – 0.61)
	Average	3.23 (0.0 – 44.80)	Average	0.11 (0.0 – 8.05)
Stream (See Appendix 10: Flumioxazin Arial Broadcast Foliar GLEAMS-Driver Modeling Results, Tables 5 and 6)	Clay	14.41 (0.60 – 82.80)	Clay	0.25 (0.0 – 1.57)
	Loam	9.75 (0.0 – 75.90)	Loam	0.13 (0.0 – 1.10)
	Sand	7.66 (0.0 – 88.50)	Sand	0.08 (0.0 – 0.88)
	Average	10.45 (0.0 – 88.50)	Average	0.16 (0.0 – 1.57)

Note: Concentrations are the average of central estimates (95% upper and lower bound).

5.2.2.4.4. Monitoring Data

Monitoring studies can be useful for comparing concentrations measured in the field with concentrations predicted by a mathematical model such as GLEAMS and models used by U.S. EPA/OPP. When available, such studies can provide a strong indication of the plausibility of modeled concentrations of a pesticide in surface water. No such studies were identified for flumioxazin.

5.2.2.4.5. Concentrations in Water Used for Risk Assessment

The modeled surface water concentrations used in this risk assessment for the six application scenarios are summarized in Table 5.2-8. As discussed in SERA 2014a, the concentrations are specified as water contamination rates (WCRs), which are the concentrations in water expected at a normalized application rate of 1 lb a.i./acre, converted to units of ppm or mg a.i./L per lb a.i./acre. These WCRs are included in Worksheet B04Rt and are adjusted based on an application rate of 0.38 lb a.i./acre as shown in Worksheet B04a.

The flumioxazin concentrations in surface water (pond and stream scenarios) from runoff for spray and granular applications are shown in Table 5.2-8; the highest concentrations were used in the risk assessment. Concentrations are also included for surface and subsurface applications. The pond size assumed in the direct surface application was 10 acres (depth: 2 to 10 feet, see worksheet B04a for water surface applications). For GLEAMS simulations of secondary transfers to a pond, surface area is 1 acre and depth is 1 to 3 meters (see Table 5.2-5). Predicted concentrations for each exposure scenario are used (e.g., swimming in pond impacted by direct application to pond or secondarily by terrestrial or aerial application).

Table 5.2-8: Concentrations in Surface Water Used in this Risk Assessment

Estimate	Peak WCR (mg a.i./L per lb a.i./acre)		Longer Term WCR (mg a.i./L per lb a.i./acre)	
Spray Applications (Backpack, Boom, Aircraft)	Pond	Stream	Pond	Stream
Central	3.2E-03	1.1E-02	1.1E-04	1.6E-04
Lower (30th percentile)	9.5E-08	3.1E-07	8.3E-10	1.4E-09
Upper	4.5E-02	8.9E-02	8.2E-03	1.6E-03
Direct Water Application - Surface				
Central	1.4E-02		2.1E-05	
Lower	6.9E-03		1.4E-06	
Upper	6.9E-02		4.7E-03	
Direct Water Application - Subsurface				
Central	4.0E-01		6.2E-04	
Lower	4.0E-01		8.3E-05	
Upper	4.0E-01		0.27E-02	
Granule Application	Pond		Stream	
Central	4.6E-03		2.0E-02	

Estimate	Peak WCR (mg a.i./L per lb a.i./acre)	Longer Term WCR (mg a.i./L per lb a.i./acre)
Lower (30th percentile)	2.7E-07	8.3E-07
Upper	3.4E-02	1.8E-01

WCR (Water contamination rates) – concentrations in units of mg a.i./L expected at an application rate of 1 lb a.i./acre. Units of mg a.i./L are used in the Excel workbooks that accompany this risk assessment.

5.2.2.5. Oral Exposure from Contaminated Fish

Chemicals may be concentrated or partitioned from water into the tissues of aquatic animals or plants. This process is referred to as bioconcentration. Bioconcentration is measured as the ratio of the concentration in the organism to the concentration in the water. For example, if the concentration in the organism is 5 mg/kg bw and the concentration in the water is 1 mg/L, the BCF is 5 L/kg [5 mg/kg bw ÷ 1 mg/L]. As with most absorption processes, bioconcentration depends initially on the duration of exposure but eventually reaches steady state. Additional information regarding bioconcentration is provided in SERA 2014a.

Three exposure scenarios are presented and include: acute exposures following an accidental spill (Worksheets D08a and D08b), acute exposures based on expected peak concentrations in water (Worksheets D09c and D09d), and chronic exposures based on estimates of longer-term concentrations in water (Worksheets D09a and D09b).

The accidental spill scenario assumes that an adult male consumes fish from a small pond shortly after an accidental spill of flumioxazin into the pond. The amount of flumioxazin in edible fish tissue consumed by the adult male is based on a study of bioconcentration of flumioxazin in bluegill. The calculation of flumioxazin doses associated with fish consumption are provided in Attachments 1 – 6 Worksheet D08a. Fish consumption by a subsistence population is also provided and detailed in Worksheet D08b. While the probability of this scenario is unlikely, this scenario assumes that the adult male is dependent on fish consumption for a substantial amount of the diet.

The acute exposure scenarios are based on the maximum peak exposure concentrations (modeled by GLEAMS-Driver). The amount of flumioxazin in edible fish tissue is based on use of the lower measured BCF in edible fish tissues. The calculation of flumioxazin doses associated with fish consumption are provided in Worksheets D09c (adult male) and D09d (subsistence populations) for acute exposure scenarios. The longer-term exposure scenarios are presented in Worksheets D09a (adult male) and D09b (subsistence populations). Table 5.2-9 also includes a summary of the central doses calculated for fish consumption. The lower and upper doses are shown in the Worksheets as described above.

Table 5.2-9: Fish Consumption Central Doses (mg a.i./kg bw/day or mg a.i./kg bw/event)

Scenario	Receptor	Spray-Backpack	Spray-Boom	Spray-Aircraft	Water-Surface	Water-Subsurface	Granules
Fish consumption (spill) (D08a)	Adult Male	8.1E-03	4.7E-02	7.2E-02	4.4E-02	2.0E+00	7.5E-01
Fish consumption (spill) (D08b)	Subsistence Populations	4.2E-02	2.4E-01	3.8E-01	2.3E-01	1.1E+01	3.9E+00

Scenario	Receptor	Spray-Backpack	Spray-Boom	Spray-Aircraft	Water-Surface	Water-Subsurface	Granules
Fish consumption (acute) (D09c)	Adult Male	1.7E-04	1.7E-04	1.7E-04	5.6E-04	1.6E-02	3.1E-04
Fish consumption (acute) (D09d)	Subsistence Populations	9.0E-04	9.0E-04	9.0E-04	3.0E-03	8.6E-02	1.6E-03
Fish consumption (chronic) (D09a)	Adult Male	1.1E-07	1.1E-07	1.1E-07	5.5E-08	1.6E-06	1.2E-07
Fish consumption (chronic) (D09b)	Subsistence Populations	9.5E-07	9.5E-07	9.5E-07	4.8E-07	1.4E-05	1.1E-06

5.2.2.6. Dermal Exposure from Swimming in Treated or Contaminated Water

Some of the sites maintained by the FS include surface waters in which the general public might swim (SERA 2014a). It is unknown if this scenario will apply to areas where flumioxazin will be used, but it has been considered as part of this risk assessment.

To assess potential risks associated with swimming in treated or contaminated water, an exposure scenario was developed of an adult female swimming in surface water for one hour (Attachments 1 – 6, Worksheet D10). The one-hour exposure period is arbitrary but provides for a unit exposure estimate where absorbed dose (and risk) will theoretically increase linearly with the duration of exposure. For example, a two-hour exposure would lead to an HQ that is twice as high as the associated exposure period of one hour. Central, low, and upper doses are shown on Table 5.2-10. The estimated doses for the backpack, boom and aerial application are the same. Direct water subsurface application was predicted to result in the highest doses.

Table 5.2-10: Adult Female Swimming-Doses (mg a.i./kg bw/day or mg a.i./kg bw/event)

	Spray Applications (Backpack, Boom, Aircaft)	Water-Surface	Water Subsurface	Granules
Central	8.5E-07	1.0E-06	3.2E-05	1.5E-06
Low	1.5E-11	3.3E-07	2.0E-05	4.0E-11
Upper	1.1E-05	8.3E-06	5.1E-05	2.2E-05

5.2.2.7. Oral Exposure from Treated or Contaminated Vegetation

FS risk assessments include standard exposure scenarios for the acute and longer-term/chronic consumption of treated or contaminated vegetation if a pesticide may be applied to vegetation. Two sets of exposure scenarios are considered: one for the consumption of treated or contaminated fruit and the other for the treated or contaminated vegetation. These scenarios are presented in Attachments 1 – 3 Worksheets D03a (fruit) and D03b (vegetation) for acute exposure and Worksheets D04a (fruit) and D04b (vegetation) for chronic exposure. The estimated central doses for spray backpack, boom, and aerial application scenarios are shown on Table 5.2-11. Lower and Upper estimates can be found in Attachments 1 – 3 Worksheets D03a and D03b.

Table 5.2-11: Non-Accidental Consumption of Treated or Contaminated Vegetation, Central Doses (mg a.i./kg bw)

Scenario	Receptor	Backpack, Boom, and Aircraft Application Methods
Contaminated fruit consumption	Adult Female	Acute: 4.47E-03 Chronic: 4.15E-04
Contaminated vegetation consumption	Adult Females	Acute: 6.16E-02 Chronic: 5.72E-03

The initial pesticide concentration on fruit and vegetation is estimated using the empirical relationships between application rate and concentration on different types of vegetation (SERA 2014a). The residue rates typically used in FS risk assessments for liquid formulations are provided by Fletcher et al. (1994). These rates are presented in Table 5.2-12 and provide estimates of pesticide concentrations on different types of vegetation (mg chemical/kg vegetation) at a normalized application rate of 1 lb a.i./acre. While the application rate of 1 lb a.i./acre is used as a convention in FS risk assessments in order to avoid rounding limitations in the GLEAMS-Driver outputs, all exposure concentrations discussed are based on the maximum single application rate of 0.38 lb a.i./acre. Multiple applications are not considered in this assessment because flumioxazin is not persistent in the environment due to rapid degradation. Although the human health risk assessments conducted by U.S. EPA do not consider this exposure scenario, the residue rates recommended by Fletcher et al. (1994) are typically used by U.S. EPA/OPP in ecological risk assessments.

Table 5.2-12: Estimated Residue Rates in Food Items

Food Item	Lower	Central	Upper
Spray Applications (mg a.i./kg wet weight per lb a.i./acre applied)			
Short grass	30	85	240
Tall grass	12	36	110
Broadleaf/forage plants and small insects	15	45	135
Fruits, pods, seeds, and large insects	3.2	7	15

Fletcher et al. (1994) provide only central and upper bound estimates of residue rates. The assessment team estimated the lower bound residues based on the assumption that the ratio of the central estimate to the upper bound estimate is identical to the ratio to the lower bound estimate. This is consistent with previous FS risk assessments (SERA 2014a). Fletcher et al. (1994) provide residue rates for four different classes of plant material, including short grass, tall grass, broadleaf vegetation, and fruits. While all four groups of plant material are used in the ecological risk assessment, only broadleaf vegetation and fruit are used in the human health risk assessment.

For longer-term exposures, the time-weighted-average concentrations are estimated using the initial pesticide concentration, the half-life on vegetation, the number of applications, and the application interval. These calculations are detailed in Worksheets B05a (fruit), B05b (broadleaf vegetation), B05c (short grass), and B05d (long grass).

5.3. Dose-Response Assessment

5.3.1. Overview

The dose-response assessment describes the degree or severity of risk as a function of dose and is generally based on reference values, or toxicity values, such as RfDs (SERA 2014a). RfDs are estimates of doses at which adverse effects are not anticipated. FS risk assessments typically defer to U.S. EPA/OPP in the derivation of reference values used in the human health risk assessment unless there is a compelling reason to differ. Relevant RfDs and toxicity values for flumioxazin developed by U.S. EPA (2012) are summarized in Table 5.3-1. Note that the proposed use patterns for flumioxazin are expected to result in dermal, inhalation, and incidental oral exposures of short- and intermediate-term durations. Because long-term dermal and inhalation exposures are not expected, these endpoints are not assessed for the general population or workers.

Table 5.3-1: U.S. EPA (2012) RfDs for Flumioxazin

Exposure Scenario	Point of Departure (Effect)	Uncertainty Factors	RfD or Toxicity Value
General Population			
Acute dietary, females only	NOAEL: 3 mg/kg/day (cardiovascular effects in fetuses)	UF_A: 10 UF_H: 10	0.03 mg/kg/day
Acute dietary, general population	Not derived		
Incidental exposure (1 – 30 days) and intermediate term (1 – 6 months)	NOAEL: 6.3 mg/kg/day (testicular atrophy and decreased pup weight[1])	MOE: 100	0.063 mg/kg/day
Chronic dietary, all populations	NOAEL: 2 mg/kg/day (nephropathy and hematological effects)	UF_A: 10 UF_H: 10	0.02 mg/kg/day

[1]EPA (2012) derived an RfD of 0.063 mg/kg/day for Incidental Oral Short (1 – 30 days) and Intermediate Term (1 – 6 months) for Dietary Exposure (non-occupational) based on results of MRID 42684935. EPA (2012) listed the effects associated with the LOAEL of 6.3 mg/kg/day as "decreased pup body weight and testicular atrophy in F1 males". However, the DER for MRID 42684935 stated that testicular atrophy was observed only at the highest dose tested of 18.9 mg/kg/day. According to the DER, testicular effects were not evaluated in rats exposed to 6.3 and 12.7 mg/kg/day.

Abbreviations: LOAEL = lowest-observed-adverse-effect level; MOE: margin of exposure; an MOE of 100 is equivalent to a composite uncertainty factor of 100 (10 for intraspecies variation and 10 for intraspecies variation); NOAEL = no-observed-adverse-effect level; RfD = reference dose; UF_A: interspecies uncertainty factor (extrapolation from animal to human); UF_H: Intraspecies uncertainty factor (intraspecies sensitivity)

U.S. EPA (2012) derived an acute oral RfD of 0.03 mg a.i./kg/day for females based on a gestational exposure study in rats, with NOAEL and LOAEL values of 3 and 10 a.i./kg/day, respectively, for fetal cardiovascular abnormalities (MRID 42684925). Although the exposure duration in this study was multiple days (GD 6 – 15), U.S. EPA/OPP generally regards effects on offspring as potentially associated with an acute exposure on a single day. Because the basis of this acute RfD is developmental effects resulting from exposure during gestation, it is applicable to women of child-bearing potential, and not to all portions of the general population (e.g., males, children, and elderly). U.S. EPA (2012) declined to develop an acute RfD for the general population, stating that

"no appropriate toxicological effects attributable to a single exposure were observed in oral toxicity studies." For incidental exposure of 1 – 30 days, an intermediate exposure of 1 – 6 months, U.S. EPA (2012) derived a toxicity value for the general population of 0.063 mg a.i./kg/day. This value is based on results of a 2-generation reproduction study in rats, with NOAEL and LOAEL values of 6.3 and 12.7 a.i./kg/day, respectively, for testicular atrophy in F1 males and decreased pup body weight (MRID 42684935). However, according to the DER for this study, microscopic examination of the testes was only assessed in the control and high dose (18.9 mg/kg/day) groups (See the footnote in Table 5.3-1 and Section 5.1.9.2 for additional details on testicular effects observed in this study). For chronic exposure, U.S. EPA (2012) derived a chronic RfD of 0.02 mg a.i./kg/day for all populations, based on results of a 24-month study in rats, with NOAEL and LOAEL values of 1.8 and 18.0 mg a.i./kg/day, respectively, for nephropathy in males and decreased hematological parameters in females (MRID 44295028).

5.3.2. Acute RfD

To assess human health risks associated with acute exposure to flumioxazin, the FS has selected two acute toxicity values: (1) the U.S. EPA (2012) acute RfD of 0.03 mg a.i./kg/day for females of childbearing potential, and (2) a surrogate acute RfD of 0.062 mg a.i./kg/day to assess risks to the general population (Table 5.3-2). As noted above, the acute RfD for females derived from the gestational exposure study (MRID 42684925) is not applicable to the general population, and U.S. EPA (2012) did not derive an acute RfD for the general population. The acute toxicity database for flumioxazin consists of single dose lethality studies in rats (reviewed in Section 5.1.4). Results of these studies show that no lethality or adverse effects were observed at the highest doses administered (2000 – 5000 mg a.i./kg/day); therefore, data are not appropriate for derivation of an acute RfD. The FS evaluated possible surrogate RfDs to assess acute risks to the general population. To derive a surrogate acute RfD for the general population, the FS considered data from subchronic toxicity studies, recognizing that effects observed in subchronic exposure studies might be due to repeated exposures, rather than a single exposure. However, a short-term exposure duration of a few days is a realistic exposure scenario for the general population. The lowest LOAELs reported in subchronic exposure studies were 60 mg a.i./kg/day (NOAEL: 30 mg a.i./kg/day) for decreased maternal body weight and body weight gain in a gestational exposure study in rats (MRID 49615801) and 12.7 mg a.i./kg/day (NOAEL: 6.3 mg a.i./kg/day) for testicular atrophy in F1 males and decreased pup weight in a 2-generation reproduction study (MRID 42684935). To derive a surrogate acute RfD based on the gestational exposure study, the NOAEL 30 mg a.i./kg/day would be divided by the recommended margin of exposure (MOE) of 100 (SERA 2014a), resulting in a surrogate acute RfD of 0.3 mg a.i./kg/day. Alternatively, to derive a surrogate acute RfD based on the 2-generation reproduction study, the NOAEL of 6.3 mg a.i./kg/day would be divided by the recommended MOE of 100 (SERA 2014a), resulting in a surrogate acute RfD of 0.063 mg a.i./kg/day. This is the same value derived by U.S. EPA (2012) for incidental exposures of 1 – 30 days, which includes a single day exposure. Taking the most conservative approach, the FS adopted the lower surrogate acute RfD of 0.063 mg a.i./kg/day derived by U.S. EPA (2012) for incidental exposure to assess acute risk to the general population. A surrogate acute RfD based on repeated exposures is highly conservative; however, use of this value to assess acute risk would be protective for exposures of the general population.

Table 5.3-2: Acute RfD and Surrogate RfD Used in the Human Health Risk Assessment for Flumioxazin

Element	Derivation of RfD	Reference
Acute Dietary Exposure for Females of Childbearing Potential (Single Exposure)		
NOAEL dose	3 mg a.i./kg/day	U.S. EPA 2012 (Table 4.5.1, page 19) MRID 42684925
LOAEL dose	10 mg a.i./kg/day	
LOAEL effects	Fetal cardiovascular abnormalities	
Species/sex	Rats/females	
Uncertainty factor	100 (10X interspecies extrapolation, 10X intraspecies variability)	
Acute RfD	0.03 mg a.i./kg/day	
Target population	Females of childbearing potential	
Acute Dietary Exposure for All Populations		
NOAEL dose	6.3 a.i./kg/day	U.S.EPA 2012 (Table 4.5.1, page 19) MRID 42684935
LOAEL dose	12.7 a.i./kg/day	
LOAEL effects	Decreased pup weight and number of live pups[1]	
Species/sex	Rats/males and females	
MOE[1]	100	
Surrogate acute RfD	0.063 mg a.i./kg/day	
Target population	All populations	

[1]EPA (2012) derived an RfD of 0.063 mg/kg/day for Incidental Oral Short (1 – 30 days) and Intermediate Term (1 – 6 months) Dietary Exposure (non-occupational) based on results of MRID 42684935 (see Table 5.3-1). EPA (2012) listed the effects associated with the LOAEL of 6.3 mg/kg/day as "decreased pup body weight and testicular atrophy in F1 males". However, the DER for MRID 42684935 stated that testicular atrophy was observed only at the highest dose tested of 18.9 mg/kg/day. According to the DER, testicular effects were not evaluated in rats exposed to 6.3 and 12.7 mg/kg/day. Therefore, for this assessment, the critical effect for MRID 42684935 is identified as decreased pup weight and number of live pups.
[2]MOE: margin of exposure; an MOE of 100 is equivalent to a composite uncertainty factor of 100 (10 for intraspecies variation and 10 for intraspecies variation) (SERA 2014a)
Abbreviations: a.i. = active ingredient; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; mg = milligram; NOAEL = no-observed-adverse-effect level; RfD = reference dose

5.3.3. Chronic RfD

As reviewed in Section 5.3.1, U.S. EPA (2012) derived a chronic RfD for flumioxazin based on the NOAEL value of 1.8 mg a.i./kg/day, with an associated LOAEL of 18 mg a.i./kg/day, for nephropathy in males and decreased hematological parameters in females (MRID 44295028). Review of the chronic toxicity database shows that the LOAEL of 18 mg a.i./kg/day is the lowest LOAEL value reported in chronic toxicity studies (see Sections 5.1.5, Subchronic or Chronic Systemic Toxic Effects and Section 5.1.10, Carcinogenicity and Mutagenicity). The U.S. EPA (2011) chronic RfD was adopted to assess chronic risks to humans. Use of this chronic RfD to assess risks to humans is a conservative approach (Table 5.3-3). Note that U.S. EPA/IRIS (2020) has not derived a chronic RfD for flumioxazin.

Table 5.3-3: Chronic RfD Used in the Human Health Risk Assessment for Flumioxazin

Element	Derivation of RfD	Reference
Chronic Exposure (Lifetime Exposure)		
NOAEL dose	1.8 mg a.i./kg/day	U.S. EPA 2012 (Table 4.5.1, page 19) MRID 44295028
LOAEL dose	18 mg a.i./kg/day	
LOAEL effects	Increased incidence of chronic nephropathy and extramedullary hematopoiesis in males and decreased hematological parameters in females	
Species/sex	Rats/male and female	
Uncertainty factor	100 (10X interspecies extrapolation, 10X intraspecies variability)	
Chronic RfD	0.02 mg a.i./kg/day	
Target population	All populations	

Abbreviations: a.i. = active ingredient; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; mg = milligram; NOAEL = no-observed-adverse-effect level; RfD = reference dose

5.3.4. Surrogate RfD for Occupational Exposures

Typically, FS and U.S. EPA risk assessments use only the chronic RfD for assessing risks to workers. For flumioxazin, U.S. EPA (2012) derived toxicity values to assess risks of dermal and inhalation exposures of flumioxazin to workers; for reference, these values are summarized in Table 5.3-4. To assess risks to workers, the U.S. EPA (2012) chronic RfD value of 0.02 mg a.i./kg/day (as described in Section 5.3.1) was adopted. This approach is based on the assumption that workers might travel from location to location and apply the pesticide repeatedly over a prolonged period of time (i.e., seasonal application of a pesticide over the course of several months). In practice, workers might only apply the pesticide infrequently over the course of a year. Therefore, use of the chronic RfD to assess occupational risks is a conservative approach.

Table 5.3-4: U.S. EPA (2012) Toxicity values for Occupational Exposure to Flumioxazin

Exposure Scenario	Point of Departure (Effect and Study)	Uncertainty Factors	Toxicity Value
Dermal (all durations)	NOAEL 30 mg a.i./kg/day (cardiovascular effects in fetuses; MRID 42684926, dermal developmental study)	UF_A: 10 UF_H: 10	0.3 mg a.i./kg/day U.S. EPA 2012 (Table 4.5.1, page 19)
Inhalation short-term and intermediate-term (1 day to 6 months)	NOAEL: 3 mg/kg/day (cardiovascular effects in fetuses; MRID 42684925, oral developmental study)	UF_A: 10 UF_H: 10	0.03 mg a.i./kg/day U.S. EPA 2012 (Table 4.5.1, page 19) MRID 42684925 (oral developmental study)

Exposure Scenario	Point of Departure (Effect and Study)	Uncertainty Factors	Toxicity Value
Inhalation long-term (>6 months)	NOAEL: 2 mg/kg/day (nephropathy and hematological effects; MRID 44295028, oral chronic study)	UF_A: 10 UF_H: 10	0.02 mg a.i./kg/day U.S. EPA 2012 (Table 4.5.1, page 19)

Abbreviations: a.i. = active ingredient; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; mg = milligram; NOAEL = no-observed-adverse-effect level; UF_A: interspecies uncertainty factor (extrapolation from animal to human); UF_H: Intraspecies uncertainty factor (intraspecies sensitivity)

5.3.5. Dose-Severity Relationships

FS risk assessments sometimes consider dose-severity relationships to more fully characterize potential risks in exposure scenarios where the doses exceed the acute or chronic RfDs. However, a brief and minimal consideration of dose-severity relationships can be based on the ratios of the LOAEL to the corresponding NOAEL for the acute and chronic RfDs. For the acute RfD for females, the ratio for LOAEL to NOAEL is 3.3 (10 mg/kg/day ÷ 3 mg/kg/day = 3.3); this LOAEL is based on fetal cardiovascular abnormalities which is a serious adverse effect. For the surrogate acute RfD for the general population, the ratio for LOAEL to NOAEL is 2.0 (12.7 mg/kg/day ÷ 6.3 mg/kg/day = 2.0); the LOAEL based on decreased pup weight and number of live births, with decreased live births as a serious effect. For the chronic RfD, the ratio for LOAEL to NOAEL is 10 (18 mg/kg/day ÷ 1.8 mg/kg/day = 10); this LOAEL is based on nephropathy and hematological effects; while adverse, these effects are not as serious as those reported for the acute RfDs.

5.4. Risk Characterization

5.4.1. Overview

The quantitative risk characterization for human health is based on the HQ approach. The HQ is defined as the estimated exposure divided by a toxicity value, such as an RfD, that is likely not to be associated with adverse effects. If the HQ is equal to or less than one, then no adverse effects are anticipated as a result of the exposure. When an HQ is greater than one, then the exposure exceeds the LOC and adverse effects are possible (SERA 2014a). Hazard quotients greater than one and less than 2, while above the LOC, might not represent significant risks, given the conservative nature of exposure estimates and NOAEL to LOAEL ratio (see Section 5.3.5).

The quantitative risk characterizations for the six application methods considered in this assessment are provided in workbooks in Attachments 1 – 6 for backpack spray (foliar directed), boom spray (aerial), aerial spray (by aircraft), application to surface of water bodies, subsurface application to water bodies, and granular application. For all workbooks, the quantitative risk characterization for workers is provided in Worksheet E02 and the risk characterization for the general public is provided in Worksheet E04. Estimated exposures are based on the maximum single application rate of 0.38 lb a.i./acre.

Exposure scenarios posing risks to workers and the general public are summarized in Table 5.4-1. As discussed in detail in the sections below, scenarios with the most serious risks (i.e., highest HQs) are general exposures of workers, especially for foliar direct spray using a backpack, and for accidental acute exposures for the general public (scenarios which involve contact or spills of concentrated

field solutions). For nonaccidental acute and chronic exposures of the general population, adult females of childbearing potential are at risk from ingestion of treated or contaminated fruit and vegetation.

Table 5.4-1: Exposure Scenarios Posing Risks to Workers and the General Public

Exposure Scenario	HQs[1] at Maximum Application Rate			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Workers: General Exposure	Backpack: 9 – 608 Boom and aircraft: <1 – 30	<1 – 1.7	<1 – 3	<1 – 28
Workers: Accidental Acute Exposure				
Glove, 1 minute	<1	<1	<1	<1
Glove, 1 hour	<1	<1	13 – 32	<1
Spill on hands, 1 hour	<1 – 1.1	<1	<1	<1
Spill on lower legs, 1 hour	<1	<1	<1 – 1.5	<1
General Public: Acute Accidental Exposure				
Direct spray of child, whole body	<1	NA	NA	NA
Direct spray of female, feet and lower legs	<1	NA	NA	NA
Water consumption (spill), child	<1 – 8	<1 – 5	9 – 213	6 – 79
Fish consumption (spill), adult male	<1 – 2	<1 – 1.4	6 – 64	5 – 24
Fish consumption (spill), subsistence population	<1 – 12	<1 – 7	34 – 337	25 – 124
General Public: Acute Non-Accidental Exposure				
Vegetation contact, shorts and T-shirt, adult female	<1	NA	NA	<1
Contaminated fruit, adult female	<1 – 2	NA	NA	<1
Contaminated vegetation, adult female	<1 – 17	NA	NA	<1
Swimming, one hour, adult female	<1	<1	<1	<1
Water consumption, child	<1	<1	<1	<1
Fish consumption, adult male	<1	<1	<1	<1
Fish consumption, subsistence population	<1	<1	1.4	<1

Exposure Scenario	HQs[1] at Maximum Application Rate			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
General Public: Chronic/Longer-Term Exposure				
Contaminated fruit, adult female	<1	NA	NA	<1
Contaminated vegetation, adult female	<1 – 2	NA	NA	<1
Water consumption, adult male	<1	<1	<1	<1
Fish consumption, adult male	<1	<1	<1	<1
Fish consumption, subsistence populations	<1	<1	<1	<1

[1]HQ ranges are for lower to upper bound exposure estimates. HQs listed as <1 or ≤1 (with no range) indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Unless otherwise specified, values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).

Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ

HQ ≤1
HQ >1 – <2
HQ ≥2

5.4.2. Workers

HQs for general and accidental exposures of workers are summarized in Table 5.4-2. Note that the FS does not estimate quantitative risks for local irritant effects of dermal and ocular exposures. As summarized in Appendix 2, Table A2-1, direct dermal or ocular exposure to flumioxazin formulations might cause brief or minor irritation to skin and eyes. For workers, irritant effects can be minimized or avoided by following prudent hygiene practices during handling of flumioxazin.

Table 5.4-2: Hazard Quotients (HQs) for Worker Exposure

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
General Exposure	Backpack 9 (lower) 84 (central 608 (upper)	<1 (lower and central)	<1 (lower and central)	<1 (lower and central)
	Boom and aircraft: <1 (lower and central)	1.7 (upper)	3 (upper)	28 (upper)
	Boom and aircraft: 30 (upper)			

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Accidental				
Glove, 1 minute	<1	<1	<1	<1
Glove, 1 hour	<1	<1	13 (lower) 20 (central) 32 (upper)	<1
Spill on hands, 1 hour	Backpack and boom <1 (lower, central and upper)	<1	<1 (lower and central)	NA
	Aircraft: <1 (lower and central)			
	Aircraft: 1.1 (upper)			
Spill on lower legs, 1 hour	<1	<1	1.5 (upper)	NA

[1]HQs listed as <1 or ≤1 only indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Unless otherwise specified, values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).

Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ

HQ ≤1
HQ >1 – <2
HQ ≥2

5.4.2.1. General Exposure

The highest HQs for general exposure of workers is for foliar directed spray applications using a backpack sprayer, with HQs ranging from 9 to 608 for lower to upper bound exposure estimates. These HQs represent a significant risk to workers; however, prudent handling practices and appropriate use of protective clothing and equipment would be expected to mitigate these risks. For aerial and boom ground spray applications, only the upper bound estimate exceeds the LOC (HQ: 30). For direct water surface and subsurface applications, upper bound estimates exceeded the LOC, with HQs of 1.7 and 3, respectively. Based on the LOAEL to NOAEL ratio of 10 (discussed in Section 5.3.5) and the conservative nature of the upper bound exposure estimates, these HQs do not raise substantial concern. For granular applications, the upper bound HQ is 28. This likely to be an overestimate of risk for exposures resulting from granular applications for the following reasons. The HQs for granular applications were based on an absorbed dose rate (ADR) of 2E-04 mg/kg bw per lb applied, the FS default value for broadcast foliar applications. However, this default value was derived based on studies of application rates of liquid formulations and has subsequently been reevaluated (SERA 2014b). The ADR for a ground broadcast of a granular formation is likely to be substantially lower than for broadcast foliar applications of liquid formulations.

5.4.2.2. Accidental Exposures

HQs for accidental exposures of workers for spray and granular applications are below the LOC (range for spray: 0.0009 – 0.5; range for granular: 0.0003 – 0.0004). Thus, for accidental exposure scenarios, adverse effects in workers are not anticipated. Accidental exposure of workers during surface applications of flumioxazin to water bodies does not appear to pose risks to workers, with HQs <1 for all accidental exposure scenarios (range: 0.005 – 0.7). For subsurface applications, HQs for exposure of contaminated gloves for 1 hour substantially exceed the LOC, with HQs for lower, central, and upper exposure estimates of 13, 20, and 32, respectively. Note that HQs for exposure of contaminated gloves for one minute do not exceed the LOC (range: 0.3 – 0.7). Even considering the NOAEL to LOAEL ratio of 10 (discussed in Section 5.3.5), exposures of workers for this scenario will exceed acceptable exposures if workers do not follow prudent handling practices. Risks could be mitigated by washing contaminated hands and replacing gloves. For a one-hour spill on lower legs, the HQ of 1.5 for the upper bound exposure modestly exceeds the LOC. However, given the conservative nature of exposure estimates, this modest exceedance is not of substantial concern.

5.4.3. General Public

5.4.3.1. Accidental Acute Exposures

HQs for accidental acute exposures of the general public are summarized in Table 5.4-3. The biggest concerns are for consumption of contaminated water by children and ingestion of contaminated fish by adult males and subsistence populations.

Table 5.4-3: Hazard Quotients (HQs) for Acute Accidental Exposures of the General Public

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Direct spray of child, whole body	<1	NA	NA	NA
Direct spray of female, feet and lower legs	<1	NA	NA	NA
Water consumption (spill), child	<1 (lower) 3 (central) 8 (upper)	<1 (lower) 1.5 (central) 5 (upper)	9 (lower) 71 (central) 213 (upper)	6 (lower) 26 (central) 79 (upper)
Fish consumption (spill), adult male	<1 (lower) 1.1 (central) 2 (upper)	<1 (lower and central) 1.4 (upper)	6 (lower) 32 (central) 64 (upper)	5 (lower) 12 (central) 24 (upper)

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Fish consumption (spill), subsistence population	<1 (lower) 6 (central) 12 (upper)	<1 (lower) 4 (central) 7 (upper)	34 (lower) 168 (central) 337 (upper)	25 (lower) 62 (central) 124 (upper)

[1]HQs listed as <1 or ≤1 only indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]HQs listed are for aerial aircraft spray; these HQs are higher than HQs for backpack directed foliar spray and boom ground spray.
Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ
HQ ≤1
HQ >1 – <2
HQ ≥2

Direct Spray (child and female). HQs are <1 for all accidental direct spray exposures of a child (whole body) and a woman (feet and lower legs). Therefore, accidental spray exposures are not expected to result in toxic effects. Although irritant effects for dermal exposure are not assessed, it is possible that minor irritation might occur.

Consumption of water (child). For exposure of a child through consumption of contaminated water, exceedances are observed for all application methods (lower, central, and upper exposure estimates). The highest HQs are for water contaminated by a spill of a field solution intended for subsurface applications into a small pond. HQs for this scenario range from 9 for the lower estimate of exposure to 213 for the upper estimated of exposure. The accidental spill scenario is presented for the acute consumption of contaminated water after an accidental spill into a small pond (0.25 acres in surface area and 1 m deep). This scenario is highly conservative and will generally overestimate exposure. Actual water concentrations will depend on the amount of compound spilled, the size of the water body, the time at which water consumption occurs relative to the time of the spill, and the amount of contaminated water that is consumed. This scenario is based on the assumption that exposure occurs shortly after the spill; therefore, no dissipation or degradation is considered. Regardless of these uncertainties in exposure, this scenario represents a significant risk to children drinking contaminated water. Accidental spill of field solutions for direct surface application also results in HQs >1, as shown in Table 5.3-3, although HQs are much lower. For spray applications, the highest HQs are observed for aerial applications (central: 1.1; upper: 2), with HQs >1 for boom applications (central: 1.6; upper: 5); HQs for backpack spray applications are <1. HQs for granular applications are lower than for direct subsurface water application; however, risks are still substantial and much higher than for spray and direct surface water applications. Based on these results, risk to children ingesting contaminated water should be considered serious for all application methods.

Fish consumption. Ingestion of contaminated fish from accidental spills presents serious risks to the general population. Although flumioxazin is not expected to bioconcentrate in fish, the high exposures from contaminated fish reflect the high flumioxazin concentrations in water for the small pond scenario. The highest HQs are for spills of subsurface field solutions into a small pond. Ranges of HQs for subsistence populations and adult males and 34– 337 and 6 – 64, respectively, indicating

substantial risks from fish ingestion. Granular applications also are associated with high risks for fish ingestion. HQ ranges for subsistence populations and adult males are 25 – 124 and 5 – 24, respectively. For spills of field solutions intended for spray applications, HQs for aerial and boom spray field solutions are also >1 for central and upper exposure estimates, with slightly higher HQs for aerial (range: 6 – 12) compared to boom (range: 4 – 8) spray solutions. Backpack spray solutions have only a modest exceedance of 1.3 for the upper bound estimate. As discussed above, exposures from actual spills into ponds depend on several variables, with the small pond scenario representing a highly conservative approach.

5.4.3.2. Nonaccidental Acute Exposures

Risks for acute, non-accidental exposures are summarized in Table 5.4-4. Risks for nonaccidental acute exposures are much less than for accidental acute exposures. The most significant risks are for adult females ingesting vegetables and fruit treated or contaminated by spray applications. For ingestion of treated or contaminated fruit, the HQ for the upper exposure estimate is 2. Although this is a relatively small exceedance at the highest modeled exposure, the acute RfD for women of childbearing potential is based on developmental effects (discussed in Section 5.3.2); therefore, an HQ of 2 represents a serious risk. For ingestion of treated or contaminated vegetation, significant risks are observed for the central (HQ: 2) and upper exposure estimates (HQ: 17). The only other HQ exceeding the LOC is for ingestion of fish by subsistence populations for subsurface applications of flumioxazin, with an HQ of 1.4. This represents a modest risk of adverse effects for this exposure scenario. HQs for other exposure scenarios are <1.

Table 5.4-4: Hazard Quotients (HQs) for Nonaccidental Acute Exposures of the General Public

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Vegetation contact, shorts and T-shirt, adult female	<1	NA	NA	<1
Contaminated fruit, adult female	<1 (lower and central) 2 (upper)	NA	NA	<1
Contaminated vegetation, adult female	<1 (lower) 2 (central) 17 (upper)	NA	NA	<1
Swimming, 1 hour, adult female	<1	<1	<1	<1
Water consumption, child	<1	<1	<1	<1
Fish consumption, adult male	<1	<1	<1	<1

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Fish consumption, subsistence population	<1	<1	1.4 (lower, central, and upper)	<1

[1]HQs listed as <1 or ≤1 only indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).
Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ
HQ ≤1
HQ >1 – <2
HQ ≥2

5.4.3.3. Chronic/Longer-Term Exposures

HQs for chronic/longer-term exposures of the general public are summarized in Table 5.4-5. For chronic/longer-term exposure, only one exposure scenario resulted in an HQ >1. For an adult female eating treated or contaminated vegetation the HQ for upper bound exposure is 2. Based on the LOAEL to NOAEL ratio of 10 for the chronic RfD (discussed in Section 5.3.5) and the conservative nature of the upper bound exposure estimates, this HQ does not raise substantial concern.

Table 5.4-5: Hazard Quotients (HQs) for Chronic/Longer-Term Exposures of the General Public

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Contaminated fruit, adult female	<1	NA	NA	<1
Contaminated vegetation, adult female	<1 (lower and central) 2 (upper)	NA	NA	<1
Water consumption, adult male	<1	<1	<1	<1
Fish consumption, adult male	<1	<1	<1	<1
Fish consumption, subsistence populations	<1	<1	<1	<1

[1]HQs listed as <1 only indicate that HQs for lower, central, and upper estimates are all <1.
[2]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).
Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ
HQ ≤1
HQ >1 – <2
HQ ≥2

5.4.4. Sensitive Subgroups

The mechanism of toxicity to mammalian species for hematological and developmental effects appears to be decreased heme synthesis through inhibition of PPO, resulting in decreased cellular heme levels (discussed in Section 2.1). Subgroups with underlying hematological disorders, including anemia and hereditary hepatic porphyrias (e.g., 5-aminolevulinic acid dehydratase deficiency porphyria, acute intermittent porphyria, porphyria cutanea tarda, hereditary coproporphyria, and variegate porphyria), could be at greater risk from flumioxazin exposure (Nordmann and Puy 2002).

The developing fetus is the most sensitive target of acute flumioxazin exposure. The potential developmental effects of flumioxazin are considered in the dose-response assessment by using the acute RfD based on fetal cardiac malformations to assess risks to women of childbearing potential.

No additional information was identified regarding other potential sensitive subgroups.

5.4.5. Cumulative Effects

Cumulative effects may involve either repeated exposures to an individual chemical or simultaneous exposures to the chemical of concern and other chemicals that might cause the same effects or effects by the same or similar mechanism of action. When determining the safety of a pesticide chemical, U.S. EPA considers available information concerning cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of action. Regarding flumioxazin, U.S. EPA (2012) stated the following:

> *The Agency does not have, at this time, available data to determine whether flumioxazin has a common mechanism of toxicity with other substances. If, in the future, the Agency determines that new information on flumioxazin is available that could potentially impact a cumulative risk assessment and result in a risk of concern, the Agency will revisit the need for a cumulative risk assessment.*

In the absence of a determination of a common mechanism of action with other pesticides, U.S. EPA/OPP has not further developed a cumulative effects determination involving flumioxazin. Therefore, the potential for cumulative effects associated with exposures to flumioxazin and other agents cannot be well characterized.

6. ECOLOGICAL RISK ASSESSMENT

6.1. Hazard Identification

6.1.1. Overview

The hazard identification for the ecological risk assessment describes the possible adverse effects associated with flumioxazin to ecological receptors through a review of the available toxicological literature. The primary source of information on receptors is taken from DERs of MRID studies submitted to U.S. EPA/OPP by registrants as part of the pesticide registration process.

Terrestrial organisms typically evaluated in FS ecological risks assessments include mammals, birds, invertebrates (honey bees and earthworms), plants, reptiles, and amphibians. Based on acute studies, U.S. EPA classified flumioxazin as having "very low to low" toxicity to mammals and as "practically non-toxic" to birds and honey bees. U.S. EPA does not have a toxicity classification scheme for effects on terrestrial plants. No data are available on the toxicity of flumioxazin to earthworms, reptiles, or amphibians.

Toxicity studies for aquatic organisms are available for freshwater and estuarine/marine fish, freshwater and estuarine/marine invertebrates, aquatic vascular plants, and algae. U.S. EPA does not have a classification scheme for toxicity to aquatic plants. For aquatic species, acute exposure to flumioxazin is classified as "slightly to moderately toxic" to freshwater and estuarine/marine fish, and "moderately to highly toxic" to freshwater and estuarine/marine invertebrates. Three environmental metabolites of flumioxazin are classified as "practically non-toxic" to freshwater fish and invertebrates based on acute exposure.

Note that in the following sections, discussions of toxicity studies focus on study results, rather than experimental details. Experimental details for each study are included in the corresponding appendices (e.g., number of animals per exposure group, animal weight and age, dosing vehicles such as dietary or gavage, static vs flow-through conditions, etc.).

6.1.2. Terrestrial Organisms

6.1.2.1. Mammals

Several standard toxicity studies are available for mammals exposed to flumioxazin. Results of these studies, discussed in Section 5.1, were used to develop toxicity values for the human health risk assessment; this discussion is not repeated here. For the ecological risk assessment, mammalian studies discussed in Section 5.1 are used to identify potential toxic effects in mammalian wildlife. Selection of the mammalian dose-response values used in the ecological risk assessment for flumioxazin is discussed in Section 6.3.

While human health risk assessments typically focus on the most sensitive species as a surrogate for humans, ecological risk assessments are concerned with population-level effects and differences in toxicity among species. Ideally, data from studies in several different species would be used to evaluate potential species differences in susceptibility to flumioxazin. For flumioxazin, acute toxicity for oral, dermal, and inhalation exposures are only available in rats; therefore, most sensitive and tolerant species of mammals cannot be identified. Acute toxicity studies classified flumioxazin as

U.S. EPA Toxicity Category III or IV for acute toxicity, which is defined as "low" or "very low," respectively (see Table 5.1-3).

6.1.2.2. Birds

Studies that describe the toxicity of technical grade flumioxazin to birds include acute oral and dietary-based toxicity studies and chronic reproductive studies. Studies are summarized in Table 6.1-1, with additional study details reviewed in Appendix 4.

Table 6.1-1: Acute and Chronic Toxicity of Technical Grade Flumioxazin to Birds

Species	Exposure Duration	Result	Reference (Classification)
Acute (Dose-based)			
Bobwhite quail	Single dose, 14-day observation	LD_{50} >2250 mg a.i./kg NOAEL: 2250 mg a.i./kg (No lethal or sublethal effects)	MRID 42684945 (Acceptable/Guideline)
Acute (Dietary-based)			
Mallard duck	5-day dietary exposure, 3-day observation	LC_{50} >1728 mg a.i./kg/day **NOAEC: 1728 mg a.i./kg/day[1]** (no lethal or sublethal effects)	MRID 42684946 (Acceptable/Guideline)
Bobwhite quail	5-day dietary exposure, 3-day observation	LC_{50} >2866 mg a.i./kg/day NOAEC: 2866 mg a.i./kg/day (no lethal or sublethal effects)	MRID 42684947 (Acceptable/Guideline)
Chronic (Dietary-based)			
Mallard duck	21-week reproduction study	**NOAEL: 32.8 mg a.i./kg/day[2]** LOAEL: 65.6 mg a.i./kg/day (reduction in embryo viability)	MRID 44295005 (Acceptable/Guideline)
Bobwhite quail	21-week reproduction study	NOAEL: 63.6 mg a.i./kg/day LOAEL >63.6 mg a.i./kg/day (no lethal or sublethal effects)	MRID 44295006 (Supplemental/Non-guideline)

[1]Value in bold was used to assess acute risks to birds.
[2]Value in bold was used to assess chronic risks to birds.
Abbreviations: a.i. = active ingredient; kg = kilogram; LC_{50} = median lethal concentration; LOAEL = lowest-observed-adverse-effect level mg = milligram; NOAEC = no-observed-adverse-effect concentration; NOAEL = no-observed-adverse-effect level

6.1.2.2.1. Acute Oral Toxicity in Birds

One study of oral dosing of avian species to technical grade flumioxazin was submitted by the registrant to U.S. EPA/OPP. Bobwhite quail (*Colinus virginianus*) were administered single gavage doses up to 2250 mg a.i./kg and observed for 14 days (MRID 42684945). No mortality or clinical signs of toxicity were observed in any dose group, and no significant difference in body weight gain or

food consumption was observed between treated and control groups. Based on these observations, the oral LD_{50} and NOAEL values were identified as >2250 and 2250 mg a.i./kg, respectively. On this basis, flumioxazin was classified as "practically non-toxic" to birds. Details of this study are provided in Appendix 4, Table A4-1.

6.1.2.2.2. Acute Dietary Toxicity Birds

Two acute studies in mallard ducks (*Anas platyrhynchos*) and bobwhite quail evaluated acute dietary exposure to technical grade flumioxazin. In both studies, birds were exposed for five days, followed by a three-day observation period. Mallard ducks were exposed to dietary concentrations up to 5620 ppm a.i., equivalent to 1728 mg a.i./kg/day (MRID 42684946). No mortality or clinical signs of toxicity were observed in any dose group, and body weight gains in treated and control birds were not significantly different, identifying LC_{50} and no-observed-adverse-effect concentration (NOAEC) values of >1728 and 1728 mg a.i./kg/day, respectively. Bobwhite quail were exposed to dietary concentrations up to 5620 ppm a.i., equivalent to 2866 mg a.i./kg/day (MRID 42684947). No mortality or clinical signs of toxicity were observed in any dose group, identifying an LC_{50} value of >2866 mg a.i./kg/day. The DER reported that food consumption decreased at the highest concentration tested; however, in the absence of decreases in body weight, decreased food consumption is not considered adverse, identifying the highest dose tested (2866 mg a.i./kg/day) as the NOAEC. The NOAEL value of 1728 mg a.i./kg/day from the study in mallard ducks is used to assess acute risks to avian species (see Section 6.3.2.2). Experimental details for these studies are summarized in Appendix 4, Table A4-1.

6.1.2.2.3. Chronic Reproductive Toxicity in Birds

Chronic reproductive studies of mallard ducks (MRID 44295005) and bobwhite quail (MRID 44295006) were submitted to U.S. EPA/OPP. The mallard study was considered a guideline study and deemed "Acceptable" by U.S. EPA/OPP, while the bobwhite quail study was classified as "Supplemental" (non-guideline) because the authors did not state whether the test was conducted with the highest dosage level at or above the maximum field residue level. Exposures for both studies were dietary. Experimental details for these studies, including specific reproductive parameters that were assessed, are provided in Appendix 4, Table A4-2.

The study in mallard ducks exposed birds to dietary concentrations of flumioxazin up to 500 ppm a.i. (equivalent to 65.6 mg a.i./kg/day) for a total of 21 weeks (MRID 44295005). No adverse effects in adults were observed at the highest concentration tested. Effects on reproductive parameters (reduction in viable embryos and live 3-week embryos) occurred at the highest dietary concentration, with NOAEL and LOAEL values of 32.8 (dietary concentration of 250 ppm a.i.) and 65.6 mg a.i./kg/day, respectively. The study in bobwhite quail also exposed birds to dietary concentrations up to 500 ppm a.i. (equivalent to 63.6 mg a.i./kg/day) for 21 weeks. No adverse effects to adult birds or effects on reproductive parameters were observed. NOAEL and LOAEL values were 63.6 and >63.6 mg a.i./kg/day, respectively. The NOAEL value of 32.8 mg a.i./kg/day from the study in mallard ducks is used to assess chronic risks to avian species (see Section 6.3.2.2).

6.1.2.3. Reptiles and Amphibians (Terrestrial-Phase)

Studies on the toxicity of flumioxazin to reptiles and terrestrial-phase amphibians are not available in the open peer-reviewed literature, the flumioxazin DERs, or the U.S. EPA (2003) ecological risk

assessment. In the absence of data, birds can be used as surrogates for these receptors. While this is standard practice in U.S. EPA ecological risk assessments, U.S. EPA (2003) did not assess risks to reptiles and terrestrial-phase amphibians and, therefore, this remains a data gap. As stated in SERA (2014a), "a fundamental principle in the FS risk assessments is that risk cannot be quantitatively characterized unless both toxicity and exposure can be characterized."

6.1.2.4. Terrestrial Invertebrates

One toxicity study of flumioxazin in terrestrial invertebrates was identified, which is an acute contact study in honey bees (*Apis mellifera*).

6.1.2.4.1. Honey Bees

The acute contact study in honey bees (MRID 42684951) is summarized in Table 6.1-2, with details in Appendix 5, Table A5-1. Bees were exposed on the thorax and/or abdomen with flumioxazin at doses up to 105 µg a.i./bee (equivalent to 905 µg a.i./kg, as described in Section 6.3.2.4.1) for 48 hours. No lethality or sublethal effects were observed. Based on these results, flumioxazin is classified as "practically non-toxic" to bees through acute contact. The NOAEL value of 905 µg a.i./kg is used to assess acute contact risks to terrestrial invertebrates. No data for ingestion of flumioxazin were identified; therefore, this remains a data gap.

Table 6.1-2: Acute Contact Toxicity of Technical Grade Flumioxazin to Honey Bees

Species	Exposure Duration	Result	Reference (Classification)
Honey bee	48 hours	LD_{50} >905 µg a.i./kg **NOAEL: 905 µg a.i./kg**[1] LOAEL: >905 µg a.i./kg (no lethal or sublethal effects)	MRID 42684951 (Acceptable/Guideline)

[1]Value in bold was used to assess acute contact toxicity to terrestrial invertebrates.
Abbreviations: a.i. = active ingredient; kg = kilogram; LC_{50} = median lethal concentration; LOAEL = lowest-observed-adverse-effect level; µg = microgram; NOAEL = no-observed-adverse-effect level

6.1.2.4.2. Earthworms

No data on the toxicity of flumioxazin to earthworms were identified. Therefore, this is considered a data gap.

6.1.2.5. Terrestrial Plants

For pesticide registration, U.S. EPA requires toxicity testing of terrestrial plants for typical end use products that are known phytotoxicants (e.g., herbicides). A typical end use product is defined as the formulation with the highest percentage of a.i. and/or is the most widely used. The testing requirements involve Tier II level tests, which measure the responses of plants at five or more test chemical concentrations compared to a control. For flumioxazin, Tier II plant testing results were submitted by registrants for technical grade flumioxazin, as discussed in Section 6.1.2.5.1. In addition to U.S. EPA-required studies, numerous field studies evaluating effects to terrestrial non-target vegetation were identified in the published literature. Results of these studies are summarized in Section 6.1.2.5.2.

As discussed in Section 2.1, flumioxazin is a light-dependent, peroxidizing herbicide that has a phototoxic mechanism of action. Toxicity tests may not include the same light wavelength and intensity as natural sunlight; therefore, flumioxazin may be more toxic to terrestrial plants under field conditions compared to laboratory conditions.

6.1.2.5.1. Standard Toxicity Studies

Two studies were submitted to U.S. EPA for Tier II testing: one study evaluated seedling emergence (MRID 44295029) and one study evaluated vegetative vigor (MRID 44295030). Results of the Tier II testing for the most sensitive and tolerant terrestrial plant species are provided in Table 6.1-3; values shown in this table are used to characterize risks to terrestrial plants. Results for all plant species tested and details of experimental conditions are summarized in Appendix 6, Tables A6-1 and A6-2.

Table 6.1-3: Toxicity of Technical Grade Flumioxazin to Terrestrial Plants for the Most Sensitive and Tolerant Plant Species

Study Type	Species	Toxicity Reference Value (lb a.i./acre)	Reference (Classification)
Seedling emergence (sensitive)	Lettuce (dicot)	EC_{25} (dry weight): 0.0008 lb a.i./acre **NOAEL: 0.0004 lb a.i./acre[1]**	MRID 44295029 (Acceptable/Guideline)
Seedling emergence (tolerant)	Soybean (dicot)	EC_{25} (dry weight and height) >0.096 lb a.i./acre **NOAEL: 0.096 lb a.i./acre[2]**	MRID 44295029 (Acceptable/Guideline)
Vegetative vigor (sensitive)	Cucumber (dicot)	EC_{25} (phytotoxicity): 0.00008 lb a.i./acre **NOAEL: 0.00005 lb a.i./acre[3]**	MRID 44295030 (Acceptable/Guideline)
Vegetative vigor (tolerant)	Corn (monocot)	EC_{25} (dry weight): >0.0104 lb a.i./acre **NOAEL: 0.0060 lb a.i./acre[4]**	MRID 44295030 (Acceptable/Guideline)

[1]Value in bold was used to assess soil application for sensitive plants.
[2]Value in bold was used to assess soil application for tolerant plants.
[3]Value in bold was used to assess foliar application for sensitive plants.
[4]Value in bold was used to assess foliar application for sensitive plants.
Abbreviations: a.i. = active ingredient; EC_{25} = concentration affecting 25% of organisms tested; lb = pound; NOAEL = no-observed-adverse-effect level

Seedling Emergence. Plant species tested for effects of technical grade flumioxazin on seedling emergence include four monocot species [corn (*Zea mays*), oat (*Avena sativa*), onion (*Allium cepa*), and ryegrass (*Lolium perenne*)] and six dicot species [cabbage (*Brassica oleracea*), cucumber (*Cucumis sativus*), lettuce (*Lactuca sativa*), radish (*Raphanus sativus*), soybean (*Glycine max*), and tomato (*Lycopersicon esculentum*)] (MRID 44295029). Flumioxazin was applied to soil at rates of 0.0004 to 0.096 lb a.i./acre and seedlings were observed for 21 days. Signs of toxicity observed in both monocots and dicots included stunted growth, leaf desiccation, and plant death. The most sensitive monocot was ryegrass (based on dry weight), with an EC_{25} of 0.0037 lb a.i./acre and a NOAEL of 0.0030 lb a.i./acre. The most sensitive dicot was lettuce (based on dry weight), with an EC_{25} of 0.0008 lb a.i./acre and a NOAEL of 0.0004 lb a.i./acre. The most tolerant monocot was corn (based on dry weight), and the most tolerant dicot was soybean (based on dry weight and height).

Overall, the most sensitive plant species for seedling emergence was lettuce, and the most tolerant plant species for seedling emergence was soybean (Table 6.1-3).

Vegetative Vigor. Vegetative vigor tests evaluated effects of technical grade flumioxazin in the same species tested in the seedling emergence study. Flumioxazin was applied to plants at rates ranging from 0.00002 to 0.096 lb a.i./acre at the 1 – 3 true leaf stage and observed for 21 days. Signs of toxicity observed in treated plants were primarily stunting, leaf desiccation, chlorosis, and plant death. The most sensitive monocot was oat (based on dry weight), with an EC_{25} of 0.0071 lb a.i./acre and a NOAEL of 0.0060 lb a.i./acre. The most sensitive dicot was cucumber (based on phytotoxicity), with an EC_{25} of 0.00008 lb a.i./acre and a NOAEL of 0.00005 lb a.i./acre.

6.1.2.5.2. Field Studies

Numerous field studies on effects of flumioxazin to non-target plants are available in the open literature. Studies on effects to representative common crops in the U.S. have been reviewed and are summarized in Table 6.1-4, with additional details provided in Appendix 6, Table A6-3. Study results cannot be directly compared due to numerous differences between studies that can influence results (e.g., timing of application, soil type and organic content, time of assessment relative to application, rainfall, temperature, etc.). However, results of these field studies indicate that adverse effects to plants occur at application rates below the approved maximum application rate of 0.38 lb a.i./acre.

Table 6.1-4: Field Studies for Preemergence and Postemergence Applications of Flumioxazin

Species	Application Type (Rate)	Adverse Effects	Reference
Soybean (*Glycine max*)	PRE (0.13 lb a.i./acre)	Visible plant injury	Mahoney et al. (2014)
	PRE, PRE-I, POST (0.063 and 0.13 lb a.i./acre)	Visible plant injury (PRE-I and POST); decreased dry biomass (POST)	McNaughton et al. (2014)
	PRE (0.066 and 0.078 lb a.i./acre)	Visual plant injury and decreased plant height	Poston et al. (2008)
	PRE (0.0071, 0.016, and 0.032 lb a.i./acre)	Visual injury (necrosis); reduced plant height, width, and yield	Stephenson et al. (2018)
	PRE (0.094, 0.18, and 0.37 lb a.i./acre)	Reduced emergence counts; visual injury; reduced stand count	Taylor-Lovell et al. (2001)
Cotton (*Gossypium hirsutum*)	PRE, POST (0.062 lb a.i./acre)	Plant injury and reduced fresh weight (PRE)	Askew et al. (2002)
	PRE (0.027, 0.054 and 0.80 lb a.i./acre)	Reduced plant height and yield	Berger et al. (2012)
	PRE (0.094 lb a.i./acre)	Visible plant injury	Price et al. (2004)

Species	Application Type (Rate)	Adverse Effects	Reference
Sweetpotato (*Ipomoea batatas*)	PRE, POST (0.13 lb a.i./acre)	Visible plant injury	Kelly et al. (2006)
	PRE (0.032, 0.064, 0.097 lb a.i./acre)	Decreased slip density, length and dry weight	Smith et al. (2018)
Grain sorghum	PRE (0.062 and 0.098 lb a.i./acre)	No adverse effects	Grichar (2006)
Peanut (*Arachis hypogaea*)	PRE (0.063 and 0.094 lb a.i./acre)	No seedling emergence; reduced root length; stunted plants; reduced number of mature pods	Johnson et al. (2006)
Sugarcane (*Saccharum* interspecific hybrids)	PRE, POST (0.25 lb a.i./acre)	Visual injury (PRE); reduced yield (POST)	Richard and Dalley (2006)
Broccoli (*Brassica oleracea*), carrot (*Daucus carota*), head lettuce (*Lactuca sativa*), bulb onion (*Allium cepa*), spinach (*Spinacia oleracea*), and processing tomato (*Lycopersicon esculentum*)	PRE (0.063, 0.125, 0.25 lb a.i./acre)	No adverse effects	Haar et al. (2002)
Green onion (*Allium cepa*)	POST (0.05 lb a.i./acre)	Decreased plant height, density, and yield	Norsworthy et al. (2007)
Dry beans (black, and white beans)	PRE, PRE-I (0.047, 0.062, and 0.12 lb a.i./acre)	Visual injury; reduced plant height, shoot dry weight, and yield (PRE)	Soltani et al. (2005)
Adzuki bean (*Vigna angularis*)	PRE (0.063 and 0.13 lb a.i./acre)	Visual injury; reduced plant stand; shoot dry weight; plant height and yield	Soltani et al. (2015)

Abbreviations: a.i. = active ingredient; lb = pound; POST = postemergence application; PRE = preemergence application; PRE-I; preemergence application with soil incorporation

6.1.2.6. Terrestrial Microorganisms

No toxicity data on the effects of flumioxazin on terrestrial microorganisms were identified.

6.1.3. Aquatic Organisms

6.1.3.1. Fish

Acute and chronic toxicity studies describing the hazard potential of flumioxazin to freshwater and estuarine/marine fish are summarized in the following sections. Acute toxicity studies in fish have evaluated effects of technical grade flumioxazin and environmental metabolites of flumioxazin.

Chronic toxicity studies have evaluated effects of technical grade flumioxazin and a formulated product of flumioxazin.

6.1.3.1.1. Acute Toxicity

Acute toxicity studies of technical grade flumioxazin were conducted in rainbow trout (*Salmo gairdneri*), bluegill sunfish (*Lepomis macrochirus*), and sheepshead minnow (*Cyprinodon variegatus*). Studies of three environmental metabolites of flumioxazin (482-HA, APF, and THPA-2Na) were conducted in fathead minnow (*Pimephales promelas*). All studies evaluated mortality and sublethal effects and identified 96-hour LC_{50}, NOAEC, and lowest-observed-adverse-effect concentration (LOAEC) values. Note that studies were conducted under flow-through condition to maintain concentration of flumioxazin in the aquaria over the study duration. Results are shown in Table 6.1-5, with experimental details summarized in Appendix 7, Table A7-1.

Table 6.1-5: Acute Studies on the Toxicity of Technical Grade Flumioxazin and Environmental Metabolites of Flumioxazin to Fish

Species	Exposure Duration	NOAEC	LOAEC	Reference (Classification)
Technical Grade Flumioxazin				
Rainbow trout (freshwater)	96 hours	**0.92 mg a.i./L[1]**	2.0 mg a.i./L	MRID 42684948 (Acceptable/Guideline)
		mortality and sublethal effects		
Bluegill sunfish (freshwater)	96 hours	3.9 mg a.i./L	6.3 mg a.i./L	MRID 42684949 (Acceptable/Guideline)
		sublethal effects; no mortality		
Sheepshead minnow (estuarine/marine)	96 hours	**4.7 mg a.i./L[2]**	>4.7 mg a.i./L	MRID 44295010 (Acceptable/Guideline)
		no mortality or sublethal effects		
Flumioxazin Metabolite 482-HA				
Fathead minnow (freshwater)	96 hours	36 mg/L	>36 mg/L	MRID 49733403 (Acceptable/Guideline)
		no mortality or sublethal effects		
Flumioxazin Metabolite APF				
Fathead minnow (freshwater)	96 hours	25 mg/L	>25 mg/L	MRID 49733404 (Acceptable/Guideline)
		no mortality or sublethal effects		
Flumioxazin Metabolite THPA-2Na				
Fathead minnow (freshwater)	96 hours	38 mg/L	>38 mg/L	MRID 49733405 (Acceptable/Guideline)
		no mortality or sublethal effects		

[1]Value in bold was used to assess acute risks to sensitive species of fish.
[2]Value in bold was used to assess acute risks to tolerant species of fish.
Abbreviations: a.i. = active ingredient; APF = 6-amino-7-fluoro-4-(2-propynyl)-2H-1,4-benzoxazin-3(4H)-one; 482-HA = 7-fluoro-6-[(2-carboxyl-1-cyclohexenoyl)amino]-4-(2-propynyl)-1,4-benzoxazin-3-(2H)-one; L = liter; mg = milligrams; THPA = 3,4,5,6-tetrahydrophthalicacid

Results of the three studies of technical grade flumioxazin indicate that rainbow trout are more sensitive than bluegill sunfish or sheepshead minnow. Rainbow trout were exposed to technical grade flumioxazin at mean measured concentrations up to 5.4 mg a.i./L for 96 hours (MRID 42684948). Significant mortality was observed at concentrations ≥2 mg a.i./L compared to controls.

Sublethal effects, including surface, on-bottom orientation, loss of equilibrium, and lethargy, were also observed at concentrations causing lethality. Based on the 96-hour LC_{50} of 2.3 mg a.i./L, U.S. EPA/OPP classified flumioxazin as "moderately toxic" to rainbow trout under acute conditions.

The study in bluegill sunfish tested mean measured concentrations of flumioxazin up to 21 mg a.i./L for 96 hours (MRID 42684949). No mortality was observed at any concentration; however, sublethal effects (fish swimming at surface and exhibiting abnormal respiration) were observed at concentrations ≥6.3 mg a.i./L. Study authors derived a 96-hour LC_{50} >21 mg a.i./L, and a 96-hour NOAEC of 3.9 mg a.i./L. U.S. EPA/OPP classified flumioxazin as "slightly toxic" to bluegill sunfish under the acute conditions of this study.

The estuarine/marine sheepshead minnow study exposed fish to technical grade flumioxazin at mean measured concentrations up to 4.7 mg a.i./L for 96 hours (MRID 44295010). No lethal or sublethal effects were observed at any test concentration. Based on the 96-hour LC_{50} >4.7 mg a.i./L, U.S. EPA/OPP classified flumioxazin as "no more than moderately toxic" to sheepshead minnow under acute conditions.

Three studies evaluated the toxicity of three environmental metabolites of flumioxazin in fathead minnow: 482-HA (MRID 49733403), APF (MRID 49733404), and THPA-2Na (MRID 49733405). The highest concentrations tested (mg metabolite/L) were 482-HA, 36; APF, 25; and THPA-2Na, 38. In each of these studies, no lethal or sublethal effects were observed at any test concentration, suggesting that environmental metabolites of flumioxazin are less toxic than parent compound. Based on these results, U.S. EPA/OPP classified the flumioxazin metabolites as "practically non-toxic."

6.1.3.1.2. Chronic Toxicity

Six studies of chronic toxicity of flumioxazin to fish were identified; five were conducted using technical grade flumioxazin, and one used the flumioxazin product Clipper™ Herbicide. One study on technical grade flumioxazin examined toxicity under standard and enhanced lighting conditions. Studies on the chronic toxicity of technical grade flumioxazin were conducted in rainbow trout, fathead minnow, and sheepshead minnow; the study on the flumioxazin product was conducted in bluegill sunfish. Note that studies were conducted under flow-through conditions with a constant flumioxazin concentration throughout the exposure period. Under field conditions, a single application of flumioxazin would be expected to degrade rapidly in water. If studies had been conducted under static conditions, it is expected that LOAEC values would have been higher (i.e., less toxic). Thus, toxicity values are likely to be overestimated and highly conservative when applied to conditions in the field. An overview of study results is provided in Table 6.1-6, with experimental details summarized in Appendix 7, Table A7-2.

Table 6.1-6: Chronic Studies on the Toxicity of Technical Grade Flumioxazin and a Flumioxazin Product to Fish

Species	Exposure Duration	NOAEC	LOAEC	Reference (Classification)
Technical Grade Flumioxazin				
Rainbow trout (freshwater)	21 days	370 µg a.i./L	610 µg a.i./L	MRID 44295007 (Supplemental/ Non-guideline)
		mortality and sublethal effects		
Rainbow trout (freshwater)	64 days	**7.7 µg a.i./L[1]**	16 µg a.i./L	MRID 44295012 (Acceptable/Guideline)
		reduced growth in post-hatch trout		
Fathead minnow (freshwater)	159 days	**0.51 µg a.i./L[2]**	0.99 µg a.i./L	MRID 49733408 (Acceptable/Guideline)
		reduction in F1 larval survival		
Fathead minnow (freshwater)	32 days	*Standard lighting conditions*		MRID 49733406 (Acceptable/Guideline)
		3.3 µg a.i./L	>3.3 µg a.i./L	
		no lethal or sublethal effects		
		Enhanced lighting conditions		
		0.35 µg a.i./L	0.78 µg a.i./L	
		reduced hatching success, larval survival, and live larvae at hatch		
Sheepshead minnow (estuarine/marine)	34 days	1.1 µg a.i./L	1.6 µg a.i./L	MRID 49733407 (Acceptable/Guideline)
		reduction in total length		
Flumioxazin Product Clipper™ Herbicide				
Bluegill sunfish (freshwater)	6 weeks	204 µg a.i./L	>204 µg a.i./L	Umphres et al. (2013)
		no lethal or sublethal effects		

[1]Value in bold was used to assess acute risks to sensitive species of fish.
[2]Value in bold was used to assess acute risks to tolerant species of fish.
Abbreviations: a.i. = active ingredient; F1 = first generation; L = liter; µg = microgram; mg = milligram

One study in rainbow trout examined mortality and sublethal effects in fish exposed to technical grade flumioxazin at mean measured concentrations up to 2.4 mg a.i./L for 21 days (MRID 44295007). Mortality (10%) and sublethal effects (discoloration, erratic swimming, loss of equilibrium, lying at bottom of aquarium, surfacing, and quiescent fish) were observed at 0.61 mg a.i./L. The NOAEC and LOAEC for the study were identified as 370 and 610 µg a.i./L, respectively. This study was classified by U.S. EPA/OPP as "supplemental/non-guideline" due to the presence of precipitate in test chambers. For this reason, the NOAEC of 370 µg a.i./L was not selected to assess risks for tolerant species of fish for chronic exposure. It is unknown if the formation of flumioxazin precipitate occurred under specific experimental conditions, or if precipitate would occur under field conditions.

Effects of chronic exposure to flumioxazin on early life-stage success were examined in three studies: a 64-day study in rainbow trout (MRID 44295012), a 34-day study in sheepshead minnow (MRID 49733407), and a 32-day study in fathead minnow conducted under standard and enhanced lighting conditions (MRID 49733406). In fathead minnow, small decreases in length (5%) and weight

(8%) in 60-day post-hatch trout were observed at the highest concentration tested (mean-measured: 16 µg a.i./L) compared to controls, identifying 7.7 and 16 µg a.i./L as the NOAEC and LOAEC, respectively. This study was classified by U.S. EPA/OPP as an "acceptable guideline" study. Sheepshead minnow were exposed to flumioxazin at mean measured concentrations up to 10 µg a.i./L for 34 days. NOAEC and LOAEC values of 1.1 and 1.6 µg a.i./L, respectively, were identified based on a 9% reduction in total length. U.S. EPA/OPP classified this study as "acceptable." The 32-day study in fathead minnow evaluated effects of chronic exposure with both standard lighting and enhanced lighting (MRID 49733406). The study DER reported standard lighting conditions as 540 – 850 lux and enhanced lighting in terms of µWatts/cm^2; unfortunately, these units cannot be converted to a common unit for comparison purposes. Under standard lighting conditions, no effects on lethality or sublethal effects (hatching success, live normal fry at hatch, post-hatch larval survival and growth, abnormal behavior, or appearance) were observed. Under enhanced lighting, the toxicity of flumioxazin increased. NOAEL and LOAEL values of 0.35 and 0.78 µg a.i./L were based on decreased hatching success, decreased post-hatch larval survival, and decreased live normal larvae (7%, 21%, and 20% reductions compared to controls, respectively). No treatment-related effects were observed for growth (total length or wet weight) of 4-week post-hatch larvae.

A study identified in the published literature evaluated the toxicity of a six-week exposure of bluegill sunfish to the flumioxazin product Clipper™ Herbicide (Umphres et al. 2013). The highest nominal concentration tested was 204 µg a.i./L; mean measured concentrations were not reported. No lethality or sublethal effects were observed. It is difficult to compare results of this study to studies conducted with technical grade flumioxazin due to differences in experimental conditions, and chronic toxicity studies on technical grade flumioxazin were not conducted in bluegill sunfish. However, results indicate that Clipper™ Herbicide is not more toxic than technical grade flumioxazin. This implies that the inert ingredients in Clipper™ Herbicide are not toxic (or are far less toxic than flumioxazin) and do not enhance the toxicity of flumioxazin.

6.1.3.2. Amphibians (Aquatic-Phase)

Studies were not identified regarding the toxicity of flumioxazin to amphibians.

6.1.3.3. Aquatic Invertebrates

As with fish, acute and chronic studies of toxicity of flumioxazin to aquatic invertebrates are required by U.S. EPA/OPP. Acute toxicity studies in aquatic invertebrates have evaluated toxicity of technical grade flumioxazin and an environmental metabolite of flumioxazin. Chronic toxicity studies have evaluated toxicity of technical grade flumioxazin.

6.1.3.3.1. Acute Toxicity

Three studies of technical grade flumioxazin and one study of the flumioxazin environmental metabolite 482-HA on acute toxicity to aquatic invertebrates were submitted. An overview of results is presented in Table 6.1-7, with study details described in Appendix 8, Table A8-1. Based on study results, U.S. EPA/OPP classified flumioxazin as "moderately" to "highly toxic" to aquatic invertebrates on an acute basis. As noted in the discussions below, precipitate was observed in the studies in water flea and eastern oyster exposed to technical grade flumioxazin. It is unknown if the formation of flumioxazin precipitate occurred under specific experimental conditions, or if precipitate would occur under field conditions.

Table 6.1-7: Acute Studies on the Toxicity of Technical Grade Flumioxazin and an Environmental Metabolite of Flumioxazin to Aquatic Invertebrates

Species	Exposure Duration	NOAEC	LOAEC	Reference (Classification)
Technical Grade Flumioxazin				
Water flea (freshwater)	48 hours	No NOAEC or LOAEC determined due to precipitate **EC_{50}: 5.5 mg a.i./L[1]**		MRID 42684950 (Supplemental/ Non-guideline)
Eastern oyster (estuarine/marine)	96 hours	<0.64 mg a.i./L	0.64 mg a.i./L	MRID 44295008 (Acceptable/Guideline)
		reduced shell growth		
Mysid shrimp (estuarine/marine)	96 hours	**0.10 mg a.i./L[2]**	0.22 mg a.i./L	MRID 44295009 (Acceptable/Guideline)
		mortality and lethargy		
Flumioxazin Metabolite 482-HA				
Water flea (freshwater)	48 hours	48 mg/L	>48 mg/L	MRID 49733402 (Acceptable/Guideline)
		no mortality or sublethal effects		

[1]Value in bold was used to derive an estimated NOAEC to assess acute risks to tolerant species of aquatic invertebrates (see discussion in Section 6.3.4.2).
[2]Value in bold was used to assess acute risks to sensitive species of aquatic invertebrates.
Abbreviations: a.i. = active ingredient; 482-HA = 7-Fluoro-6-[(2-carboxyl-1-cyclohexenoyl)amino]-4-(2-propynyl)-1,4-benzoxazin-3-(2*H*)-one; L = liter; LOAEC = lowest-observed-adverse-effect concentration; mg = milligram; NOAEC = no-observed-adverse-effect concentration

Two of the submitted acute toxicity studies are considered "acceptable guideline" studies by U.S. EPA/OPP; both evaluated estuarine/marine species. The study in eastern oysters (*Crassostrea virginica*) evaluated test concentrations (mean measured) up to 4.4 mg a.i./L for a 96-hour exposure period (MRID 44295008). Throughout the exposure period, precipitate was observed in the mixing chamber and in chemical cell solutions of the two highest concentrations, though none was observed in the exposure aquaria. No mortality occurred at any concentration tested, but significantly reduced shell growth (33 – 65%) occurred at all tested concentrations compared to controls. The authors derived a 96-hour EC_{50} of 2.4 mg a.i./L and identified <0.64 mg a.i./L as the 96-hour NOAEC. The study in mysid shrimp tested flumioxazin concentrations up to 0.39 mg a.i./L for a 96-hour exposure period (MRID 44295009). Significant mortality (30%) and lethargy in all shrimp were observed at 0.22 mg a.i./L. Study authors identified a 96-hour LC_{50} of 0.23 mg a.i./L and a 96-hour NOAEC of 0.10 mg a.i./L.

One acute study evaluated the toxicity of flumioxazin to water flea (*Daphnia magna*) in a 48-hour flow-through test (MRID 42684950). Flumioxazin precipitate was observed in all test chambers; NOAEC and LOAEC values could not be determined due to daphnid immobility at every test concentration (3.73 – 9.25 mg a.i./L, mean measured centrifuged concentrations), possibly due, in part, to the presence of precipitate in the test chambers. Study authors derived a 48-hour EC_{50} of 5.5 mg a.i./L. U.S. EPA/OPP classified the study as supplemental/non-guideline.

The acute toxicity of the flumioxazin metabolite 482-HA was assessed in a 48-hour exposure of water fleas (MRID 49733402). The highest mean measured concentration tested was 48 mg/L. No immobility (mortality) or sublethal effects were observed at any test concentration. The authors determined the 48-hour EC_{50} was >48 mg/L and the 48-hour NOAEC was 48 mg/L. U.S. EPA/OPP

classified 482-HA as "practically non-toxic" to daphnids for acute toxicity based on this acceptable guideline study. Metabolite 482-HA appears to be much less toxic than flumioxazin.

6.1.3.3.2. Chronic Toxicity

Two submitted studies evaluated the chronic toxicity of technical grade flumioxazin. Both studies evaluated reproductive success and mortality. An overview of results is presented in Table 6.1-8, with study details described in Appendix 8, Table A8-2.

Table 6.1-8: Chronic Studies on the Toxicity of Technical Grade Flumioxazin to Aquatic Invertebrates

Species	Exposure Duration	NOAEC	LOAEC	Reference (Classification)
Water flea (freshwater)	21 days	**28 µg a.i./L[1]**	57 µg a.i./L	MRID 44295011 (Acceptable/Guideline)
		mortality and reduced number of neonates per adult		
Mysid shrimp (estuarine/marine)	28 days	**15 µg a.i./L[2]**	27 µg a.i./L	MRID 44295013 (Acceptable/Guideline)
		mortality, reduced number of neonates per adult, and reduced growth		

[1]Value in bold was used to assess chronic risks to tolerant species of aquatic invertebrates.
[2]Value in bold was used to assess chronic risks to sensitive species of aquatic invertebrates.
Abbreviations: a.i. = active ingredient; L = liter; LOAEC = lowest-observed-adverse-effect concentration; µg = microgram; NOAEC = no-observed-adverse-effect concentration

A 21-day study in water fleas evaluated exposure to technical grade flumioxazin at concentrations up to 205 µg a.i./L (mean measured) (MRID 44295011). At 57 µg a.i./L, 5% mortality/immobility and a 43% reduction in neonates produced per adult were observed, compared to controls. Study authors identified a 21-day NOAEC of 28 µg a.i./L and a 21-day LOAEC of 57 µg a.i./L. In a 28-day study, mysid shrimp were exposed to flumioxazin at concentrations up to 55 µg a.i./L (mean measured) (MRID 44295013). At 27 µg a.i./L, 18% mortality, reduced growth, and a 56% reduction in the number of young/female per reproductive day were observed compared to controls. The 28-day NOAEC and LOAEC values for mortality and reproductive effects in mysid shrimp were identified as 15 and 27 µg a.i./L, respectively.

6.1.3.4. Aquatic Plants

Studies to assess the toxicity of technical grade flumioxazin to aquatic plants have been conducted on duckweed (an aquatic macrophyte) and several species of algae. In addition, studies also have assessed toxicity of three environmental metabolites of flumioxazin in duckweed and algae. As an herbicide, flumioxazin is expected to be toxic to aquatic plants.

6.1.3.4.1. Aquatic Macrophytes

Results of the available toxicity studies on the effects of flumioxazin in vascular plants were conducted in duckweed (*Lemna gibba*), a common indicator species. Results are summarized in Table 6.1-9; values reported are for the most sensitive endpoints measured. Experimental details are

summarized in Appendix 9, Table A9-1. Studies assessed the toxicity of technical grade flumioxazin and three environmental metabolites of flumioxazin.

Table 6.1-9: Toxicity of Technical Grade Flumioxazin and Environmental Metabolites of Flumioxazin to Aquatic Macrophytes (Duckweed)

Exposure Duration	Most Sensitive Endpoints	NOAEC	LOAEC	Reference (Classification)
Technical Grade Flumioxazin				
14 days	Frond density and biomass	**0.22 µg a.i./L[1]**	0.44 µg a.i./L	MRID 44295035 (Acceptable/Guideline)
Flumioxazin Metabolite 482-HA				
7 days	Final biomass	0.974 µg/L	3.94 µg/L	MRID 49198802 (Acceptable/Guideline)
Flumioxazin Metabolite APF				
7 days	Frond number and frond number growth rate	3080 µg/L	8880 µg/L	MRID 49198804 (Acceptable/Guideline)
Flumioxazin Metabolite THPA-2Na				
7 days	Frond number, frond growth rate, final biomass, biomass growth rate	10100 µg/L	>10100 µg/L	MRID 49198806 (Acceptable/Guideline)

[1]Value in bold was used to assess chronic risks to aquatic macrophytes.
Abbreviations: a.i. = active ingredient; APF = 6-amino-7-fluoro-4-(2-propynyl)-2*H*-1,4-benzoxazin-3(4*H*)-one; 482-HA = 7-fluoro-6-[(2-carboxyl-1-cyclohexenoyl)amino]-4-(2-propynyl)-1,4-benzoxazin-3-(2*H*)-one; L = liter; LOAEC = lowest-observed-adverse-effect concentration; µg = microgram; mg = milligram; NOAEC = no-observed-adverse-effect concentration; THPA = 3,4,5,6-tetrahydrophthalicacid

The toxicity study on technical grade flumioxazin exposed duckweed for 14 days to mean measured concentrations up to 1.7 µg a.i./L (MRID 44295035). NOAEC and LOEAC values of 0.22 and 0.44 µg a.i./L, respectively, were identified based on decreased frond density and frond biomass. Signs of toxicity included chlorotic fronds and fronds with reduced root formation or of smaller size than controls.

Three studies examined the toxicity of environmental metabolites of flumioxazin: 482-HA (MRID 49198802), APF (MRID 49198804), and THPA-2Na (MRID 49198806). All metabolites were less toxic than the parent compound. Metabolite 482-HA was identified as the most toxic metabolite, with NOAEL and LOAEL values of 0.974 and 3.94 µg/L, respectively. Comparison of LOAEL values indicates that 482-HA is approximately nine times less toxic than the parent compound (3.94 µg/L ÷ 0.44 µg a.i./L ≈9). However, direct comparison of toxicity values for 482-HA and parent compound may be misleading because exposure durations were not the same; the exposure duration was seven days for 482-HA and 14 days for parent compound. Typically, lower toxicity values are observed for longer compared to shorter exposure durations (ten Berge et al. 1986). Metabolites APF and THPA-2NA are also likely to be less toxic than the parent compound based on the 14-day LOAEL for flumioxazin of 0.44 µg/L (0.00044 mg a.i./L) compared to the LOAEL for APF of 8.88 mg/L.

6.1.3.4.2. Algae

Acute toxicity tests of flumioxazin are available for technical grade flumioxazin and three flumioxazin environmental metabolites. Studies were conducted using several algal species. Results for the most sensitive endpoints are summarized in Table 6.1-10; experimental details are summarized in Appendix 9, Table A9-2.

Table 6.1-10: Toxicity of Technical Grade Flumioxazin and Environmental Metabolites of Flumioxazin to Algae

Species	Exposure Duration	NOAEC	LOAEC	Reference (Classification)
Technical Grade Flumioxazin				
Freshwater green algae (*Selenastrum capricornutum)*	120 hours	**0.79 µg a.i./L[1]**	2 µg a.i./L	MRID 44295031 (Acceptable/ Guideline)
		Cell density		
Freshwater blue-green algae (*Anabaena flos-aquae*)	48 hours	**0.022 µg a.i./L[2]**	0.073 µg a.i./L	MRID 44295034 (Acceptable/ Guideline)
		Cell density		
Freshwater diatom *(Navicula pelliculosa*)	120 hours	<0.042 µg a.i./L	0.042 µg a.i./L	MRID 44295032 (Acceptable/ Guideline)
		Cell density		
Marine diatom (*Skeletonemia costatum*)	120 hours	1.9 µg a.i./L	3.7 µg a.i./L	MRID 44295033 (Acceptable/ Guideline)
		Cell density		
Flumioxazin Metabolite 482-HA				
Freshwater green algae (*Selenastrum capricornutum*)	72 hours	2.89 µg/L	7.57 µg/L	MRID 49198801 (Supplemental/ Guideline)
		AUC for growth		
Flumioxazin Metabolite APF				
Freshwater green algae (*Selenastrum capricornutum*)	72 hours	2970 µg/L	10900 µg/L	MRID 49198803
		Yield, growth rate, and AUC for growth		
Flumioxazin Metabolite THPA-2Na				
Freshwater green algae (*Selenastrum capricornutum*)	72 hours	9600 µg/L	>9600 µg/L	MRID 49198805
		No effects on yield, growth rate, and AUC for growth		

[1]Value in bold was used to assess chronic risks to tolerant species of algae.
[2]Value in bold was used to assess chronic risks to sensitive species of algae.
Abbreviations: a.i. = active ingredient; APF = 6-amino-7-fluoro-4-(2-propynyl)-2*H*-1,4-benzoxazin-3(4*H*)-one; AUC = area under the curve; 482-HA = 7-fluoro-6-[(2-carboxyl-1-cyclohexenoyl)amino]-4-(2-propynyl)-1,4-benzoxazin-3-(2*H*)-one; L = liter; LOAEC = lowest-observed-adverse-effect concentration; µg = microgram; mg = milligram; NOAEC = no-observed-adverse-effect concentration; THPA = 3,4,5,6-tetrahydrophthalicacid

The toxicity of technical grade flumioxazin was evaluated in freshwater green algae (MRID 44295031), freshwater blue-green algae (MRID 44295034), freshwater diatom (MRID 44295032), and marine diatom (MRID 44295033). For all studies, the most sensitive endpoint was cell density.

LOAEC values for technical grade flumioxazin range from 0.042 µg a.i./L in freshwater diatom to 2 µg a.i./L in freshwater green algae. Based on LOAEC values, freshwater diatom is the most sensitive species tested; however, a NOAEC was not identified in this study as effects were observed at the lowest concentration tested. An estimated NOAEC could be derived using the RQ method for endangered aquatic species, as described in SERA (2014a). This method estimates a NOAEC value by dividing the study EC50 value (1.4 µg a.i./L) by 20 (1.4 µg a.i./L ÷ 20 = 0.07 µg a.i./L). The estimated NOAEC of 0.07 µg a.i./L is higher than the NOAEC value of 0.022 µg a.i./L observed in freshwater blue-green algae. Therefore, the NOAEC value of 0.022 µg a.i./L value is identified as the most sensitive toxicity value for algae.

Similar to aquatic vascular plants, studies in freshwater green algae indicate that environmental metabolites of flumioxazin are less toxic than the parent compound. Metabolite 482-HA appears to be the most toxic metabolite, with a LOAEC of 7.57 µg/L. Metabolites APF and THPA-2Na are much less toxic, with LOAECs of 10.9 and >9.6 mg/L, respectively.

6.2. Exposure Assessment

6.2.1. Overview

A standard set of exposure assessments for terrestrial and aquatic organisms is provided in the Excel workbooks for flumioxazin (Attachments 1 – 6). The workbooks contain a set of worksheets that detail each exposure scenario. In FS risk assessments, the methodology and results of calculations are provided in the worksheets. For each exposure scenario, the worksheets provide the calculation of an exposure dose that is then compared to dose-response values in Section 6.3. These dose-values are then used to calculate HQs, as described in Section 0.

Calculations of exposure are based on the maximum application rates for each scenario (e.g., backpack application of a liquid or granules applied to the soil), which introduces a conservative bias into the resulting HQs. The maximum recommended labeled rate for formulations of flumioxazin in single aerial terrestrial applications relevant to FS activities is 0.38 lb a.i./acre. For application to the surface of water bodies, the maximum application rate is also 0.38 lb a.i./acre, and for subsurface applications, the recommended maximum application concentration is 400 ppb. The maximum application rate of the granular product is 0.38 lb a.i./acre. Only a single application rate is considered in the exposure assessment; however, as discussed in Section 2.3, different formulations have different recommended re-application frequencies. The Excel workbooks for the six application methods are provided in workbooks in Attachments 1 – 6 for backpack spray, boom spray, aerial spray, application to surface of water bodies, subsurface application to water bodies, and granular application.

As flumioxazin is an herbicide, all terrestrial and aquatic organisms aside from plants are considered "non-target." This HHERA evaluates potential effects on mammals, birds, invertebrates (i.e., honey bees), and plants, that could be exposed to flumioxazin during or after application. No toxicity data were identified for earthworms, reptiles, and amphibians; therefore, these receptors are not evaluated in this HHERA. Toxicity studies for aquatic organisms are available for freshwater and estuarine/marine fish, freshwater and estuarine/marine invertebrates, aquatic vascular plants, and algae.

For mammals and birds, the highest exposures are predicted to be associated with the consumption of treated or contaminated vegetation. This is a common pattern for pesticides that are applied to or intended to treat vegetation.

For terrestrial plants, five exposure scenarios are considered quantitatively: direct spray, spray drift, runoff, wind erosion, and the use of contaminated irrigation water. Similar to terrestrial invertebrates, the highest exposures for terrestrial plants are predicted to be associated with direct spray and spray drift. Nonetheless, as discussed in the risk characterization, runoff and sediment losses are also significant sources of potential exposure for terrestrial plants in sites that might favor runoff, particularly sites with predominantly clay soils. Potential exposures involving the use of contaminated water for irrigation are also significant. Wind erosion of soil does not appear to be a significant source of exposure; however, the product labels for flumioxazin provide cautionary language on this exposure route.

Exposures of aquatic organisms and plants to flumioxazin are based on the same information used to assess the exposure to terrestrial species from treated or contaminated water.

6.2.2. Terrestrial Organisms

6.2.2.1. Mammals and Birds

Terrestrial exposures for mammals and birds are estimated for direct spray, consumption of treated or contaminated vegetation or prey, ingestion of treated or contaminated water, and consumption of contaminated fish. For these exposure scenarios, five mammals and four birds of varying sizes are considered and summarized in Table 6.2-1.

Table 6.2-1: Terrestrial Mammals and Birds Used in the Ecological Risk Assessment

Animal	Representative Species	Body Weight (grams)	Food Consumption	Water Consumption
Mammals				
Small omnivore	Mice	20	2.514 $W^{0.507}$ [Eq 3-48]	0.099 $W^{0.9}$ [Eq 3-17]
Larger omnivore	Squirrels	400	2.514 $W^{0.507}$ [Eq 3-48]	0.099 $W^{0.9}$ [Eq 3-17]
Canid	Fox	5000	0.6167 $W^{0.862}$ [Eq 3-47]	0.099 $W^{0.9}$ [Eq 3-17]
Large Herbivore	Deer	70,000	1.518 $W^{0.73}$ [Eq 3-46]	0.099 $W^{0.9}$ [Eq 3-17]
Large Carnivore	Small bear	70,000	0.6167 $W^{0.862}$ [Eq 3-47]	0.099 $W^{0.9}$ [Eq 3-17]
Birds				
Small bird	Passerines	10	2.123 $W^{0.749}$ [Eq 3-36]	0.059 $W^{0.67}$ [Eq 3-15]
Predatory (carnivorous) bird	Owls	640	1.146 $W^{0.749}$ [Eq 3-37]	0.059 $W^{0.67}$ [Eq 3-15]
Piscivorous (fish-eating) bird	Herons	2,400	1.916 $W^{0.704}$ [Eq 3-38]	0.059 $W^{0.67}$ [Eq 3-15]

Animal	Representative Species	Body Weight (grams)	Food Consumption	Water Consumption
Large herbivorous bird	Geese	4000	1.146 $W^{0.749}$ [Eq 3-37]	0.059 $W^{0.67}$ [Eq 3-15]

Mammal Sources: U.S. EPA/ORD 1993.
Bird Sources: U.S. EPA/ORD 1993
Food consumption for vertebrates, based on allometric relationships estimating field metabolic rates in kcal/day for omnivores, herbivores, and non-herbivores. For mammals and birds, the estimates are based on Nagy (1987) as adapted by U.S. EPA/ORD (1993). The equation numbers refer to U.S. EPA/ORD (1993).
Abbreviations: W = body weight.

Because of the relationship of body weight to surface area and to the consumption of food and water, for any type of exposure, the dose for small animals is generally higher, in terms of mg/kg body weight, than the dose for large animals. Also, due to the differences in diet, not all the mammal and avian receptors are considered in each exposure scenario (SERA 2014a).

Flumioxazin exposures for each of these exposure pathways are estimated as described in the following subsections. The results of the exposure assessments for mammals are summarized in Worksheet G01a. Worksheet G01b include the results for birds.

6.2.2.1.1. Direct Spray

When conducting broadcast applications of any pesticide, the unintentional direct spray of wildlife species might occur. The amount of pesticide absorbed will depend on the application rate, surface area of the organism, and rate of absorption of the pesticide by the organism.

For this risk assessment, two different types of direct spray or broadcast exposures are estimated. The first scenario of direct spray exposures for mammals assumes a small (20 g) mammal is sprayed directly over one half of the body surface during flumioxazin application by broadcast spray (Attachments 1 – 3 Worksheet F01a). The absorbed dose over the first day is estimated using the assumption of first-order dermal absorption (Section 5.1.3.1.3). The estimated absorption rate for humans is used as a protective assumption. An empirical relationship between body weight and surface area is used to estimate the surface area of the animal. The estimates of absorbed doses of flumioxazin for this exposure scenario are intended to bracket the plausible levels of exposure for small mammals.

The second scenario of direct spray exposures for mammals assumes a small (20 g) mammal is sprayed directly with 100% absorption over one day of exposure (Worksheet F01b in Attachments 1 – 3). These estimates of absorbed doses of flumioxazin for this exposure scenario are intended to be the conservative upper limit of exposures and account for uncertainties in the estimation of flumioxazin doses associated with direct spray.

Direct spray exposure scenarios are not evaluated for large mammals. Based on allometric scaling of parameters used in the calculation of dose rates, larger mammals are predicted to be exposed to lower amounts of flumioxazin per kg body weight compared to smaller mammals. Exceedances are not observed under the assumption of first-order dermal absorption. As a result, calculation of direct

spray exposure scenarios for large mammals are predicted to have no impact on the characterization of risk.

For birds, exposure scenarios are evaluated for ingestion of contaminated fruit, foliage, water, and fish. Dermal exposure of waterfowl or aquatic or semi-aquatic mammals through direct spray or contact with treated or contaminated water during wading and swimming are not considered in this assessment. There is significant uncertainty associated with dermal exposures for ecological receptors and no standard regulatory approaches have been developed to determine the contribution of deposition to fur or feathers on dermal absorption. The ecological assessment assumes that ingestion is the primary route of exposure.

6.2.2.1.2. Dermal Contact with Treated or Contaminated Vegetation

When estimating the potential significance of dermal contact with treated or contaminated vegetation, it is assumed that there is a relationship between the application rate and dislodgeable foliar residue, as well as a transfer rate from the treated or contaminated vegetation to the skin. While estimates of transfer rates are available for the human health risk assessment, there are no transfer rates available for wildlife species. Therefore, the lack of data regarding kinetics of this process precludes a quantitative assessment for this exposure scenario. However, the inability to quantify dermal contact with treated or contaminated vegetation adds relatively little uncertainty to this risk assessment because the consumption of treated or contaminated vegetation is the greatest source of exposure.

6.2.2.1.3. Ingestion of Treated or Contaminated Vegetation or Contaminated Prey

The ingestion of contaminated or treated vegetation may occur following foliar applications of pesticides. Exposures associated with the ingestion of treated or contaminated vegetation are evaluated for all mammals and birds, with the exception of the large carnivorous mammal and predatory bird.

The initial concentrations of flumioxazin on treated or contaminated food items are based on the residues rates from Fletcher et al. (1994) as summarized in Table 5.2-12. Residue rates are provided for four different classes of plant material, including short grass, tall grass, broadleaf vegetation, and fruits. Fruit has the lowest pesticide residue rate while short grass has the highest pesticide residue rate. For each of these four types of vegetation, both acute and chronic exposure scenarios are developed and summarized in Worksheet G01a (mammals) and G01b (birds) of Attachments 1 – 3. The methods of estimating the peak and time-weighted average concentrations of flumioxazin in vegetation are identical to those used in the human health risk assessment (Section 5.2.2.7).

The acute and chronic exposure scenarios are based on the conservative assumption that mammals consume vegetation at the site of application for 100% of their diet (SERA 2014a). This may not be realistic for some acute exposures and seems less likely in chronic exposures given that animals might move in and out of the treated areas over a prolonged period of time. While estimates of the proportion of the treated or contaminated food items can be adjusted in the exposure assessment, the estimates would be arbitrary.

Other estimates used in the exposure assessment include food consumption rates and field metabolic rates. The estimated food consumption rates by various species of mammals and birds are based on field metabolic rates (kcal/day) adapted from U.S EPA (U.S. EPA/ORD 1993). The field metabolic rates are based on the caloric value (kcal/day dry weight) of the food items considered in the risk assessment and estimates of the water content of the various foods. Additional information on food consumption rates and field metabolic rates is provided in the FS risk assessment guidance (SERA 2014a).

In addition to exposure scenarios for the ingestion of treated or contaminated vegetation, similar scenarios are provided for the consumption of small mammals by either a predatory mammal (Worksheet F10a) or a predatory bird (Worksheet F10b) in Attachments 1 – 3 and 6. The consumption of contaminated insects by a small mammal, a larger (400 g) mammal, and a small bird are also considered (Worksheets F09a-c) in Attachments 1 – 3.

6.2.2.1.4. Ingestion of Treated or Contaminated Water

Mammals might be exposed to flumioxazin by direct ingestion of treated or contaminated surface water. The methods for estimating flumioxazin concentrations in water are identical to those used in the human health risk assessment (Section 5.2.2.4.5), except for the body weight and quantity of water consumed by the mammal or bird. The results of exposure assessments for mammals and birds are summarized in Worksheets F02a-f (accidental spill), Worksheets F08a-f (peak/acute concentrations), and Worksheets F16a-f (chronic concentrations) in Attachments 1 – 6.

While food and water consumption rates in mammals and birds vary substantially with diet, season, and other factors, quantitative estimates regarding the variability of water consumption rates are not well documented. Therefore, this variability is not considered in the exposure assessment. Regardless, the upper and lower bound estimates of flumioxazin concentrations in surface water vary substantially, as summarized in Table 5.2-7. Given this variability in the estimated concentrations of flumioxazin in surface water, it is unlikely that a quantitative consideration of the variability in water consumption rates of mammals and birds would have a substantial impact on the risk assessment.

6.2.2.1.5. Consumption of Contaminated Fish

In addition to the consumption of contaminated vegetation, insects, and other terrestrial prey, the consumption of contaminated fish is a potential route of exposure. Exposure scenarios are developed for the consumption of contaminated fish after an accidental spill (Attachments 1 – 6 Worksheets F03a-c), expected peak exposures (Worksheets F011a-c), and estimated longer-term concentrations (Worksheets F17a-c). These exposure scenarios are applied to 5 and 70 kg carnivorous mammals as well as a 2.4 kg piscivorous bird. The 70 kg carnivorous mammal is representative of a small or immature brown bear (*Ursus arctos*), which is a large mammal that actively feeds on fish (SERA 2014a). As summarized in Table 6.2-1, the 5 kg mammal is representative of a fox, and the 2.4 kg bird is representative of a heron.

Exposures associated with the consumption of contaminated fish depend on the flumioxazin concentration in water and the BCF for flumioxazin in fish (SERA 2014a). The concentrations of flumioxazin in water are summarized in Section 5.2.2.4.5. A BCF of 22.4 for whole fish was derived as

described in Table 2.1-1. This BCF is used for the exposure scenarios involving the consumption of contaminated fish by mammalian or avian receptors.

6.2.2.2. Terrestrial Invertebrates

Terrestrial invertebrates might be exposed to flumioxazin through direct contact or consumption of treated or contaminated vegetation or prey. This section summarizes the exposure associated with the direct spray and drift, ingestion of treated or contaminated vegetation or prey, and contact with contaminated soil. Table 6.2-2 includes a list of the invertebrates used to assess exposure levels.

Table 6.2-2: Terrestrial Invertebrates Used in the Ecological Risk Assessment

Animal[1]	Representative Species	Body Weight (grams)	Food Consumption
Honey bees[2]	*Apis mellifera*	0.116	≈2 (1.2 – 4)[3]
Herbivorous insects	Various	Not used	1.3 (0.6 – 2.2)

[1] Sources of honey bee data in this table: Humphrey and Dykes 2008; Reichle et al. 1973

[2] A surface area of 1.42 cm^2 is used for the direct spray scenario of the honey bee. This value is based on the algorithms suggested by Humphrey and Dykes (2008) for a bee with a body length of 1.44 cm.

[3] For honey bees, food consumption based on activity and caloric requirements. Used only when estimates of concentrations in nectar and/or pollen can be made, which is not the case in the current risk assessment.

6.2.2.2.1. Direct Spray and Spray Drift

Because of the relationship of body size to surface area, very small organisms such as bees and other terrestrial invertebrates might be exposed to a much higher dose of flumioxazin per unit body weight compared to small mammals. Honey bees are typically used by U.S. EPA as a surrogate for other terrestrial insects, and honey bee exposure levels associated with broadcast applications are modeled as a simple physical process based on the application rate and surface area of the bee (SERA 2014a). FS risk assessments use 1.42 cm^2 as the surface area of the honey bee, which is based on the algorithms suggested by Humphrey and Dykes (2008) for a bee with a body length of 1.44 cm.

Estimated levels of exposure to honey bees following terrestrial applications are provided in Worksheet G09 of Attachments 1 – 3. The amount of the pesticide deposited on a bee or shortly after application is dependent on how close the bee is to the application site, as well as foliar interception of the spray prior to deposition on the bee. The estimated proportions of the nominal application rate at various distances downwind given in Worksheet G09 in Attachments 1 – 3 are based on Tier 1 estimates from AgDRIFT (Bird et al. 2002) for distances of 0 (direct spray) to 900 feet downwind of the treated site. Further details on the use of AgDRIFT are discussed in Section 6.2.2.3.2 (Off-Site Drift) with respect to non-target vegetation.

In addition to drift, FS risk assessments take into consideration that foliar interception of a pesticide might occur after application. The impact of foliar interception depends on the nature of the canopy above the bee. According to a study summarized by SERA 2014a, Wimmer et al. (1993) report that deposition in the lower canopy, relative to the upper canopy, generally ranged from about 10% (90% foliar interception in the upper canopy) to 90% (10% foliar interception by the upper canopy). Based

on this information, FS risk assessments use the foliar interception rates of 0% (no interception), 50%, and 90% as shown in Worksheet G09 in Attachments 1 – 3.

6.2.2.2.2. Ingestion of Treated or Contaminated Vegetation or Prey

Terrestrial invertebrates might be exposed to flumioxazin through the consumption of treated or contaminated vegetation (or other plant products; in the case of honey bees, nectar) or contaminated prey. The exposure scenario was not completed because no toxicity data were found for earthworms.

6.2.2.3. Terrestrial Plants

When applying an herbicide, the primary hazard to non-target terrestrial plants is typically unintended direct deposition or spray drift. Other potential hazards include the transportation of herbicides by percolation, runoff, or movement of contaminated soil particles by wind. As a result, five exposure scenarios are considered quantitatively for terrestrial plants: direct spray, spray drift, runoff, contaminated irrigation water, and wind erosion. The following subsections describe the risks associated with these exposure scenarios.

6.2.2.3.1. Direct Spray

Exposure levels associated with unintended direct spray are equivalent to the application rate. It is also plausible that some non-target plants immediately adjacent to the application site could be sprayed directly. Exposure estimates from direct spray are included in Attachments 1 – 3 Worksheet G05. This worksheet also includes the scenario that assesses offsite drift (Section 6.2.2.3.2).

6.2.2.3.2. Off-Site Spray Drift

Off-site drift is based on estimates from AgDRIFT (Bird et al. 2002). These estimates are summarized in Worksheets G05a and G05b of the Attachments. The worksheets were customized to include estimates of drift for backpack, boom (ground broadcast) and aerial applications. The AgDRIFT estimates are based on using Tier 1 analyses for aerial and ground broadcast applications. The term *Tier 1* is used to designate relatively generic and simple assessments, which can be viewed as plausible upper limits of drift (SERA 2014a). In Worksheet G05a, aerial drift estimates are based on Tier 1 analyses using American Society of Agricultural Engineers (ASAE) fine to medium drop size distributions. Tier 1 estimates of drift for ground broadcast applications are modeled using both low boom and high boom options in AgDRIFT. For both types of applications, the values are based on very fine to fine drop size distributions and the 90th percentile values from AgDRIFT. The use of small droplet sizes in Worksheet G05a is intended to generate extremely conservative estimates of drift that would not be anticipated in typical FS applications.

In Worksheet G05b, aerial drift estimates are based on Tier 1 analyses using ASAE coarse to very coarse droplet size distributions (VMD≈440 µm), and the ground broadcast applications are based on ASAE fine to medium coarse drop size distributions (VMD≈340 µm). The product label for SureGuard™ Herbicide states that the "largest droplet size consistent with acceptable efficacy" should be used. Based on this information, the drift values given in Worksheet G05b are likely to reflect estimates of drift that would be more typical of FS applications compared to the extremely conservative estimates of drift given in Worksheet G05a.

Drift associated with backpack applications (directed foliar applications) is likely to be much less than drift from ground broadcast applications. Few studies, however, are available for quantitatively assessing drift after backpack applications. Consistent with previous FS risk assessments, estimates of drift from backpack applications are based on an AgDRIFT Tier 1 run of a low boom ground application using fine to medium/coarse drop size distributions (rather than very fine to fine) as well as 50th percentile estimates of drift (rather than the 90th percentile used for ground broadcast applications).

It is important to note that the values for drift used in this risk assessment are intended to be general estimates. Actual drift will vary according to a number of conditions (e.g., the topography, soils, weather, drop size distribution, carrier, and the pesticide formulation).

6.2.2.3.3. Runoff and Sediment Loss

Herbicides may be transported from the soil at the application site by runoff, sediment loss, or percolation. As summarized in Section 5.2.2.4, runoff, sediment loss, and percolation are considered in estimating contamination of ambient water. However, for assessing off-site soil contamination, only runoff and sediment loss are considered. This is because off-site runoff and sediment transport have the potential for contaminating the off-site soil surface, which might impact non-target plants. In contrast, percolation represents the amount of the herbicide that is transported below the root zone, which might have an impact to water quality but no off-site vegetation. The exception to this is if the contaminated water is used for irrigation. The use of contaminated water for irrigation is discussed in Section 6.2.2.3.4.

Exposures associated with runoff and sediment losses from the treated site to an adjacent untreated site are summarized in Worksheet G04 of Attachments 1 – 3 and 6. The exposure scenario for runoff and sediment losses assumes that the pesticide is lost from the treated field and spread uniformly over an adjacent untreated field of the same size. More severe exposures could occur if all the runoff losses were distributed into a much smaller area. Conversely, lower exposures would occur if runoff losses were distributed from the treated field to a much larger area.

The results of the GLEAMS modeling are used to provide estimates of runoff and sediment loss. Specifically, the off-site application rates used in Worksheet G04 are taken from the results of the GLEAMS-Driver modeling summarized in Appendix 10: Flumioxazin Arial Broadcast Foliar GLEAMS-Driver Modeling Results

(Table 1). The estimated runoff is taken as the average of values of clay, loam, and sand, which are presented as central, lower, and upper estimates (i.e., 0.03 (0.00000011 – 0.3) lb/acre). These values are rounded to one significant place in Worksheet G04.

The input parameters used to estimate runoff and sediment losses are identical to those used in the GLEAMS-Driver modeling for concentrations of flumioxazin in surface water as discussed in Section 5.2.2.4.3. This includes using the same soil types (i.e., clay, loam, and sand) and nine sites that represent different temperatures and rainfall patterns. As presented in Appendix 10: Flumioxazin Arial Broadcast Foliar GLEAMS-Driver Modeling Results

, the results of the standard GLEAMS modeling of runoff and sediment will vary substantially with different types of climates (i.e., temperature and rainfall), as well as soils.

6.2.2.3.4. Contaminated Irrigation Water

The levels of exposure associated with this scenario will depend on the concentration of flumioxazin in the ambient water used for irrigation and the amount of irrigation water that is applied. Concentrations in ambient water are based on the peak concentrations modeled in the human health risk assessment, which are discussed in Section 5.2.2.4.5. In the environment, flumioxazin photodegrades rapidly in water and in soil; it is classified as having medium soil mobility potential (U.S. EPA 2012). Flumioxazin is relatively volatile in water and soil.

The amount of irrigation water that may be applied is highly dependent on the climate, soil type, topography, and plant species under cultivation. Thus, the selection of an irrigation rate is somewhat difficult. In the absence of any general approach of determining and expressing the variability of irrigation rates, the application of one inch of irrigation water with a range of 0.25 to 2 inches is used in FS risk assessment (SERA 2014a). The exposure levels associated with this scenario are summarized in Worksheet G06a in Attachments 1 – 6.

6.2.2.3.5. Wind Erosion

Wind erosion might lead to pesticides being transported off-site. The amount of flumioxazin that might be transported by wind erosion depends on several factors, including the application rate, depth of incorporation into the soil, persistence in the soil, wind speed, and topographical and surface conditions of the soil (SERA 2014a). Potential effects of wind erosion are estimated in Worksheet G06b of Attachments 1 – 3 and 6. For this risk assessment, it is assumed that flumioxazin is incorporated into the top 1 cm of soil, which is identical to the depth of incorporation used in GLEAMS modeling. It is also estimated that average soil losses range from 1 to 10 metric tons/ha/year with a central estimate of 5 tons/ha/year. These estimates are typically used in FS risk assessments and are based on the results of agricultural field studies, which reported annual soil losses ranging from 2 to 6.5 metric tons/ha (SERA 2014a).

As summarized in Worksheet G06b, off-site losses from wind erosion are estimated to reach a maximum of 0.014% of the application rate (approximately 0.005 lb a.i./A for the upper bound estimate). According to one study, total soil erosions from all sources in well-managed forests typically range from 0.12 to 0.24 metric tons/ha/year, which is below the range used in Worksheet G06b (i.e., 1 – 10 metric tons/ha/year) (Patric 1976). Thus, losses due to wind erosion following pesticide applications under forest canopies or heavily vegetated areas might be much less than the estimates used in this risk assessment.

Another study reported that wind erosion of other herbicides could be associated with losses up to 1.5% of the nominal application rate following soil incorporation or 4.5% following surface application (Larney et al. 1999). However, in this study, much higher soil losses were noted by the authors (i.e., up to 56.6 metric tons/ha from a fallow field). Based on this, the losses reflected in Worksheet G06b (1, 5 and 10 tons of soil/hectare/year) might be more realistic for forest or rangeland application since forestry application of herbicides are rarely applied to fallow areas.

No specific studies are available on wind erosion for flumioxazin. Product labels state not to apply when weather conditions favor drift; however, this applies to drift of spray volume rather than wind erosion of treated soil. As discussed further in Section 6.4.2.5.4, the current risk assessment does not raise concerns for wind erosion relative to other routes of exposure. In addition, the open

literature does not include field studies that address the issue of non-target damage by flumioxazin due to the wind erosion. Regardless, the product labels must be considered carefully prior to applying flumioxazin.

6.2.3. Aquatic Organisms

The concentrations of flumioxazin in surface water used to estimate exposures for aquatic species are identical to those used in the human health risk assessment. This information is provided in Section 5.2.2.4.5.

6.3. Dose-Response Assessment

6.3.1. Overview

The toxicity values used in the ecological risk assessment are summarized in Table 6.3-1. The derivation of each of these values is discussed in the subsections below. Based on the available toxicity data, the dose-response assessments are divided into eight classes of organisms, which include:

1. Terrestrial mammals
2. Birds
3. Terrestrial invertebrates
4. Terrestrial plants
5. Fish
6. Aquatic invertebrates
7. Aquatic macrophytes
8. Aquatic algae

Experimental details for each study are included in the corresponding appendices (e.g., number of animals per exposure group, animal weight and age, dosing vehicles such as dietary or gavage, static vs flow-through conditions, etc.). Based on the lack of toxicity data for reptiles or terrestrial or aquatic phase amphibians, no dose-response assessments were developed for these organisms. Also, to maintain consistency with the exposure assessment, which is necessary for the development of the HQs in the risk characterization, all toxicity values in Table 6.3-1 are expressed as active ingredient. The toxicity values in Table 6.3-1 are used in conjunction with exposure estimates calculated using the maximum labeled application rate of 0.38 lb a.i./acre (see Section 6.2) to develop HQs. The HQ is the estimated exposure (mg/kg/day) divided by the toxicity value (mg/kg/day). HQs >1 indicate that the estimated exposure exceeds the toxicity value.

Table 6.3-1: Toxicity Values Used in the Ecological Risk Assessment for Flumioxazin

Group/ Organism	Type	Endpoint and Toxicity Value	Effect	Reference
Terrestrial Animals				
Acute				
Mammals	NA	Acute gavage NOAEL (rat): 3 mg a.i./kg/day	Fetal cardiovascular abnormalities	MRID 42684925

Group/ Organism	Type	Endpoint and Toxicity Value	Effect	Reference
Birds	NA	Acute dietary NOAEL (mallard duck): 1728 mg a.i./kg	No lethality or sublethal effects	MRID 42684946
Honey Bee	NA	Acute contact assay NOAEL: 905 mg a.i./kg	No lethality or sublethal effects	MRID 42684951
Chronic				
Mammals	NA	Chronic dietary NOAEL (rat): 1.8 mg a.i./kg/day	Increased incidence of chronic nephropathy and extramedullary hematopoiesis in males and decreased hematological parameters in females	MRID 44295028
Birds	NA	Chronic dietary NOAEL (mallard duck): 32.8 mg a.i./kg/day	Reduction in viable embryos and live 3-week embryos	MRID 44295005
Terrestrial Plants				
Soil	Sensitive	Dicot seedling emergence NOAEL (lettuce): 0.0004 lb a.i./acre	Reduced dry eight	MRID 44295029
	Tolerant	Dicot seedling emergence NOAEL (soybean): 0.096 lb a.i./acre	Reduced dry weight and height	
Foliar	Sensitive	Dicot vegetative vigor NOAEL (cucumber): 0.00005 lb a.i./acre	Phytotoxicity	MRID 44295030
	Tolerant	Monocot vegetative vigor NOAEL (corn): 0.0060 lb a.i./acre	Reduced dry weight	
Aquatic Animals				
Acute				
Fish	Sensitive	Lethal and sublethal effects NOAEC (rainbow trout): 0.92 mg a.i./L	Lethal and sublethal effects (swimming at surface, loss of equilibrium and lethargy)	MRID 42684948
	Tolerant	Sublethal effects NOAEC (sheepshead minnow): 4.7 mg a.i./L	No lethality or sublethal effects observed	MRID 44295010
Invertebrates	Sensitive	Sublethal effects NOAEC (mysid shrimp): 0.10 mg a.i./L	Lethality and sublethal effects (lethargy)	MRID 44295009
	Tolerant	Estimated NOAEC for immobility (water flea): 0.27 mg a.i./L	Immobility[1]	MRID 42684950

Group/ Organism	Type	Endpoint and Toxicity Value	Effect	Reference
Chronic				
Fish	Sensitive	2-generation reproduction NOAEC (fathead minnow): 0.51 µg a.i./L	Reduced larval survival in F1 generation	MRID 49733408
	Tolerant	Sublethal effects NOAEC (rainbow trout): 7.7 µg a.i./L	Reduced length and weight in 60-day post-hatch trout	MRID 44295012
Invertebrates	Sensitive	Sublethal effects NOAEC (mysid shrimp): 15 µg a.i./L	Impaired reproduction and reduced growth (length and weight)	MRID 44295013
	Tolerant	Sublethal effects NOAEC (water flea): 28 µg a.i./L	Reduction in neonates produced per adult	MRID 44295011
Aquatic Plants				
Macrophytes	NA	NOAEC (duckweed): 0.22 µg a.i./L	Reduced frond density and frond biomass	MRID 44295035
Algae	Sensitive	NOAEC (freshwater blue-green algae): 0.022 µg a.i./L	Reduced cell density	MRID 44295034
	Tolerant	NOAEC (freshwater green algae): 0.79 µg a.i./L	Reduced cell density	MRID 44295031

[1]One study was identified to assess acute toxicity to freshwater invertebrates. In this study, precipitate and daphnia immobility were observed at every concentration tested. In the U.S. EPA DER for this study, U.S. EPA stated that "the material does not appear to have toxicological characteristics that we would consider serious thus presenting probable high risk to test organisms represented by Daphnia." An estimated NOAEC was calculated using the RQ method for endangered aquatic species, as described in SERA (2014a).
Abbreviations: a.i. = active ingredient; DER = Data Evaluation Record; U.S. EPA = U.S. Environmental Protection Agency; F1 = first generation; L = liter; µg = microgram; mg = milligram; NA = not applicable; NOAEC = no-observable-adverse-effect concentration; level; NOAEL = no-observable-adverse-effect level

In general, FS risk assessments defer to U.S. EPA/OPP on study selection for the most sensitive species within the classes of organisms covered in the ecological risk assessment, unless there is other available information or a specific reason for deviating from U.S. EPA. An exception to this is mammals. In characterizing risks to mammalian wildlife, FS risk assessments generally use the NOAELs which serve as the basis for the acute and chronic RfDs from the human health risk assessment (SERA 2014a). Another example involves the endpoints used for risk characterization. For acute exposures, the U.S. EPA will often use LD_{50} or comparable definitive toxicity values (e.g., EC_{50}, EC_{25}) for risk characterization, but the FS prefers to use NOAEL or NOAEC values (SERA 2014a). NOAECs are based on non-parametric assays for differences between groups while EC_{25} values are based on non-linear curve-fitting. The use of these different statistical methods may lead to NOAEC values that exceed the EC_{25} values. In these cases, the lowest toxicity values (EC_{25} or NOAEC) are selected for the FS risk assessment.

6.3.2. Terrestrial Organisms

6.3.2.1. Mammals

When data are available in more than one species, risks to sensitive and tolerant species among subgroups of mammals may be assessed.

Acute. As discussed in Section 5.3.1, U.S. EPA (2012) derived an acute RfD of 0.03 mg a.i./kg/day for females of child-bearing potential. This RfD is based on the NOAEL of 3 mg a.i./kg/day for cardiovascular abnormalities from a gestational exposure study in rats, divided by an MOE 100 (3 mg a.i./kg/day ÷ 100 = 0.03 mg a.i./kg/day) (MRID 42684925). Although the exposure duration in this study was multiple days (GD 6 – 15), U.S. EPA/OPP generally regards effects on offspring as potentially associated with exposure on a single day. In addition, developmental effects are considered appropriate for ecological risk assessments as these effects can influence population dynamics. Therefore, the NOAEL value of 3 mg a.i./kg/day is used to assess acute risk to mammals.

Chronic. U.S. EPA (2012) derived a chronic RfD of 0.02 mg a.i./kg/day for flumioxazin based on the NOAEL value of 1.8 mg a.i./kg/day for nephropathy in male rats and decreased hematological parameters in female rats and a total uncertainty factor of 100 (1.8 mg a.i./kg/day ÷ 100 = 0.02 mg a.i./kg/day); the associated LOAEL is 18 mg a.i./kg/day (MRID 44295028); additional details are provided in Section 5.3.2. The NOAEL value of 1.8 is mg a.i./kg/day is used to assess chronic risks to sensitive mammalian species.

6.3.2.2. Birds

Acute. U.S. EPA (2003) classified the acute toxicity of flumioxazin to avian species as "practically non-toxic" based on an acute oral (gavage) LD_{50} >2250 mg a.i./kg in bobwhite quail (MRID 42684945) and an acute dietary LC_{50} of >5620 ppm in mallard ducks (MRID 42684946), equivalent to >1728 mg a.i./kg (see Table A5-1 for calculation details); these values are the highest doses/concentrations tested. The FS prefers to use NOAELs or NOAECs rather than LD_{50} or LC_{50} values for risk characterization of acute exposures of birds. Acute toxicity studies in birds are available for gavage exposure of bobwhite quail (MRID 42684945) and dietary exposure in mallard ducks (MRID 42684946) and bobwhite quail (MRID 42684947). As discussed in Section 6.1.2.2.1 with study details in Table A5-1, no lethality or adverse effects were observed in either study; therefore, the highest doses tested are taken as NOAEL values. The lowest acute NOAEL of 1728 mg a.i./kg in mallard ducks is used to assess acute risks to birds.

Chronic. U.S. EPA (2003) characterized chronic risks to birds using a NOAEL value of 100 ppm (equivalent to 32.8 mg a.i./kg/day) for reduction in viable embryos and live three-week embryos in an avian reproduction study in mallard ducks (MRID 44295005). Two chronic dietary exposure studies in birds are available: the study used by U.S. EPA (2003) in mallard ducks and a study in bobwhite quail that did not identify any adverse effects at the highest dose tested of 63.5 mg a.i./kg/day (MRID 44295006). To assess risks to birds, the NOAEL value 32.8 mg a.i./kg/day in mallard ducks is used.

6.3.2.3. Reptiles and Amphibians (Terrestrial-Phase)

Due to the lack of available toxicity data for reptiles or terrestrial-phase amphibians, a dose-response assessment for flumioxazin cannot be derived for this group of organisms.

6.3.2.4. Terrestrial Invertebrates

6.3.2.4.1. Honey Bees

Acute Contact. Contact toxicity studies are typically used to assess the effects of direct spray or spray drift to terrestrial insects. One acute contact study in honey bees was identified (MRID 42684951). U.S. EPA (2003) classified acute toxicity of flumioxazin to honey bees as "practically non-toxic" based on the LD_{50} value of >105 µg a.i./bee; no mortality was observed (MRID 42684951). The FS considers LD_{50} >105 µg a.i./bee to be a NOAEL, as no treatment-related morality or clinical signs of toxicity were observed in this study. Taking the average body weight of 116 mg for a bee, this NOAEL is equivalent to a dose of approximately 905 mg a.i./kg [0.105 mg ÷ 0.000116 kg = 905 mg a.i./kg]. This NOAEL is used for the risk characterization of honey bees .

Acute Oral Toxicity. FS risk assessments attempt to characterize risks to terrestrial invertebrates from the consumption of treated or contaminated vegetation (or other plant products such as nectar in the case of honey bees) when adequate data are available. However, acute oral toxicity studies on oral toxicity of flumioxazin to honey bees were not identified.

6.3.2.4.2. Soil Toxicity Values (Earthworms)

Due to the lack of available toxicity data on earthworms, a dose-response assessment for flumioxazin cannot be derived for this group of organisms.

6.3.2.5. Terrestrial Plants (Macrophytes)

As summarized in Section 6.1.3.4.1 and Table 6.1-9, adequate data are available for developing toxicity values for plant species involving soil exposures (i.e., herbicide runoff to an untreated field) and foliar exposures (direct spray, wind erosion, or drift). Studies on seedling emergence are used to assess risks associated with exposures to soil residues of flumioxazin. Studies on vegetative vigor are used to assess risks associated with the deposition of flumioxazin onto plants. As an herbicide, it is anticipated that exposure to non-target vegetation will cause toxicity. As discussed in Section 2.1, flumioxazin is a light-dependent peroxidizing herbicide that has a phototoxic mechanism of action. Toxicity tests might not include the same light wavelength and intensity as natural sunlight; therefore, flumioxazin might be more toxic under field conditions compared to laboratory conditions. Results of seedling emergence and vegetative vigor studies are summarized in Section 6.1.3.4.1, with details provided in Tables A6-1 and A6-2.

Seedling Emergence. Seedling emergence studies show that dicots are more sensitive than monocots (MRID 44295029). In dicots the most sensitive species is lettuce, with a NOAEL of 0.0004 lb a.i./acre; in comparison, onion was the most sensitive monocot species with a NOAEL of 0.0015 lb a.i./acre. Therefore, the NOAEL of 0.0004 lb a.i./acre in lettuce is used to assess risks to sensitive plants from soils exposure (MRID 44295029). To assess risks to tolerant species for seedling emergence, the highest NOAEL value of 0.096 lb a.i./acre in soybean is used (MRID 44295029).

Vegetative Vigor. To assess risks of foliar application of flumioxazin to plants, the lowest NOAEL value of 0.00005 lb a.i./acre for oats, corn, rye grass, and onion (monocots) is used to assess risks of foliar application to sensitive species (MRID 44295030). To assess risks to the most tolerant species, the highest NOAEL value of 0.0060 lb a.i./acre for oats, corn, rye grass, and onion is used (MRID 44295030).

6.3.2.6. Terrestrial Microorganisms

Due to the lack of available toxicity data for terrestrial microorganisms, a dose-response assessment was not derived for this group of organisms.

6.3.3. Aquatic Organisms

The FS prefers to use NOAECs rather than LC_{50} values used by U.S. EPA/OPP for risk characterization of acute exposures of aquatic species. When data are available, the FS assesses risks for both sensitive and tolerant species; however, U.S. EPA/OPP typically does not derive separate risk estimates for potentially tolerant species of fish. In the U.S. EPA (2003) assessment of flumioxazin, risks to freshwater and estuarine/marine species were evaluated separately. The FS typically does not conduct separate assessments for freshwater and estuarine/marine species; instead, data from both freshwater and estuarine/marine species are used to identify the most sensitive and tolerant species of fish and aquatic invertebrates.

6.3.4. Fish

Acute. Acute toxicity data are available in freshwater and estuarine/marine fish species. U.S. EPA (2003) used the 96-hour LC_{50} value of 2.3 mg a.i./L in rainbow trout (MRID 42684948) to characterize risks to freshwater fish and the 96-hour LC_{50} value of >4.7 mg a.i./L in sheepshead minnow (no mortality was observed) to characterize acute risks to estuarine/marine fish (44295010). Review of NOAEC values in fish indicates that the most sensitive species is rainbow trout, with a NOAEC value of 0.92 mg a.i./L for lethality and sublethal effects (MRID 42684948); this value is used to assess risks to sensitive species of fish for acute exposure. The highest NOAEC value in fish is a NOAEC value of 4.7 mg a.i./L in sheepshead minnow (MRID 44295010); this value is used to assess acute risks to tolerant species of fish. Details of these studies are provided in Table A7-1. Notes that acute toxicity studies on environmental flumioxazin metabolites conducted in fathead minnow show that metabolites classified as “practically non-toxic”” are less toxic than flumioxazin (see discussion in Section 6.1.3.1.1).

Chronic. As with acute exposure, chronic toxicity data are available in freshwater and estuarine/marine fish species. To assess chronic risks to freshwater fish, U.S. EPA (2003) used the NOAEC value of 7.7 µg a.i./L (0.0077 mg a.i./L) from an early life-stage study in rainbow trout (MRID 44295012). However, U.S. EPA (2003) did not assess chronic risks of estuarine/marine fish to flumioxazin because no studies in this species category were identified at the time that the 2002 risk assessment was finalized. An early life stage study in sheepshead minnow, conducted in 2015 and recently submitted to U.S. EPA (MRID 49733407), reported a NOAEC value of 1.1 µg a.i./L for decreased total length in sheepshead minnow. The FS has selected the lowest NOAEC of 0.51 µg a.i./L (0.00051 mg a.i./L) for reduced larval survival from a 2-generation study in fathead minnow to assess chronic risks to sensitive species of fish (MRID 49733408). To assess chronic risks to tolerant fish, the highest NOAEC of 0.0077 mg a.i./L for reduced growth from an early life-stage study in rainbow trout (MRID 44295012) was selected; this is the same endpoint used by U.S. EPA (2003). Details of these studies are provided in Table A7-2.

As noted in above Section 6.3.2.5, flumioxazin is a light-dependent peroxidizing herbicide that has a phototoxic mechanism of action. While this mechanism might enhance toxicity to plants under field conditions compared to laboratory conditions, it is not expected that toxicity of flumioxazin in non-

plant species would increase under enhanced lighting conditions. However, early life-stage tests in fathead minnow under standard and enhanced lighting conditions showed that enhanced lighting increased toxicity, with a NOAEC of 3.3 for standard conditions and a NOAEC of 0.35 µg a.i./L for enhanced lighting conditions (MRID 49733406; see Table A8-2 for study details). As noted in Section 6.1.3.1.2, the study DER reported standard lighting conditions as 540 – 850 lux and enhanced lighting as 1330 – 1728 µWatts/cm^2; unfortunately, these units cannot be converted to a common unit for comparison purposes. The NOAEC of 0.35 µg a.i./L in fathead minnow under enhanced lighting conditions is slightly lower than the NOAEC of 0.51 µg a.i./L in fathead minnow used to assess chronic risks to freshwater fish. The potential for increased toxicity under enhanced lighting conditions is further considered in the risk characterization.

6.3.4.1. Amphibians (Aquatic-Phase)

The lack of toxicity data on aquatic phase amphibians precludes the development of a dose-response assessment for this group of organisms. U.S. EPA uses fish as surrogates for aquatic phase amphibians.

6.3.4.2. Aquatic Invertebrates

6.3.4.2.1. Acute

Studies have been conducted in water flea (MRID 42684950), mysid shrimp (MRID 44295009), and eastern oyster (MRID 44295008). U.S. EPA (2003) used the 48-hour LC_{50} value of 5.5 mg a.i./L in water flea to assess risks to freshwater invertebrates and the 96-hour LC_{50} value of 0.23 mg a.i./L from the study in mysid shrimp to assess risk to estuarine/marine invertebrates. To assess risks of acute exposure to aquatic invertebrates for sensitive species, the FS evaluated data from the studies in mysid shrimp and eastern oyster, as these species have very similar toxicity values, which are lower than those reported for water flea. The study in mysid shrimp identified 96-hour EC_{50}, LOAEC, and NOAEC values of 0.23, 0.22, and 0.10 mg a.i./L, respectively. The study in eastern oyster identified 96-hour EC_{50}, LOAEL, and NOAEC values of 2.4, 0.64, and <0.64 mg a.i./L, respectively. A NOAEC value was not identified in eastern oyster, with sublethal effects (reduced shell growth) observed at all concentration of flumioxazin tested. An estimated NOAEL of 0.27 mg a.i./L in eastern oyster can be calculated using the RQ method for endangered aquatic species, as described in SERA (2014a):

Estimated NOAEC = $EC_{50} \div 20$
Estimated NOAEC = 24 mg a.i./L ÷ 20 = 0.12 mg a.i./L

The estimated NOAEC value of 0.12 mg a.i./L in eastern oyster is nearly identical to the empirical NOAEC value in mysid shrimp of 0.10 mg a.i./L. To characterize risks to sensitive aquatic invertebrates, the NOAEC value of 0.10 mg a.i./L in mysid shrimp is used. Details of these studies are provided in Table A8-1.

The study in water fleas is used to evaluate risks of acute exposure of tolerant species of aquatic invertebrates (MRID 42684950). In this study, precipitate was observed in test chambers at all concentrations of flumioxazin tested (see discussion in Section 6.1.3.3.1 and Table A8-1). The U.S. EPA DER initially classified this study as unacceptable due to the precipitate, however, following a request for reconsideration by the registrant and re-review the study, the study classification was

upgraded to supplemental. The DER states that, "the material does not appear to have toxicological characteristics that we would consider serious thus presenting probable high risk to test organisms represented by Daphnia." Toxicity data for this study are based on centrifuged mean measured concentrations. OPP/U.S. EPA (2003) used the 48-hour LC_{50} value of 5.5 mg a.i./L to assess risks to freshwater aquatic invertebrates. Due to daphnid immobility at every test concentration tested, possibly due, in part, to the presence of precipitate, LOAEL and NOAEL values for this study could not be determined. For this assessment, an estimated NOAEL of 0.27 mg a.i./L was calculated using the RQ method for endangered aquatic species, as described in SERA (2014a):

Estimated NOAEC = $EC_{50} \div 20$
Estimated NOAEC = 5.5 mg a.i./L ÷ 20 = 0.27 mg a.i./L

6.3.4.2.2. Chronic

Two chronic exposure studies in aquatic invertebrates were identified: one study in water flea (MRID 44295011) and one in mysid shrimp (MRID 44295013). To assess chronic risks to aquatic invertebrates, U.S. EPA (2003) used the 21-day NOAEC value of 28 µg a.i./L for freshwater invertebrates and the 28-day NOAEC value of 15 µg a.i./L for estuarine/marine invertebrates. For this assessment, comparison of LOAEC values shows that mysid shrimp (28-day LOAEC: 27 µg a.i./L) are more sensitive that water flea (21-day LOAEC: 57 µg a.i./L) under chronic exposure conditions. Therefore, the NOAEC values of 15 µg a.i./L in mysid shrimp and 28 µg a.i./L in water flea are used to assess chronic risks to aquatic invertebrates in sensitive and tolerant species, respectively. Study details are summarized in Table A8-2.

6.3.4.3. Aquatic Plants

As an herbicide, it is anticipated that exposure to flumioxazin will be toxic to aquatic plants. As discussed above (Section 6.3.2.5), flumioxazin is a light-dependent peroxidizing herbicide that has a phototoxic mechanism of action. Data from laboratory toxicity tests are not likely to mimic all field conditions. Therefore, flumioxazin could be more or less toxic under field conditions compared to controlled laboratory conditions.

6.3.4.3.1. Aquatic Macrophytes

Studies evaluating toxicity of flumioxazin to aquatic macrophytes are summarized in Section 6.1.3.4.1 and Table A9-1. The lowest NOAEC reported is 0.22 µg a.i./L (MRID 44295035) for decreased frond density and biomass in a 14-day exposure study in duckweed. This value is used to assess risks to aquatic macrophytes. U.S. EPA (2003) included this study to assess risks to aquatic plants.

6.3.4.3.2. Algae

Bioassays in several algal species have been conducted to assess the toxicity of flumioxazin (see Section 6.1.3.4.2 and Table A9-2). The most sensitive species is the freshwater blue-green alga *Anabaena flos-aquae*, with a NOAEC value of 0.022 µg a.i./L for decreased biomass (MRID 44295034). The most tolerant species is the freshwater green alga *Selenastrum capricornutum*, with a NOAEC value of 0.79 µg a.i./L for decreased biomass (MRID 44295031). The NOAEC values of 0.022 and 0.79 µg a.i./L are used to characterize risks to sensitive and tolerant species of algae,

respectively. U.S. EPA (2003) used results of several studies, including the two studies used in this assessment, to assess risks to algae.

6.4. Risk Characterization

6.4.1. Overview

The quantitative risk characterization for ecological receptors is based on the HQ approach, as discussed in Section 5.4.1. Risks for ecological receptors are evaluated for the six application methods considered in this assessment. Detailed quantitative risk characterizations are provided in each of the six workbooks on the following worksheets: G02a, terrestrial mammals; G02b, birds; G03, aquatic species (including aquatic plants); G05, terrestrial plants (spray drift); G06a, terrestrial plants (irrigation); G06b, terrestrial plants (wind erosion); and G09, honey bees. All estimated exposures are based on the maximum single application rate of 0.38 lb a.i./acre.

As with most ecological risk assessments, the characterization of risks for flumioxazin is limited by the available data on species that might be exposed and on interactions that could occur among species that could affect risk. Although the goal is to select species that are representative, flumioxazin has been tested in a small number of species under conditions that might not well-represent natural populations of nontarget organisms. This leads to uncertainties that might result in over- or underestimates of risk.

6.4.1.1. Terrestrial Organisms

Exposure scenarios posing risks to terrestrial organisms are summarized in Tables 6.4-1, with details discussed in the sections that follow. For exposures to mammals, HQs for several acute scenarios exceed the LOC, with the highest risks for the consumption of water or fish, with consistently elevated risks for consumption of fruits and vegetation treated with or contaminated by spray applications. Risks for chronic exposure are less than for acute exposures. Smaller mammals are at higher risk than larger mammals. Chronic exposure of birds results in modest exceedances, with no HQs >1 for acute exposures. Flumioxazin is expected to pose serious risk to non-target terrestrial vegetation, as anticipated for an herbicide.

Table 6.4-1: Exposure Scenarios Posing Risks Terrestrial Species

Exposure Scenario	HQs[1] at Maximum Application Rate			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Accidental acute exposure of mammals				
Direct spray, 100% absorption	1.5 – 6	NA	NA	NA
Water consumption	<1	<1	<1 – 5	<1 – 1.8
Fish consumption	<1 – 6	<1 – 4	<1 – 177	<1 – 65
Non-accidental acute exposure of mammals				
Fruit consumption	<1 – 7	NA	NA	<1
Broadleaf foliage consumption	≤1 – 49	NA	NA	<1
Tall grass consumption	≤1 – 40	NA	NA	<1
Short grass consumption	<1 – 88	NA	NA	<1

Exposure Scenario	HQs[1] at Maximum Application Rate			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Water consumption	<1	<1	<1	<1
Insect consumption	<1 – 12	NA	NA	<1
Fish consumption	<1	<1	<1	<1
Chronic exposure of mammals				
fruit consumption	<1 – 1.1	NA	NA	<1
Broadleaf foliage consumption	≤1 – 8	NA	NA	<1
Tall grass consumption	<1 – 6	NA	NA	<1
Short grass consumption	<1 – 14	NA	NA	<1
Water consumption	<1	NA	NA	<1
Fish consumption	<1	NA	NA	<1
Accidental acute exposure of birds				
Water consumption	<1	<1	<1	NA
Fish consumption	<1	<1	<1	NA
Acute exposure of birds				
Fruit consumption	<1	NA	NA	<1
Broadleaf foliage consumption	<1	NA	NA	<1
Tall grass consumption	<1	NA	NA	<1
Short grass consumption	<1	NA	NA	<1
Insect consumption	<1	NA	NA	<1
Water consumption	<1	NA	NA	<1
Fish consumption	<1	NA	NA	<1
Fruit consumption	<1	NA	NA	<1
Chronic exposure of birds				
Fruit consumption	<1	NA	NA	<1
Broadleaf foliage consumption	≤1	NA	NA	<1
Tall grass consumption	<1	NA	NA	<1
Short grass consumption	<1 – 1.8	NA	NA	<1
Water consumption	<1	NA	NA	<1
Fish consumption	<1	NA	NA	<1
Fruit consumption	<1	NA	NA	<1
Acute exposure of terrestrial invertebrates				
Honey bee, topical exposure	<1	NA	NA	NA

Exposure Scenario	HQs[1] at Maximum Application Rate			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Terrestrial plants				
Spray drift	<1 – 7600	NA	NA	NA
Run-off	<1 – 285	NA	NA	<1 – 366
Irrigation	<1 – 306	<1 – 63	45 – 362	<1 – 612
Wind erosion	<1	<1	<1	<1

[1]HQ ranges are for lower to upper bound exposure estimates. HQs listed as <1 or ≤1 (with no range) indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).
Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ

HQ ≤1
HQ >1 – <2
HQ ≥2

6.4.1.2. Aquatic Organisms

Table 6.4-2 summarizes exposure scenarios that pose risks to aquatic species. Compared to terrestrial species, risks to aquatic species are much more substantial. Aquatic macrophytes and algae are the most sensitive organisms to flumioxazin exposure, followed by aquatic invertebrates and then fish. For aquatic plants, significant toxicity, including death of macrophytes and algae, is anticipated for all exposure scenarios. This outcome is not unexpected, as flumioxazin is approved for use to control aquatic plants. The most substantial risks to aquatic invertebrates are for accidental acute exposures, with only marginal risks for chronic/longer-term exposures. Fish are the least sensitive species, but risks including mortality are anticipated as the toxicity value is based on a NOAEC for mortality and sublethal effects; this is especially a concern for high accidental exposures due to spills of field solutions into water bodies. Note that there is uncertainty in the risk estimates developed for fish. As discussed below in Section 6.4.3.1, environmental metabolites of flumioxazin are less toxic than flumioxazin which could result in an overestimate of risks of acute exposure to fish. However, enhanced lighting conditions enhances the toxicity of flumioxazin to fish, which could result in an underestimate of risks if fish habitat is in shallow water.

Table 6.4-2: Exposure Scenarios Posing Risks Aquatic Species

Exposure Scenario	HQs[1] at Maximum Application Rate			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Fish				
Accidental acute exposure	<1 – 4	<1 – 2	2 – 107	1.5 – 39
Non-accidental acute exposure	<1	<1	<1	<1
Chronic exposure	<1 – 6	<1 – 9	<1 – 53	<1 – 15

Exposure Scenario	HQs[1] at Maximum Application Rate			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Aquatic Invertebrates				
Accidental acute exposure	1.3 – 348	<1 – 212	36 – 9.8E03	24 – 3.6E03
Non-accidental acute exposure	<1 – 3	<1 – 7	1.5 – 40	<1 – 7
Chronic exposure	<1	<1	<1 – 1.8	<1
Aquatic macrophytes				
Accidental acute exposure	1.6E03 – 1.5E04	963 – 9.6E03	4.4E04 – 4.5E05	3.3E04 – 1.6E05
Non-accidental acute exposure	<1 – 154	31 – 314	1.8E03	<1 – 307
Chronic exposure	14	21	2 – 122	35
Algae				
Accidental acute exposure	183 – 1.6E05[3]	112 – 9.6E04	5.2E03 – 4.5E06	3.8E03 – 1.6E06
Non-accidental acute exposure	<1 – 1.5E03	4 – 3.1E03	211 – 1.8E04	<1 – 3.1E03
Chronic exposure	<1 – 140	<1 – 212	<1 – 1.2E03	<1 – 348

[1]HQ ranges are for lower to upper bound exposure estimates. HQs listed as <1 or ≤1 (with no range) indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).

Key: cells are colored for the highest HQ

HQ ≤1
HQ >1 – <2
HQ ≥2

6.4.1.3. Secondary Effects

While the risk characterization for flumioxazin focuses on the potential for direct toxic effects, there is potential for secondary effects. Terrestrial and direct water applications of any effective herbicide, including flumioxazin, are likely to alter vegetation within the treatment area. This alteration could have secondary effects on terrestrial or aquatic animals, including changes in food availability and habitat quality. These secondary effects might be beneficial to some species and detrimental to others. Also, the magnitude of secondary effects is likely to vary over time. While these concerns are acknowledged, they are not specific to flumioxazin or herbicide applications.

6.4.2. Terrestrial Organisms

6.4.2.1. Mammals

6.4.2.1.1. Accidental Acute Exposures

Quantitative risk estimates for accidental acute exposure of mammals are summarized in Table 6.4-3. The toxicity value used to assess these risks is the NOAEL value 3 mg a.i./kg/day, with a LOAEL value of 10 mg a.i./kg/day; this yields a NOAEL to LOAEL ratio of 3.3 (10 ÷ 3 = 3.3). Thus, HQs ranging from >1 to 3 are likely to overestimate risks (i.e., <LOAEL). For direct spray applications of small mammals assuming 100% absorption, HQs exceed the LOC (central estimate HQ: 3; upper estimate HQ: 6). Although the 100% absorption assumption from dermal exposure is highly unlikely, other factors, such as grooming, might contribute to absorption from ingestion. Exceedances are not

observed under the assumption of first-order dermal absorption. For ingestion of water, HQs for subsurface applications of flumioxazin to water bodies range from 1.1 (central estimate) for a large mammal to 5 (upper bound estimate) for a small mammal. For granular application, HQ for ingestion of water slightly exceed the LOC (range: 1.0 – 1.8) only for the upper bound estimate of exposure; therefore, exceedances are considered modest for mammals for this application method. For consumption of contaminated fish, HQs exceed the LOC for all application methods, with the highest risks observed for subsurface water application with HQs ranging from 11 (central estimate for larger animal) to 177 (upper estimate for canid). Adverse effects to mammals are anticipated from consumption of fish contaminated by an accidental spill.

Table 6.4-3: Hazard Quotients (HQs) for Accidental Acute Exposures of the Mammals

Exposure Scenario[1]	HQs[2] for Application Methods			
	Spray[3]	Direct Water Surface	Direct Water Subsurface	Granular
Direct Spray				
First-order absorption, Small mammal	<1[4]	NA	NA	NA
100% absorption, Small mammal	1.5 (lower)[4] 3 (central)[4] 6 (upper)[4]	NA	NA	NA
Consumption of Contaminated Water (Spill)				
Small mammal	<1	<1	<1 (lower) 2 (central) 5 (upper)	<1 (lower and central) 1.8 (upper)
Larger mammal	<1	<1	<1 (lower) 1.8 (central) 4 (upper)	<1 (lower and central) 1.3 (upper)
Canid	<1	<1	<1 (lower) 1.4 (central) 3 (upper)	≤1
Large mammal	<1	<1	<1 (lower) 1.1 (central) 2 (upper)	<1
Consumption of Contaminated Fish (Spill)				
Larger mammal	<1 (lower and central) 4 (upper)	<1 (lower and central) 3 (upper)	<1 (lower) 11 (central) 123 (upper)	<1 (lower) 4 (central) 45 (upper)

Exposure Scenario[1]	HQs[2] for Application Methods			
	Spray[3]	Direct Water Surface	Direct Water Subsurface	Granular
Canid	<1 (lower and central)	<1 (lower and central)	<1 (lower)	<1 (lower)
	6 (upper)	4 (upper)	16 (central) 177 (upper)	6 (central) 65 (upper)

[1]Small mammal (20 g); larger mammal (400 g); canid (5 kg); large mammal (70 kg)
[2]HQs listed as <1 or ≤1 only indicate that HQs for lower, central, and upper estimates are all ≤1.
[3]Unless otherwise indicated, HQs are for aircraft aerial spray application; HQs for backpack directed foliar spray and boom ground spray are lower.
[4]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).
Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ
HQ ≤1
HQ >1 – <2
HQ ≥2

6.4.2.1.2. Non-Accidental Acute Exposures

HQs for acute (non-accidental) exposures of mammals are provided in Table 6.4-4. HQs exceed the LOC only for spray applications for consumption of treated or contaminated fruit, vegetation, and insects. Risks are inversely proportional to the size of the mammal. The highest HQ of 88 (upper bound estimate) is for ingestion of treated or contaminated short grass by a small mammal. Most HQs exceeding the LOC are for central and upper bound exposure estimates. Given that most HQs are above 3, adverse effects are anticipated for mammals, especially smaller mammals, for most exposure scenarios for consumption of treated or contaminated vegetation and insects.

Table 6.4-4: Hazard Quotients (HQs) for Acute Exposures of the Mammals

Exposure Scenario[1]	HQs[2] for Application Methods			
	Spray[3]	Direct Water Surface	Direct Water Subsurface	Granular
Contaminated Fruit (Lowest Residue Rates)				
Small Mammal	<1 (lower) 2 (central) 7 (upper)	NA	NA	<1
Larger Mammal	<1 (lower and central) 1.7 (upper)	NA	NA	<1
Large Mammal	≤1.0	NA	NA	<1
Contaminated Broadleaf Foliage				
Small Mammal	1 (lower) 10 (central) 49 (upper)	NA	NA	<1

Exposure Scenario[1]	HQs[2] for Application Methods			
	Spray[3]	Direct Water Surface	Direct Water Subsurface	Granular
Larger Mammal	<1 (lower) 2 (central) 11 (upper)	NA	NA	<1
Large Mammal	≤1 (lower) 1.3 (central) 6 (upper)	NA	NA	<1
Contaminated Tall Grass				
Small Mammal	<1 (lower) 8 (central) 40 (upper)	NA	NA	<1
Larger Mammal	<1 (lower) 1.8 (central) 9 (upper)	NA	NA	<1
Large Mammal	≤1 (lower and central) 5 (upper)	NA	NA	<1
Contaminated Short Grass (Highest Residue Rate)				
Small mammal	1.9 (lower) 18 (central) 88 (upper)	NA	NA	<1
Larger Mammal	<1 (lower) 4 (central) 20 (upper)	NA	NA	<1
Large Mammal	<1 (lower) 2 (central) 11 (upper)	NA	NA	<1
Contaminated Insects				
Small Mammal	<1 (lower) 2 (central) 12 (upper)	NA	NA	<1
Larger Mammal	<1 (lower and central) 3 (upper)	NA	NA	<1
Contaminated Water				
Small Mammal	<1	<1	<1	<1
Larger Mammal	<1	<1	<1	<1
Canid	<1	<1	<1	<1
Large Mammal	<1	<1	<1	<1

Exposure Scenario[1]	HQs[2] for Application Methods			
	Spray[3]	Direct Water Surface	Direct Water Subsurface	Granular
Consumption of a Small Mammal				
Canid	<1	NA	NA	<1
Consumption of Contaminated Fish				
Large Mammalian Carnivore	<1	<1	<1	<1
Canid	<1	<1	<1	<1

[1]Small mammal (20 g); larger mammal (400 g); canid (5 kg); large mammal (70 kg)
[2]HQs listed as <1 or ≤1 only indicate that HQs for lower, central, and upper estimates are all ≤1.
[3]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).
Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ
HQ ≤1
HQ >1 – <2
HQ ≥2

6.4.2.1.3. Chronic/Longer-Term Exposures

For chronic/longer-term exposures of mammals, risks appear much lower than for accidental acute and non-accidental acute exposures. HQs are summarized in Table 6.4-5. Exceedances are limited to consumption of contaminated broadleaf foliage, tall grass, and short grass for spray applications only, with higher risks for smaller mammals. Most HQs based on the central exposure estimate only modestly exceed 1.

Table 6.4-5: Hazard Quotients (HQs) for Chronic Exposures of the Mammals

Exposure Scenario[1]	HQs[2] for Application Methods			
	Spray[3]	Direct Water Surface	Direct Water Subsurface	Granular
Contaminated Fruit (Lowest Residue Rates)				
Small mammal	<1 (upper and central) 1.1 (upper)	NA	NA	<1
Larger mammal	<1	NA	NA	<1
Large mammal	<1	NA	NA	<1
Contaminated Broadleaf Foliage				
Small mammal	<1 (lower) 1.5 (central) 8 (upper)	NA	NA	<1
Larger mammal	<1 (upper and central) 1.7 (upper)	NA	NA	<1
Large mammal	≤1	NA	NA	<1

Exposure Scenario[1]	HQs[2] for Application Methods			
	Spray[3]	Direct Water Surface	Direct Water Subsurface	Granular
Contaminated Tall Grass				
Small mammal	<1 (lower) 1.2 (central) 6 (upper)	NA	NA	<1
Larger mammal	<1 (lower) 1.4 (upper)	NA	NA	<1
Large mammal	<1	NA	NA	<1
Contaminated Short Grass (Highest Residue Rate)				
Small mammal	<1 (lower) 3 (central) 14 (upper)	NA	NA	<1
Larger mammal	<1 (upper and central) 3 (upper)	NA	NA	<1
Large mammal	<1 (upper and central) 1.8 (upper)	NA	NA	<1
Contaminated Water				
All mammals	<1	<1	<1	<1
Consumption of Contaminated Fish				
Large mammalian carnivore	<1	<1	<1	<1
Canid	<1	<1	<1	<1

[1]Small mammal (20 g); larger mammal (400 g); canid (5 kg); large mammal (70 kg)
[2]HQs listed as <1 or ≤1 only indicate that HQs for lower, central, and upper estimates are all ≤1.
[3]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).
Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ
HQ ≤1
HQ >1 – <2
HQ ≥2

6.4.2.2. Birds

For accidental and non-accidental acute exposures of birds, no HQs exceed the LOC for any exposure scenario for any of the application methods. For chronic/longer-term exposures, a marginal exceedance was derived for small birds for consumption of treated or contaminated short grass (HQ: 1.8) for upper bound exposure. Therefore, adverse effects to avian species are not expected.

6.4.2.3. Reptiles and Amphibians (Terrestrial-Phase)

No quantitative risk characterization was developed for reptiles or terrestrial-phase amphibians because the available toxicity data do not support a dose-response assessment (Section 6.3.2.3). As

discussed in Section 6.1.2.3, EPA typically uses birds as surrogates for reptiles and terrestrial-phase amphibians.

6.4.2.4. Terrestrial Invertebrates

HQs were developed for direct spray and spray drift exposures to honey bees. All HQs are well below the LOC. The highest HQ is 0.03 for direct spray with no foliar interceptions. Direct exposure to flumioxazin at the maximum application rate does not pose risks to honey bees. No toxicity data on ingestion of contaminated water or nectar by honey bees were located; this is considered a data gap. No data are available for other species of terrestrial invertebrates.

6.4.2.5. Terrestrial Plants

Flumioxazin is an effective herbicide and adverse effects on nontarget plant species are likely for several application scenarios. This is demonstrated by the high HQs discussed in the following sections. For exposures involving spray application, care should be taken to minimize exposure of non-target vegetation. As noted in the dose-response section (6.3.2.5), flumioxazin is a light-dependent, peroxidizing herbicide that has a phototoxic mechanism of action. Toxicity tests may not include the same light wavelength and intensity as natural sunlight; therefore, flumioxazin may be more toxic under field conditions compared to laboratory conditions. Therefore, risks to plants might be underestimated by the HQs derived in this assessment.

6.4.2.5.1. Direct Spray and Spray Drift

HQs for direct spray and spray drifts are shown in Table 6.4-6. Direct spray of flumioxazin will damage both sensitive and tolerant non-target plant species. HQs indicate exposures through spray drift will also damage plants. However, site-specific conditions, such as wind speed and foliar interception, might affect the extent of damage. For example, application conducted in low wind in areas with adjacent vegetation would limit risks.

Table 6.4-6: Hazard Quotients (HQs) for Direct Spray and Spray Drift Exposure of Terrestrial Plants

Distance Downwind (feet)	HQs[1] for Spray Applications
Sensitive Species	
0	7600
25	1695
50	1300
100	744
300	237
500	147
900	94

Distance Downwind (feet)	HQs[1] for Spray Applications
Tolerant Species	
0	63
25	14
50	11
100	6
300	2.0
500	1.2
900	0.8

[2]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).

Key: cells are colored for the highest HQ

HQ ≤1
HQ >1 – <2
HQ ≥2

6.4.2.5.2. Soil Exposures by Runoff

Soil runoff exposure of terrestrial plants applies to spray and granular applications only. HQs for spray and granular application methods are similar, with higher estimates for granular applications (Table 6.4-7). For sensitive species of plants, HQs for granular applications to soil for central and upper bound estimates are 43 and 366, respectively. For tolerant plants, upper bound estimates only modestly exceed the LOC for spray (HQ: 1.2) and granular (HQ: 1.5) applications. Soil type and rainfall will influence the extent of flumioxazin runoff.

Table 6.4-7: Hazard Quotients (HQs) for Soil Exposure by Runoff of Terrestrial Plants

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Sensitive species	<1 (lower)	NA	NA	<1 (lower)
	29 (central) 285 (upper)			43 (central) 366 (upper)
Tolerant species	<1 (lower and central)	NA	NA	<1 (lower and central)
	1.2 (upper)			1.5 (upper)

[1]HQs listed as <1 or ≤1 only indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).
Abbreviation: NA = not applicable

Key: cells are colored for the highest HQ

HQ ≤1
HQ >1 – <2
HQ ≥2

6.4.2.5.3. Contaminated Irrigation Water

HQs for exposure of non-target vegetation through contaminated irrigation water are summarized in Table 6.4-8. For sensitive species, contamination of irrigation water from all application methods is expected to damage sensitive species of non-target vegetation. For tolerant species, risks are much lower, and damage is likely to be minimal, even for the highest exposures. Risks are highest for direct subsurface application to water bodies and granular applications.

Table 6.4-8: Hazard Quotients (HQs) for Irrigation Exposure of Terrestrial Plants

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Sensitive species	<1 (lower)	<1 (lower)	45 (lower)	<1 (lower)
	19 (central)	6 (central)	181 (central)	34 (central)
	306 (upper)	63 (upper)	362 (upper)	612 (upper)
Tolerant species	<1 (lower and central)	<1	<1 (lower)	<1 (lower and central)
	3 (upper)		1.5 (central)	5 (upper)
			3 (upper)	

[1]HQs listed as <1 or ≤1 only indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]Values include the range of HQs for all spray application methods (backpack directed foliar spray, boom ground spray, and aircraft aerial spray).

Key: cells are colored for the highest HQ

	HQ ≤1
	HQ >1 – <2
	HQ ≥2

6.4.2.5.4. Wind Erosion

Risks to non-target vegetation are not expected for wind erosion of soil following spray applications. The highest HQ is 1.0 for the upper bound estimate for sensitive species for spray and granular applications, and the highest HQ for tolerant species of 0.004 for the same exposure scenarios.

6.4.2.6. Terrestrial Microorganisms

The toxicity of flumioxazin to terrestrial microorganisms is not addressed in the available literature (Section 6.1.2.6). Consequently, no risk characterization for this group of organisms was developed.

6.4.3. Aquatic Organisms

6.4.3.1. Fish

HQs for exposures of fish to flumioxazin are summarized in Table 6.4-9. HQs exceed the LOC for accidental acute (e.g., accidental spills of field solutions into water bodies), non-accidental acute, and chronic/longer-term exposures. The greatest concern (e.g., highest HQs) for toxicity to fish is for accidental acute exposure from spills of subsurface field solutions, with HQs ranging from 2 for the lower bound estimate in tolerant species to 107 for the upper bound estimate in sensitive species. HQs for granular applications are slightly lower than for spills of subsurface field solutions. Spray and direct surface water risks exceed 1 but are much lower. For spray and direct surface water spills,

adverse effects in sensitive species of fish are possible but only for higher exposures, whereas toxicity is expected to occur to sensitive and tolerant species for spills of subsurface field solutions and granular product. No adverse effects in fish are expected for non-accidental acute exposures, with all HQs below the LOC. For chronic/longer-term exposure, although HQs indicate that toxicity is likely to occur at higher exposures for all application methods, risks may be overestimated. The toxicity value used to assess chronic risk was obtained from a study conducted under flow-through conditions (e.g., a constant concentration of flumioxazin over the exposure period). Under field conditions, a single application of flumioxazin would be expected to degrade rapidly in water. If studies had been conducted under static conditions, it is expected that LOAEC values would have been higher (i.e., less toxic). Thus, chronic HQs based on a flow-through toxicity values are likely to be overestimated and highly conservative.

Table 6.4-9: Hazard Quotients (HQs) for Exposure of Fish

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Accidental Acute Exposure				
Sensitive	<1 (lower) 1.9 (central) 4 (upper)	<1 (lower) 1.2 (central) 2 (upper)	11 (lower) 53 (central) 107 (upper)	8 (lower) 20 (central) 39 (upper)
Tolerant	<1	<1	2 (lower) 10 (central) 21 (upper)	1.5 (lower) 4 (central) 8 (upper)
Non-Accidental Acute Exposure				
Sensitive	<1	<1	<1	<1
Tolerant	<1	<1	<1	<1
Chronic/Longer-Term Exposure				
Sensitive	<1 (lower and central) 6 (upper)	<1 (lower and central) 9 (upper)	<1 (lower) 1.2 (central) 53 (upper)	<1 (lower and central) 15 (upper)
Tolerant	<1	<1	<1 (lower and central) 3 (upper)	≤1

[1]HQs listed as <1 or ≤1 only indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]HQs are for aircraft aerial application; these HQs are higher than for backpack directed foliar spray and boom ground spray.

Key: cells are colored for the highest HQ
- HQ ≤1
- HQ >1 – <2
- HQ ≥2

Two findings from studies in fish add considerable uncertainty to this assessment: (1) lower toxicity of metabolites, and (2) increased toxicity under enhanced lighting conditions. Acute toxicity studies on environmental flumioxazin metabolites conducted in fathead minnow show that metabolites are less toxic than flumioxazin (see discussion in Section 6.1.3.1.1) and are classified as “practically non-

toxic" to fish. Therefore, acute risks to fish could be overestimated if exposure under field conditions is dominated by metabolites rather than parent compound. However, a study in fathead minnow showed that flumioxazin toxicity was increased under enhanced lighting conditions, compared to standard lighting conditions (MRID 49733406; see discussion in Section 6.1.3.1.1). No data were available to assess effects of enhanced lighting in other aquatic species. Considering that flumioxazin has a photoactive mechanism, fish could be much more sensitive to flumioxazin under actual exposure conditions. Thus, risks to fish, and possibly other aquatic species, could be underestimated in this assessment.

6.4.3.2. Amphibians (Aquatic-Phase)

As discussed in Section 6.3.3.2, no dose-response assessment can be developed for aquatic-phase amphibians due to the lack of toxicity data. In the absence of data, U.S. EPA typically uses fish as surrogates for aquatic-phase amphibians.

6.4.3.3. Aquatic Invertebrates

As summarized in Table 6.4-10, HQs for accidental acute exposure of sensitive aquatic invertebrates for all application methods greatly exceed 1, indicating that severe toxicity will occur, even at lower exposure estimates. Although HQs are lower for tolerant species, risks also are substantial. For non-accidental exposures, toxicity to sensitive species of aquatic invertebrates is expected for all application methods, with the highest risks associated with direct subsurface application. For non-accidental acute exposure of tolerant species, the only HQ exceeding the LOC is 1.5 for direct subsurface application to water. Chronic/longer-term exposure is unlikely to cause toxicity to aquatic invertebrates; the only HQ >1 is 1.8 for the upper exposure for subsurface water applications for sensitive species.

Table 6.4-10: Hazard Quotients (HQs) for Exposure of Aquatic Invertebrates

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Accidental Acute Exposure				
Sensitive	35 (lower) 174 (central) 348 (upper)	21 (lower) 106 (central) 212 (upper)	984 (lower) 4.9E03 (central) 9.8E03 (upper)	726 (lower) 1.8E03 (central) 3.6E03(upper)
Tolerant	1.3 (lower) 6 (central) 13 (upper)	<1 (lower) 4 (central) 8 (upper)	36 (lower) 182 (central) 364 (upper)	27 (lower) 67 (central) 134 (upper)
Non-Accidental Acute Exposure				
Sensitive	<1 (lower and central 3 (upper)	<1 (lower) 1.4 (central) 7 (upper)	40 (lower, central, upper)	<1 (lower and central 7 (upper)
Tolerant	<1	<1	1.5 (lower, central, upper)	<1

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Chronic/Longer-Term Exposure				
Sensitive	<1	<1	<1 (lower and central 1.8 (upper)	<1
Tolerant	<1	<1	≤1	<1

[1]HQs listed as <1 or ≤1 only indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]HQs are for aircraft aerial application; these HQs are higher than for backpack directed foliar spray and boom ground spray.

Key: cells are colored for the highest HQ
HQ ≤1
HQ >1 – <2
HQ ≥2

6.4.3.4. Aquatic Plants

As a light-dependent, peroxidizing herbicide, flumioxazin has a phototoxic mechanism of action. Toxicity tests for aquatic plants may not include the same light wavelength and intensity as natural sunlight; therefore, flumioxazin may be more toxic under field conditions compared to laboratory conditions. Therefore, risks to aquatic plants might be underestimated by the HQs derived in this assessment.

6.4.3.4.1. Macrophytes

Risks to aquatic macrophytes are substantial, with very high HQs for all applications of flumioxazin (Table 6.4-11). This is not an unexpected result, as flumioxazin is approved for control of aquatic vegetation. The only toxicity data available for aquatic macrophytes is from studies in duckweed; therefore, a more tolerant species of macrophytes was not identified.

Table 6.4-11: Hazard Quotients (HQs) for Exposure of Aquatic Macrophytes

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Accidental Acute Exposure				
Sensitive	1.6E03 (lower) 7.9E03 (central) 1.5E04 (upper)	963 (lower) 4.8E03 (central) 9.6E03 (upper)	4.4E04 (lower) 2.2E05 (central) 4.5E05 (upper)	3.3E04 (lower) 8.2E04 (central) 1.6E05 (upper)
Tolerant	No toxicity data	No toxicity data	No toxicity data	No toxicity data
Non-Accidental Acute Exposure				
Sensitive	<1 (lower) 19 (central) 154 (upper)	31 (lower) 63 (central) 314 (upper)	1.8E03 (lower, central, upper)	<1 lower) 34 (central) 307 (upper)
Tolerant	No toxicity data	No toxicity data	No toxicity data	No toxicity data

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Chronic/Longer-Term Exposure				
Sensitive	<1 (lower and central) 14 (upper)	<1 (lower and central) 21 (upper)	<1 (lower) 3 (central) 122 (upper)	<1 (lower and central) 35 (upper)
Tolerant	No toxicity data	No toxicity data	No toxicity data	No toxicity data

[1]HQs listed as <1 or ≤1 only indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]HQs are for aircraft aerial application; these HQs are higher than for backpack directed foliar spray and boom ground spray.

Key: cells are colored for the highest HQ

	HQ ≤1
	HQ >1 – <2
	HQ ≥2

6.4.3.4.2. Algae

Similar to aquatic macrophytes, risks to algae for both sensitive and tolerant species for all application methods are substantial, with most HQs greatly exceeding the LOC for all exposure scenarios and applications (Table 6.4-12). This is an expected outcome, as flumioxazin is used as an aquatic herbicide.

Table 6.4-12: Hazard Quotients (HQs) for Exposure of Algae

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Accidental Acute Exposure: Algae				
Sensitive	1.6E04 (lower) 7.9E04 (central) 1.6E05 (upper)	9.6E03 (lower) 4.8E04 (central) 9.6E04 (upper)	4.5E05 (lower) 2.2E06 (central) 4.5E06 (upper)	3.3E05 (lower) 8.2E05 (central) 1.6E06 (upper)
Tolerant	183 (lower) 916 (central) 1.8E03 (upper)	112 (lower) 558 (central) 1.1E03 (upper)	5.2E03 (lower) 2.6E04 (central) 5.2E04 (upper)	3.8E03 (lower) 9.5E03 (central) 1.9E04 (upper)
Non-Accidental Acute Exposure: Algae				
Sensitive	<1 (lower) 190 (central) 1.5E03 (upper)	314 (lower) 628 (central) 3.1E03 (upper)	1.8E04 (lower, central, upper)	<1 (lower) 344 (central) 3.1E03 (upper)
Tolerant	<1 (lower) 2 (central) 18 (upper)	4 (lower) 7 (central) 36 (upper)	211 (lower, central, upper)	<1 (lower) 4 (central) 36 (upper)

Exposure Scenario	HQs[1] for Application Methods			
	Spray[2]	Direct Water Surface	Direct Water Subsurface	Granular
Chronic/Longer-Term Exposure: Algae				
Sensitive	<1 (lower)	<1 (lower and central)	4 (lower) 28 (central) 1.2E03 (upper)	<1 (lower)
	1.9 (central)	212 (upper)		2 (central) 348 (upper)
	140 (upper)			
Tolerant	<1 (lower and central)	<1 (lower and central)	<1 (lower and central)	<1 (lower and central)
	1.6 (upper)	2 (upper)	34 (upper)	4 (upper)

[1]HQs listed as <1 or ≤1 only indicate that HQs for lower, central, and upper estimates are all ≤1.
[2]HQs are for aircraft aerial application; these HQs are higher than for backpack directed foliar spray and boom ground spray.

Key: cells are colored for the highest HQ

HQ ≤1
HQ >1 – <2
HQ ≥2

1

7. REFERENCES

For this risk assessment, MRID studies were not available for review. All data attributed to specific MRID studies were taken from DERs developed by U.S. EPA for MRID studies are listed in the table below (sorted by MRID number). All other references cited in the document follow.

MRID	Citation
MRID42684905	Katagi T, Takahashi N, Nambu K, et al. 1990. Hydrolysis of THP-(Carbon-14)-S-53482 in buffered aqueous solutions. Sumitomo Chemical Co. Submitted to the U.S. Environmental Protection Agency. MRID42684905.
MRID42684906	Fathulla R. 1991. Aerobic soil metabolism of (Carbon-14)-S-53482. Hazleton Laboratories America, Inc. Submitted to the U.S. Environmental Protection Agency. MRID42684906.
MRID42684907	Fathulla R. 1992. Column leaching characteristics of (Phe-(carbon-14))-V-53482 in typical agricultural soils (unaged study). Hazleton Laboratories America, Inc. Submitted to the U.S. Environmental Protection Agency. MRID42684907.
MRID42684908	Fathulla R. 1992. Column leaching characteristics of (THP-(carbon-14))-V-53482 in typical agricultural soils (unaged soils). Hazleton Laboratories America, Inc. Submitted to the U.S. Environmental Protection Agency. MRID42684908.
MRID42684909	Fathulla R. 1992. Column leaching characteristics of Phe-(carbon-14)|-V-53482 in typical agricultural soils (aged soils). Hazleton Laboratories America, Inc. Submitted to the U.S. Environmental Protection Agency. MRID42684909.
MRID42684910	Wustner D. 1993. Bioaccumulation in fish of V-53482 (Waiver Request 165-4). Valent USA Corporation. Submitted to the U.S. Environmental Protection Agency. MRID42684910.
MRID42684911	Hiromori T. 1989. Acute oral toxicity study of S-53482 in rats. Sumitomo Chemical Company. Submitted to the U.S. Environmental Protection Agency. MRID42684911.
MRID42684912	Baldrick P, Healing G. 1991. Acute oral toxicity to rats of V-53482. Huntingdon Resarch Centre. Submitted to the U.S. Environmental Protection Agency. MRID42684912.
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Appendix 1: Literature Review Exclusion Criteria

The following keywords and criteria were referenced when excluding studies from the HHERA:

Keyword	Description
Abstract	Studies where only an abstract is available.
Altered	Studies that describe the effects on surgically altered or genetically altered organisms.
Chem Method	Studies that only report methods for the analyses and purification of the herbicide/pesticide.
CP	Results that are reported in conference and symposium proceedings. Attempts will be made to identify the primary literature.
Date	Literature published prior to 1965.
Dead	Studies reporting results on dead organisms.
Dup	Studies reporting results that are duplicated in a separate publication. The publication with the earlier year will be used.
Ecological	Studies of ecological processes that do not investigate effects of herbicide/pesticide exposure.
Formulation	Studies that do not report the formulation of the herbicide/pesticide or the formulation is not clearly identified.
Method	Studies reporting methods or methods development without useable results for the HHERA.
No Control	Studies that do not provide any control data.
No Dose	Exposure dose (or exposure concentration) is not reported or is not clear.
No Duration	Studies that do not report the duration of exposures or the length of the toxicity study.
No Peer	Literature from non-peer reviewed journals. These citations will receive an extra level of critical review to determine if they are acceptable for inclusion in the HHERA.
No Toxicity	Toxic effect data or no effect data are not reported.
No Units	Exposure or toxicity units are either not reported or not clear.
Not Avail	Literature identified as part of the search that could not be obtained for review.
Nutrient Deficient	Toxicity studies where animals are exposed to nutrient deficient diets.
Physiology	Physiology studies where adverse effects are not associated with exposure to the chemical of concern.
Published As	Author states that the information in the report was published in another source. Data will only be recorded from the primary source.
Regulation	Literature that reports regulations and related publications.
Review	Studies in which data reported in the article are not primary data from the research conducted by the author. The publication is a compilation of data published elsewhere. These publications will be reviewed manually to identify other relevant literature.
Study Design	Design of the toxicity study is reported to meet the requirements of EPA's OPPTS harmonized guidelines but do not upon review.
Unrelated	Literature that is not related to the herbicide/pesticide or the HHERA.

Abbreviations: U.S. EPA = U.S. Environmental Protection Agency; HHERA = Human Health and Ecological Risk Assessment; OPPTS = Office of Prevention, Pesticides and Toxic Substances

Appendix 2. Acute Toxicity Data for Flumioxazin Formulated Products

Table A2-1: Acute Toxicity Data for Flumioxazin Products as Reported in Product Safety Data Sheets

Formulation (% a.i.) [U.S. EPA Registration No]	Oral LD_{50} (mg a.i./kg)	Dermal LD_{50} (mg a.i./kg)	Inhalation LC_{50} (mg a.i./L)	Eye irritation	Skin irritation	Skin sensitizer
Formulation type: water dispersible granule (WDG) applied as a liquid						
Alligare Flumigard™ Herbicide (51.5% a.i.) [81927-68][1]	>5000 (rat)	>2000 (rat)	>2.18 (rat, 4 hour)	Brief and/or minor irritation	Brief and/or minor irritation	Not a sensitizer
Chateau® Herbicide WDG (51% a.i.) [59639-119][1]	>5000 (rat)	>2000 (rabbit)	>0.969 (rat, 4 hour)	Brief and/or minor irritation	Brief and/or minor irritation	Not expected to cause allergic skin reactions
Clipper™ Herbicide (51% a.i.) [59639-161][1]	>5000 (rat)	>2000 (rabbit)	>0.969 (rat)	Brief and/or minor irritation	Brief and/or minor irritation	Probably non-sensitizer
Flumioxazin 51% WDG (51% a.i.) [85678-34][2]	>5000 (rat)	>2000 (rabbit)	>0.97 (rat)	Minimal – brief/minor	Minimal – brief/minor	Not a contact sensitizer (guinea pig)
Lockdown Herbicide™ (51% a.i.) [71368-103][2]	>5000 (rat)	>2000 (rat)	>2.18 (rat, 4 hour)	Brief and/or minor irritation	Brief and/or minor irritation	Probably non-sensitizer
Promenade™ Herbicide (51.5% a.i.) [81927-67][1]	>5000 (rat)	>2000 (rat)	>2.18 (rat, 4 hour)	Brief and/or minor irritation	Brief and/or minor irritation	Not a sensitizer
SureGuard™ (51% a.i.) [59639-120][1]	>5000 (rat)	>2000 (rabbit)	>2.18 (rat, 4 hour)	Brief and/or minor irritation	Brief and/or minor irritation	Probably non-sensitizer
Warfox (51% a.i.) [6622-252]	NR	NR	NR	NR	NR	NR

Formulation (% a.i.) [U.S. EPA Registration No]	Oral LD_{50} (mg a.i./kg)	Dermal LD_{50} (mg a.i./kg)	Inhalation LC_{50} (mg a.i./L)	Eye irritation	Skin irritation	Skin sensitizer
Formulation type: liquid concentrate						
Alligare Flumi SC Herbicide (42% a.i.) [81927-78][1]	>5000 (rat)	>5000 (rat)	>2.10 (rat, 4 hour)	Non-irritating	Slightly irritating	Not a contact sensitizer
Panther® SC Herbicide (41.4% a.i.) [71368-113][2]	>5000 (rat)	>5000 (rat)	>2.10 (rat)	Non-irritating (rabbit)	Slightly irritating (rabbit)	Not a contact sensitizer in LLNA (mice)
PondKlear Aquatic Herbicide (44% a.i.) [8959-61][2]	>5000 (rat)	>5000 (rat)	>2.10 (rat)	NR	NR	NR
SureGuard® SC Herbicide (41.4% a.i.) [71368-114][2]	>5000 (rat)	>5000 (rat)	>2.10 (rat)	Non-irritating (rabbit)	Slightly irritating (rabbit)	Not a contact sensitizer in LLNA (mice)
Valor® EZ Herbicide (41.4% a.i.) [59639-221][2]	>5000 (rat)	>5000 (rabbit)	>2.11 (rat)	Mildly irritating (rabbit)	Slightly irritating (rabbit)	Non-sensitizer (guinea pig)
Formulation type: granule applied to soil						
Broadstar™ Herbicide (0.25% a.i.) [59639-128][1]	>5000 (rat)	>2000 (rat)	>2.18 (rat)	Mildly irritating (rabbit)	Brief and/or minor irritation (rabbit)	Non-sensitizer (guinea pig)

[1]No toxicology information is available for this specific product. Information is from studies on technical grade flumioxazin, formulations containing approximately 50% flumioxazin, or a substantially similar product.
[2]SDS does not specify if toxicity data in on the specific product, technical material, or a similar product.
Abbreviations: a.i. = active ingredient; U.S. EPA = U.S. Environmental Protection Agency; kg = kilogram; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; LLNA = Local Lymph Node Assay; NR = not reported; SDS = Safety Data Sheet

Appendix 3: Toxicity to Mammals

In the following tables, all data attributed to MRID studies were taken from DERs of MRID studies. MRID studies were not available for review.

Table A3-1: Acute Oral Toxicity Studies on Technical Grade Flumioxazin and a Formulated Flumioxazin Product

Species	Exposure	Response	Reference
Technical Grade Flumioxazin			
Rat, Sprague-Dawley, 6-week-old males and females (5 rats/sex/dose) M initial body weight: 217 – 235 g F initial body weight: 157 – 177 g	S-53482 Technical (purity: 94.8% a.i.) suspended in 1% aqueous methylcellulose Doses: Single gavage dose of 0 or 5000 mg a.i./kg bw (250 mg/mL at a volume of 20 mL/kg) Fasted 20 hours prior to dosing; 14-day observation period.	M: LD_{50} >5000 mg a.i./kg bw F: LD_{50} >5000 mg a.i./kg bw No mortality or clinical signs of toxicity observed in any dose group. No body weight or body weight gain differences between treated and control animals. Classified as U.S. EPA Toxicity Category IV for acute oral toxicity.	MRID 42684911 Hiromori (1989) Acceptable
Rat, Wistar, 8-week-old females (2 groups of 3 rats/dose) Initial body weight not reported.	Flumioxazin Technical (purity: 98.19 – 98.63% a.i.) in analytical grade water with 0.2% Tween 80 Dose: 2000 mg a.i./kg bw (200 mg/mL) No further details provided.	F: LD_{50} >2000 mg a.i./kg bw No mortality or clinical signs of toxicity observed in any animal; no gross pathological alterations observed at necropsy. All animals gained weight. No further details provided. Classified as U.S. EPA Toxicity Category III for acute oral toxicity.	MRID 50353608 Patil (2016) Acceptable

Species	Exposure	Response	Reference
Formulated Product			
Rat, Sprague-Dawley, 6-week-old males and females (5 rats/sex/dose) M initial body weight: 112 – 127 g F initial body weight: 104 – 113 g	V-53482 50 WDG (purity: 50% a.i.) suspended in 50% w/v distilled water Doses: Single gavage dose of 0 or 5000 mg/kg bw [2500 mg a.i./kg bw] (50% w/v at a volume of 10 mL/kg) Fasted overnight prior to dosing and 4 hours after dosing; 14-day observation period.	M: LD_{50} >2500 mg a.i./kg bw F: LD_{50} >2500 mg a.i./kg bw No mortality in any dose group. All rats exhibited piloerection within 3 minutes of dosing and for the first 24 hours; complete recovery after Day 1. No other clinical signs or macroscopic abnormalities. Classified as U.S. EPA Toxicity Category IV for acute oral toxicity; expressed as a.i., this would be classified as U.S. EPA Toxicity Category III for acute oral toxicity.	MRID 42684912 Baldrick and Healing (1991) Acceptable

Abbreviations: a.i. = active ingredient; bw = body weight; U.S. EPA = U.S. Environmental Protection Agency; F = female; g = gram; kg = kilogram; LD_{50} = median lethal dose; M = male; mg = milligram; mL = milliliter; WDG = water dispersible granule; w/v = weight per volume

Table A3-2: Subchronic and Chronic Oral Toxicity Studies on Technical Grade Flumioxazin

Species	Exposure	Response	Reference
Subchronic			
Rat, Crj:CD Sprague Dawley, 5-week-old males and females (16 rats/sex/dose) M initial body weight: 132 – 156 g F initial body weight: 105 – 130 g	S-53482 Technical (purity: 94.8% a.i.) in CRF-1 rodent diet Doses: 0, 30, 300, 1000, and 3000 ppm in diet (M: 0, 1.9, 19.3, 65.0, and 196.7 mg a.i./kg/day; F: 0, 2.2, 22.4, 72.9, and 218.4 mg a.i./kg/day) 90-Day oral toxicity.	M: NOAEL 19.3 mg a.i./kg/day; LOAEL 65.0 mg a.i./kg/day F: NOAEL 22.4 mg a.i./kg/day; LOAEL 72.9 mg a.i./kg/day LOAELs based on toxicological and statistically significant alterations in hematological and histologic parameters associated with anemia in males and females compared to controls. Note that the DER reported female NOAEL of 30 ppm (2.2 mg a.i./kg/day) and LOAEL of 300 ppm (22.4 mg a.i./kg/day). However, hematological changes in the 300 ppm group were very small and not toxicologically significant. No treatment-related effects were observed on body weight, food or water consumption, or urinalysis at any dose. <u>30 ppm</u>: No effects in males or females <u>300 ppm</u>: In females, 3% decreases in MCH and MCV compared to controls, and extramedullary hematopoiesis observed in spleen of 1/10 animals, but changes were small and not toxicologically significant. No effect in males.	MRID 42684922 Adachi (1990) Acceptable

Species	Exposure	Response	Reference
		1000 ppm: In females, 14% decrease in MCV, 17% decrease in MCH, 4% decrease in MCHC, and 23% decrease in myeloid/erythroid ratio in femoral bone marrow compared to controls. In males, 6% decrease in MCV and 7% decrease in MCH compared to control; extramedullary hematopoiesis observed in spleen of 1/10 treated males; relative kidney weight was 6% higher in treated males compared to controls. 3000 ppm: One female died during week 12; no other mortality observed. Clinical signs of toxicity (pale eyes and pallor) noted in 2/9 females. In females, 18% decrease in MCV, 25% decrease in MCH, and 9% decrease in MCHC compared to controls, and 3.9% increase in reticulocyte count compared to controls. Reticulocyte ratio is 401% of control value, and erythroblast ratio increased from 0 to 103 per 100 WBC compared to controls. 61% decrease in myeloid/erythroid ratio compared to control females. A 27% decrease in α1-globulins compared to controls was observed in females. Extramedullary hematopoiesis observed in spleen in all 10 treated females and in liver of 5/10 treated females. Relative weights of liver, kidney, spleen, and heart in treated females increased by 20%, 20%, 275%, and 40% compared to controls, respectively. In males, 11% decrease in MCV, 14% decrease in MCH, and 9%	

Species	Exposure	Response	Reference
		decrease in MCHC compared to controls; reticulocyte ratio is 178% of control value, and erythroblast ratio increased from 0 to 5 per 100 WBC compared to controls; 67% decrease in myeloid/erythroid ratios in femoral bone marrow compared to controls; extramedullary hematopoiesis observed in spleen of 6/10 treated males. Relative weights of liver, kidney, and thyroid in treated males increased by 13%, 8%, and 40% compared to controls, respectively.	
Rats, Crj:CD(SD), 5-week-old males and females (12 rats/sex/dose) M initial body weight: 118 – 137 g F initial body weight: 104 –119 g	S-53482 (purity: 98.4% a.i.) in diet Doses: 0, 30, 300, 1000, or 3000 ppm in diet (M: 0, 2.3, 20.7, 69.7, or 243.5 mg a.i./kg/day; F: 0, 2.2, 21.7, 71.5, or 229.6 mg a.i./kg/day) 13-Week toxicity study.	M: NOAEL 20.7 mg a.i./kg/day; LOAEL 69.7 mg a.i./kg/day F: NOAEL 21.7 mg a.i./kg/day; LOAEL 71.5 mg a.i./kg/day LOAELs based on hematological effects consistent with anemia and bone marrow response in males and females. No treatment-related effects were observed on mortality, clinical signs of toxicity, ophthalmology, food or water consumption, or urinalysis at any dose level. <u>30 ppm</u>: In females, 9% decrease in LAP compared to controls, but change was small and toxicologically insignificant. No effects in males. <u>300 ppm</u>: No effects in males or females.	MRID 42684923 Hagiwara (1990) Core Supplementary (missing data re: stability of test material in prepared diet, clinical chemistry data for individual males, and gross pathology data for 0, 30, and 300 ppm animals)

Species	Exposure	Response	Reference
		1000 ppm: In males, 3.8% decrease in MCV and 1% decrease in Na^+ compared to controls. In females, platelet count increased 23% compared to controls and LAP decreased 13% compared to controls. 3000 ppm: In males, body weight in treated animals was 91.5% of controls, and mean body weight gain was 89% of controls. An 8.2% decrease in hemoglobin, 8.4% decrease in hematocrit, 9.2% decrease in MCV, 8.3% decrease in MCH, and 89% increase in reticulocytes were observed in treated males compared to controls. Erythroblasts were increased from 0.4 to 7.8 per 100 WBC in males and the granulocyte/erythroblast ratio was decreased from 1.7 to 1.0. Platelet count was 39% higher in treated males and increased in a dose-dependent manner but was not significantly different from controls. There were 21% and 11% decreases in GOT and LAP in treated males compared to controls. Relative spleen weight in males increased by 40% compared to controls; males had spleen hematopoiesis, consistent with anemia, upon microscopic pathology. In females, body weight and weight gain in treated animals were 90.2% and 83% of controls, respectively. An 11.2% decrease in in erythrocyte count, 25.5% decrease in hemoglobin, 25.1% decrease in hematocrit, 15.9% decrease in MCH, and 15.3% decrease	

Species	Exposure	Response	Reference
		in MCV observed in treated females compared to controls. Reticulocytes increased by 158% compared to controls, erythroblasts increased from 0.4 to 31.3 per 100 WBC, and granulocyte/erythroblast ratio decreased from 1.7 to 0.4 in treated females. Platelet counts increased by 70% compared to controls, along with WBC count (from 55.2 × 10^2/mm^3 in controls to 91.2 × 10^2/mm^3 in treated animals). Levels of albumin increased by 7% compared to controls, A/G ratio increased by 9% compared to controls, and 27% and 21% decreases in GOT and ALP, respectively, were observed in treated females compared to controls. Dose-related increase in relative spleen weights of 69% in females compared to controls. Females had spleen hematopoiesis, consistent with anemia, upon microscopic pathology.	
Mice, CD-1, males and females (9 mice/sex/dose) [age and body weight not specified – see MRID 44295018]	S-53482 Technical (purity: 94.8% a.i.) in diet Doses: 0, 1000, 3000, or 10000 ppm a.i. in diet Doses: M: 0, 180, 540, or 1800 mg a.i./kg/day; F: 0, 200, 590, or 2000 mg a.i./kg/day (doses calculated by multiplying dietary concentration by food conversion factor[1]) 4-Week dietary exposure.	M: NOAEL 180 mg a.i./kg/day; LOAEL 540 mg a.i./kg/day F: NOAEL 200 mg a.i./kg/day; LOAEL 590 mg a.i./kg/day LOAELs based on increases in relative liver weights in M/F mice compared to controls. No treatment-related effects were observed on mortality, body weight, clinical signs, food consumption, hematology, clinical chemistry, gross necropsy, or histopathology.	MRID 44307301 Seki (1990) Acceptable/Guideline

Species	Exposure	Response	Reference
		1000 ppm: No effects in males or females. 3000 and 10,000 ppm: Increased relative liver weight was noted in M/F animals (9 – 14% increase compared to controls).	
Dog, Beagle, 6-month-old males and females (4 dogs/sex/dose) M initial body weight: 8.3 – 11.6 kg F initial body weight: 7.2 – 10.8 kg	V-53482 (purity: 94.8% a.i.) in gelatin capsule Dose: Single oral dose of 0, 10, 100, or 1000 mg a.i./kg/day once daily for 13 weeks.	M: NOAEL 100 mg a.i./kg/day; LOAEL 1000 mg/kg/day F: NOAEL 100 mg a.i./kg/day; LOAEL 1000 mg/kg/day LOAELs based on significant increase in total cholesterol and phospholipid levels, ALP activity, and liver effects. Note that the DER reported male/female NOAEL of 10 mg a.i./kg/day and LOAEL of 100 mg a.i./kg/day. However, increases in total cholesterol, phospholipid levels, and ALP activity at 100 mg/kg/day were small and not toxicologically significant. No mortality, treatment-related clinical signs or effects on food consumption, ophthal-mology, or urinalysis were observed in any dose group. 10 and 100 mg/kg/day: No effects in males or females. 1000 mg/kg/day: Mean body weight in treated animals was not significantly different from controls, although overall weight gain was	MRID 42684924 Nakano (1993) Core Supplementary (no data provided re: stability of the test material in capsules)

Species	Exposure	Response	Reference
		decreased by 56% in females compared to controls. In males, total cholesterol and phospholipid were increased by 50% and 30%, respectively, compared to controls at study termination. In females, ALP was increased by 195% compared to controls at study termination. Chronic focal inflammation of the liver was observed in all treated males. Histopathological liver lesions were noted males and females.	
Chronic			
Dogs, Beagle, 6 – 7-month-old males and females (4 dogs/sex/dose) M initial body weight: 6.5 – 10.7 kg F initial body weight: 5.9 – 10.1 kg	Flumioxazin (purity: 94.8% a.i.) in gelatin capsule Doses: 0, 10, 100, or 1000 mg a.i./kg/day (administered as 1/8 ounce in a gelatin capsule) Dogs received 1 capsule per day for 12 months.	M: NOAEL 100 mg a.i./kg/day; LOAEL 1000 mg a.i./kg/day F: NOAEL 100 mg a.i./kg/day; LOAEL 1000 mg a.i./kg/day LOAELs based on clinical chemistry and liver histopathology. No mortality was observed; the only clinical sign of toxicity observed was occasional loose feces by dogs in each treatment group. No significant treatment-related effects on body weight, body weight gain, food consumption, food efficiency, ophthalmology, hematology, urinalysis, liver function, bone marrow examination, or gross pathology were observed at any dose. No neoplastic tissue was observed in any animals in the study. <u>10 and 100 mg/kg/day</u>: No toxicologically significant effects in males or females.	MRID 44295017 Nakano (1993) Acceptable/Guideline

Species	Exposure	Response	Reference
		1000 mg/kg/day: In males, 89% increase in cholesterol, 55% increase in phospholipids, 27% increase in α_2-globulin, and 370% increase in ALP compared to controls. Relative liver weights were 42% higher in treated males than controls. In females, ALP was increased 260% in treated animals compared to controls. Non-neoplastic liver abnormalities noted in treated males and females included minimal hyperplasia of connective tissue adjacent to the gall bladder along with hemosiderin and/or iron negative pigment and bile duct proliferation (in 1/4 males and ¼ females); liver congestion, mononuclear and inflammatory cell infiltration in 1/4 females; and proliferation and dilation of smooth endoplasmic reticulum in hepatocytes of 2/4 males and 1/4 females. 1/4 males had minimal to slight increases in extramedullary hematopoiesis and/or hemosiderin pigment associated with the spleen.	

[1]Average daily food consumption: 5.71E-3 kg/day for males, 4.84E-3 kg/day for females; average body weight: 0.0316 kg for males, 0.0246 kg for females; food conversion factor: 5.71E-3 kg/day ÷ 0.0316 kg = 0.18 (males); 4.84E-3 kg/day ÷ 0.0246 kg = 0.20 (females).
Abbreviations: A/G = albumin/globulin ratio, or total serum protein; a.i. = active ingredient; ALP = alkaline phosphatase; DER = Data Evaluation Record; F = female; g = gram; GOT = glutamic oxaloacetic transaminase; kg = kilogram; LAP = leucyl aminopeptidase; LOAEL = lowest-observed-adverse-effect level; M = male; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; mg = milligram; NOAEL = no-observed-adverse-effect level; WBC = white blood cells

Table A3-3: Acute and Subchronic Neurotoxicity Studies on Technical Grade Flumioxazin

Species	Exposure	Response	Reference
Acute Neurotoxicity Screening Battery			
Rats, Crl:CD(SD), 6-week-old males and females (12 rats/sex/dose) M initial body weight: 148 – 233 g F initial body weight: 136 – 189 g	Flumioxazin TG (purity: 99.6% a.i.) in 0.5% methylcellulose Doses: Single gavage dose of 0, 200, 700, or 2000 mg a.i./kg bw (dose volume of 10 mL/kg) 14-Day observation period.	M: NOAEL 2000 mg a.i./kg/day; LOAEL >2000 mg a.i./kg/day F: NOAEL 2000 mg a.i./kg/day; LOAEL >2000 mg a.i./kg/day No mortality or clinical signs of toxicity observed. No treatment-related effects on body weight, FOB testing, locomotor activity, gross pathology, or histopathological evaluation of central or peripheral nervous tissue.	MRID 48402405 Herberth (2011) Acceptable/Guideline
Subchronic Neurotoxicity Screening Battery			
Rat, Crl:CD(SD), 6-week-old males and females (12 rats/sex/group) M initial body weight: 143 – 204 g F initial body weight: 125 – 170 g	Flumioxazin TG (purity: 99.6% a.i.) in diet Doses: 0, 500, 1500, or 4500 ppm (M: 0, 37, 110, or 323 mg a.i./kg/day; F: 0, 41, 124, or 358 mg a.i./kg/day) Administered continuously in diet for 90 days.	**Neurotoxicity** M: NOAEL 323 mg a.i./kg/day; LOAEL >323 mg a.i./kg/day F: NOAEL 358 mg a.i./kg/day; LOAEL >358 mg a.i./kg/day No treatment-related effects on FOB testing, motor activity, brain weight or measurement, or microscopic neurohistopathology were observed. **Systemic Toxicity** M: NOAEL 37 mg a.i./kg/day; LOAEL 110 mg a.i./kg/day F: NOAEL 41 mg a.i./kg/day; LOAEL 124 mg a.i./kg/day	MRID 48651401 Herberth (2011) Acceptable/Guideline

Species	Exposure	Response	Reference
		LOAELs based on signs of anemia in males and females at 1500 ppm. No treatment-related mortality or effects on clinical signs, body weight, body weight gain, food consumption, ophthalmology, or gross pathology were observed. 500 ppm: In treated males, hematological effects included 3% decrease in MCV and MCH compared to controls; in treated females, 29% decrease in WBC, 70% increase in EOS, and 31% decrease in absolute lymphocytes were observed compared to controls. These effects were determined to be minor and toxicologically insignificant. 1500 ppm: In males, treatment-related hematological effects included 6% decreases in hemoglobin and hematocrit, 8% decreases in MCV and MCH, and a 67% increase in EOS compared to controls. In treated females, hematological effects included 8% decrease in hemoglobin, 5% decrease in hematocrit, 29% decrease in WBC, 9% increase in RBC, 13% decrease in MCV, 15% decrease in MCH, 3% decrease in MCHC, 100% increase in EOS, and 32% decrease in absolute lymphocytes compared to controls. 4500 ppm: In males, treatment-related hematological effects included 13% decrease	

Species	Exposure	Response	Reference
		in hemoglobin, 10% decrease in hematocrit, 13% decrease in MCV, 16% decrease in MCH, 4% decrease in MCHC, and 94% increase in reticulocytes compared to controls. In treated females, hematological effects included 23% decrease in hemoglobin, 16% decrease in hematocrit, 19% decrease in MCV, 26% decrease in MCH, 9% decrease in MCHC, 24% increase in platelets, 171% increase in reticulocytes, 40% decrease in MONO, and 60% decrease in LUC compared to controls.	

Abbreviations: a.i. = active ingredient; bw = body weight; EOS = eosinophils; F = female; FOB = functional observational battery; g = gram; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; LUC = leukocytes; M = male; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; mg = milligram; mL = milliliter; MONO = monocytes; NOAEL = no-observed-adverse-effect level; ppm = parts per million; RBC = red blood cells; WBC = white blood cells

Table A3-4: Subchronic Immunotoxicity Toxicity Studies on Technical Grade Flumioxazin

Species	Exposure	Response	Reference
Rats, Sprague-Dawley, 7-week-old females (TDAR group: 10 rats/dose; Hematology group: 5 rats/dose) TDAR initial body weight: 150 – 189 g Hematology initial body weight: 157 – 187 g	Flumioxazin (purity: 99.6% a.i.) in diet. Positive control: cyclophosphamide Doses: 0, 500, 1500, or 4500 ppm (TDAR group: 0, 44, 127, or 375 mg a.i./kg/day; Hematology group: 0, 42, 126, or 371 mg a.i./kg/day) Administered daily in diet for 28 days.	**Immunotoxicity** F: NOAEL 375 mg a.i./kg/day; LOAEL >375 mg a.i./kg/day No treatment-related effects on thymus weight, AFC response, or histopathology in immunological tissues were observed at any dose. 500 and 1500 ppm: No immunotoxicological effects observed. 4500 ppm: Mean relative spleen weights were increased 35% compared to controls, but this may be a response to anemia, as no effects were observed on the AFC response in the spleen. **Systemic Toxicity** F: NOAEL 42 mg a.i./kg/day; LOAEL 126 mg a.i./kg/day LOAEL based on signs of anemia (decreased hemoglobin and hematocrit). No treatment-related mortality or effects on clinical signs, body weight or body weight gain, food consumption, water consumption, or gross pathology at any dose level.	MRID 48402408 Crittenden (2011) Acceptable/Guideline

Species	Exposure	Response	Reference
		500 ppm: No treatment-related effects observed. 1500 ppm: Observed hematological effects include 7.3% decrease in MCV and 7.7% decrease in MCH compared to controls. 4500 ppm: Observed hematological effects include 16% decrease in hemoglobin, 11.6% decrease in hematocrit, 9.3% decrease in MCV, 13.9% decrease in MCH, and 4.% decrease in MCHC compared to controls; and 75.5% increase in WBC, 194% increase in percent reticulocyte, 113% increase in absolute neutrophil, and 74.6% increase in absolute lymphocyte counts compared to controls.	

Abbreviations: AFC = antibody-forming cell; a.i. = active ingredient; g = gram; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; mg = milligram; NOAEL = no-observed-adverse-effect level; ppm = parts per million; TDAR = T-cell dependent antibody response; WBC = white blood cells

Table A3-5: Reproductive and Maternal Toxicity Studies on Technical Grade Flumioxazin

Species	Exposure	Response	Reference
Developmental			
Oral Exposure			
Rats, Sprague-Dawley, 10-week-old pregnant females (20 rats/group) F initial body weight: 258.9 – 332.8 g	Flumioxazin (purity: 99.67% a.i.) in 0.5% methylcellulose Doses: Daily single gavage of 0, 15, 30, or 60 mg a.i./kg/day Treated on GD 6 – 15. Study terminated on GD 20. 10 females/dose necropsied on GD 14; 10 females/dose necropsied on GD 20.	**Maternal** NOAEL 30 mg a.i./kg/day, LOAEL 60 mg a.i./kg/day LOAEL based on significantly decreased body weight and body weight gain and clinical signs of toxicity. No mortality or treatment-related effects on gross pathology were observed. <u>15 and 30 mg a.i./kg/day</u>: No treatment-related effects. <u>60 mg a.i./kg/day</u>: 10% and 23% decreases in body weight and body weight gain at GD 20 and GD 6 – 20, respectively. Clinical signs of toxicity observed in 3/20 dams exhibiting red fluid near genital region. **Developmental** NOAEL 15 mg a.i./kg/day; LOAEL 30 mg a.i./kg/day LOAELs based on increased incidence and severity of pale yoke sacs and embryos, adverse effects on erythrocytes, and cardiac abnormalities.	MRID 49615801 Hosokawa (2015) Acceptable/ Non-guideline

Species	Exposure	Response	Reference
		Note that the DER did not determine a male/female developmental NOAEL and reported a LOAEL of 15 mg a.i./kg/day based on adverse effects on erythroblasts and increased litter incidence of ventricular septal defects. However, effects observed at 15 mg a.i./kg/day were considered relatively small and not toxicologically significant. No treatment-related external fetal effects were observed. 15 mg a.i./kg/day: Increased incidence in erythrocytes with iron deposits (40.8% of treated animals have 0 iron deposits, while 52.7% of controls have 0 iron deposits), though this effect is considered relatively small and not toxicologically significant. 30 mg a.i./kg/day: 2000% increase in incidence of erythroblasts with iron deposits compared to controls; 390% increase in incidence of massive distribution of positive iron granules compared to controls); 300% increased incidence of cardiac anomalies in fetuses compared to controls; 1300% increased incidence of fetuses with ventricular septal defect compared to controls. Histo-pathological effects on embryonic hearts included degenerative erythroblasts (16/20), thin ventricular walls (7/20), and dilation of atrium (1/20).	

Species	Exposure	Response	Reference
		60 mg a.i./kg/day: Increased incidence of iron deposits in erythroblasts (46.2% of treated animals have 0 iron deposits, while 52.7% of controls have 0 iron deposits); 66% decrease in mean number of live fetuses; 800% increase in number of dead fetuses per dam compared to controls; 62.5% postimplantation loss compared to 5.8% loss in controls; 13% and 12% decrease in male and female fetal weight, respectively, compared to controls; 300% increase in incidence of dams with cardiac anomalies in fetuses; 2500% increased incidence of fetuses with ventricular septal defect compared to controls. Histo-pathological effects on embryonic hearts included degenerative erythroblasts (20/20), thin ventricular walls (15/20), and dilation of atrium (4/20); effects on embryonic livers included dilation of sinusoidal vessels (5/20) and hepatic necrosis (4/20).	
Rats, Sprague-Dawley, 10-week-old pregnant females (22 rats/dose) F body weight at GD 0: 215 – 259 g	S-53482 (purity: 94.8% a.i.) in 0.5% aqueous solution methylcellulose Doses: Daily gavage dose of 0, 1, 3, 10, or 30 mg a.i./kg/day, administered at constant volume of 5 mL/kg bw Administered on GD 6 – 15; animals observed up to GD 20.	**Maternal** F: NOAEL 30 mg a.i./kg/day; LOAEL >30 mg a.i./kg/day No mortality, clinical signs of toxicity, or treatment-related effects on body weight, food consumption, or gross pathology were observed in dams. **Developmental** F: NOAEL 3 mg a.i./kg/day; LOAEL 10 mg a.i./kg/day	MRID 42684925 Kawamura (1990) Core Supplementary (lacking individual fetal observation data: body weight, external observations, visceral findings, skeletal findings)

Species	Exposure	Response	Reference
		M: NOAEL 3 mg a.i./kg/day; LOAEL 10 mg a.i./kg/day LOAELs based on significant increase in cardiovascular abnormalities (especially ventricular septal defect). 1 and 3 mg a.i./kg/day: No treatment-related effects observed. 10 mg a.i./kg/day: Increased incidence of persistent atrioventricular canal (0.7% of fetuses affected) and ventricular septal defect (4.2% of fetuses affected); incidence was not statically significant, but when all other cardiac malformations and variations were combined with ventricular septal defect, 9% of fetuses were effected. This was considered to be biologically significant and exceeded historical controls. 30 mg a.i./kg/day: Decreased number of live fetuses and fetal weight (14.3% decrease in males and 15.2% decrease in females), increased incidence of cardiac abnormalities (25.5% increase in ventricular septal defect) and skeletal malformations (9.0% increase in curved scapula, 24.3% increase in wavy ribs).	
Rats, Sprague-Dawley, 10-week-old pregnant females (24 rats/dose)	S-54382 (purity: 94.8% a.i.) in corn oil	**Maternal** F: NOAEL 300 mg a.i./kg/day; LOAEL >300 mg a.i./kg/day	MRID 42684926 Kawamura (1991)

Species	Exposure	Response	Reference
F body weight at GD 0: 200 – 257 g	Doses: 0, 30, 100, or 300 mg a.i./kg, applied dermally at constant volume of 2 mL/kg bw Administered daily on GD 6 – 15 by 6-hour dermal application to the clipped back and covered with gauze and tape. After 6 hours, gauze was removed and application site cleaned thoroughly. Animals observed up to GD 20.	No mortality, clinical signs of toxicity, or treatment-related effects on body weight, food consumption, or gross pathology were observed in dams. **Developmental** F: NOAEL 30 mg a.i./kg/day; LOAEL 100 mg a.i./kg/day M: NOAEL 30 mg a.i./kg/day; LOAEL 100 mg a.i./kg/day LOAELs based on increased incidence in cardiac abnormalities. 30 mg a.i./kg/day: No treatment-related effects observed. 100 mg a.i./kg/day: Increased incidence of general cardiac abnormalities (6.9% of fetuses in 31.8% of litters). Response, though not statistically significant, was dose related and considered biologically significant and outside the historical range. 300 mg a.i./kg/day: Significantly fewer live fetuses (40% decrease compared to controls), along with significantly more resorptions (510% increase compared to controls) and a 9% decrease in male fetal bw. Statistically significant increase in cardiac fetal malformations (ventricular septal defect in 14.8% of fetuses; persistent right azygous vein	Core Supplementary (lacking individual fetal observation data: body weight, external observations, visceral findings, skeletal findings~~)~~

Species	Exposure	Response	Reference
		in 9.1% of fetuses) and skeletal malformations (wavy ribs in 20% of fetuses). Mean number of ossified sacrococcygeal vertebral bodies significantly decreased in females at 300 mg/kg/day.	
Rabbit, New Zealand White, 6-month-old pregnant females (20 rabbits/dose) F body weight at study initiation: 2.9 – 4.2 kg	S-53482 (purity: 94.8% a.i.) in 0.5% (w/w) methylcellulose Doses: Daily gavage dose of 0, 300, 1000, or 3000 mg a.i./kg/day, administered at volume of 5 mL/kg bw Administered on GD 7 – 19. Animals observed up to GD 29.	**Maternal** F: NOAEL 1000 mg a.i./kg/day; LOAEL 3000 mg a.i./kg/day LOAEL based on decrease in body weight gain. No mortality, clinical signs of toxicity, or gross pathological findings were observed. <u>300 and 1000 mg a.i./kg/day</u>: No treatment-related effects observed on does. <u>3000 mg a.i./kg/day</u>: 71% decrease in maternal body weight gain and 17% decrease in food consumption on GD 7 – 19. **Developmental** F: NOAEL 3000 mg a.i./kg/day; LOAEL >3000 mg a.i./kg/day M: NOAEL 3000 mg a.i./kg/day; LOAEL >3000 mg a.i./kg/day No effects on fetal deaths, resorptions, malformations, or variations in treated animals versus controls.	MRID 42684928 Hoberman (1991) Acceptable/Guideline

Species	Exposure	Response	Reference
Rats, Sprague-Dawley, pregnant females (1 – 4 rats/group) Rabbits, JW:NIBS, pregnant females (2 rabbits/group)	S-53482 (purity not reported) Dose: 0 or 1000 mg a.i./kg via single gavage dose on GD 12 Dams sacrificed at 6, 12 (rats only), 24, 36 (rats only), or 48 hours post treatment for examination of embryos.	NOAEL and LOAEL cannot be determined from information provided (executive summary only).	MRID 42884004 Kawamura (1993) Unacceptable
Rats, Crj:CD, pregnant females (2 – 4 litters/dose) Rabbits, JW:NIBS, pregnant females (2 litters/group)	S-53482 (purity not reported) Dose: 0 or 1000 mg a.i./kg via single gavage dose on GD 12 Dams sacrificed at 6, 12 (rats only), 24, 36 (rats only), or 48 hours post treatment for examination of embryos.	NOAEL <1000 mg a.i./kg LOAEL 1000 mg a.i./kg Rats: 48-hours after dosing, embryonic mortality increased to 93% over controls. Treated animals had increased incidence of cardiovascular changes in rat embryos including thin ventricular wall and peripheral vascular dilation starting 24 hours after dosing; histopathological changes in erythroblasts and hepatocytes starting 12 – 24 hours after dosing; and liver changes in rat embryos within 48 hours of treatment including sinusoidal vessel dilation and hepatocytic necrosis. Rabbits: No treatment-related effects (number of live or dead embryos, intrauterine deaths, external abnormalities) were observed in rabbit embryos.	MRID 44295020 Kawamura and Yoshioka (1997) Acceptable/Non-guideline Also published as Kawamura et al. (1996)

Species	Exposure	Response	Reference
Rats, Sprague-Dawley, pregnant females (5 groups; number per group not reported)	S-53482 (purity not reported) Dose: 0 or 400 mg a.i./kg via single gavage dose on GD 11, 12, 13, 14, or 15 Sacrificed on GD 20.	F: NOAEL <400 mg a.i./kg; LOAEL 400 mg a.i./kg Study was designed to identify the most sensitive developmental stage for fetal toxicity, not to assess the overall developmental toxicity of flumioxazin. Authors identified GD 12 as most sensitive developmental stage based on incidence of embryonic death (resorption; 39.4% incidence at GD 12 compared to incidences ranging from 2.7% at GD 11 to 16.1% at GD 13), fetal body weight (lowest for male and females on GD 12), and incidence of ventricular septal defects (14.0% incidence at GD 12 compared to incidences ranging from 2.2% at GD 15 to 6.9% at GD 11). (only executive summary provided)	MRID 42884006 Kawamura (1993) Supplementary Not a guideline study and does not satisfy requirements for an oral developmental toxicity study.
Dermal Exposure			
Rats, Sprague-Dawley, pregnant females (24 rats/dose) Body weight not reported.	S-53482 (purity not reported) in corn oil Doses: 0, 30, 100, or 300 mg a.i./kg, applied dermally at dose volume of 2 mL/kg Administered daily on GD 6 – 15 by 6-hour dermal application to the clipped back in a 4 × 5 cm area and covered with gauze and tape. After 6 hours, gauze was	**Maternal** F: NOAEL 300 mg a.i./kg/day; LOAEL >300 mg a.i./kg/day No mortality, clinical signs of toxicity, or treatment-related effects on body weight or body weight gain, food consumption, or necropsy were observed in dams. **Developmental** F: NOAEL 100 mg a.i./kg/day; LOAEL 300 mg a.i./kg/day	Kawamura et al. (2014)

Species	Exposure	Response	Reference
	removed and application site cleaned thoroughly. Animals observed up to GD 20.	M: NOAEL 100 mg a.i./kg/day; LOAEL 300 mg a.i./kg/day LOAELs based on increased incidence of embryo mortality, decreased number of live fetuses, decreased male fetal body weight, and increased incidence of ventricular septal defect and wavy ribs. 30 and 100 mg a.i./kg/day: No treatment-related effects observed. 300 mg a.i./kg/day: Gravid uterine weight was decreased 38% compared to controls; postimplantation loss was increased 580% compared to controls; number of live fetuses/dam decreased 40% compared to controls; and male fetal body weight was 8% less than controls. Incidence of ventricular septal defect was 1200% higher than in controls; incidence of persistent right azygos vein was 700% higher than in controls; incidence of wavy ribs was 18/90 compared to 0/159 controls; and incidence of 14th rib was 0/90 treated animals versus 14/159 controls.	
Inhalation Exposure			
Rats, Crl:CD(SD), pregnant females (8 rats/dose) Age and body weight not reported.	Flumioxazin (purity: 99.7% a.i.) in filtered air	**Maternal** F: NOAEC 0.010 mg a.i./L (10 mg a.i./m^3) LOAEC 0.030 mg a.i./L (30 mg a.i./m^3)	MRID 50207105 (Range-finding) Herberth (2017) Acceptable/Guideline

Species	Exposure	Response	Reference
	Doses: 0, 0.003, 0.010, 0.030, or 0.100 mg a.i./L via nose-only inhalation Administered on GD 6 – 19. Study terminated on GD 20. 12 females/dose were used for toxicokinetic analysis on GD 6, 12, and 19. An additional 12 females received 30 mg a.i./kg/day in 0.5% methylcellulose in DI water by gavage on GD 6 – 19.	LOAEC based on decreased body weight gain and gravid uterus weight compared to controls, and macroscopic findings, and reproductive effects (decreased viable fetuses, increased resorptions and post-implantation loss). No treatment-related effects were observed on mortality, food consumption, pregnancy rate, number of corpora lutea, implantation sites, or sex ratio. 0.003 and 0.010 mg a.i./L: No treatment-related effects 0.030 mg a.i./L: 3/8 dams displayed clinical signs of toxicity (red vaginal discharge); mean body weight gains for GD 15 – 20 and 6 – 20 of 49% and 34% compared to controls; 54% decrease in gravid uterine weight; 4/8 dams had dark red uterine contents upon macroscopy. Total litter resorption occurred in 4/8 dams; mean numbers and litter proportions of viable fetuses decreased by 54% and 59%, respectively, compared to controls; mean litter proportions of resorptions and post-implantation loss were increased by 1900% compared to controls; and mean fetal body weights for surviving fetuses were decreased by 16 – 19% compared to controls.	

Species	Exposure	Response	Reference
		0.100 mg a.i./L: 3/8 dams displayed clinical signs of toxicity (red vaginal discharge). 90% and 67% decreases in mean body weight gains for GD 15 – 20 and 6 – 20, respectively, compared to controls; and 91% decrease in gravid uterine weight compared to controls were observed. 4/8 dams had dark red uterine contents upon necropsy, and total litter resorption occurred in all dams. **Developmental** F: NOAEC 0.010 mg a.i./L (10 mg a.i./m^3) LOAEC 0.030 mg a.i./L (30 mg a.i./m^3) M: NOAEC 0.010 mg a.i./L (10 mg a.i./m^3) LOAEC 0.030 mg a.i./L (30 mg a.i./m^3) LOAECs based on decreased mean fetal body weights and visceral malformations and variations. No treatment-related external fetal malformations or variations were observed. 0.003 and 0.010 mg a.i./L: No treatment-related effects 0.030 mg a.i./L: 17-fold increase in early resorptions compared to controls; 16 – 19% decrease in mean fetal body weight for surviving fetuses compared to controls. Visceral malformations (interventricular septal defect) observed in 2 fetuses; major blood vessel variation observed in 4 fetuses; and accessory hepatic lobules present in 2 fetuses.	

Species	Exposure	Response	Reference
		0.100 mg a.i./L: No fetal evaluations could be done at this exposure concentration due to total litter resorption.	
Rats, Crl:CD(SD), 12-week-old pregnant females (24 rats/dose) F initial body weight: 221 – 266 g	Flumioxazin (purity: 99.7% a.i.) in filtered air Doses: 0, 0.003, 0.010, or 0.020 mg a.i./L via nose-only inhalation MMAD: 1.8 – 1.9 µm Administered on GD 6 – 19. Study terminated on GD 20. 12 females/dose were used for toxicokinetic analysis on GD 6, 12, and 19. An additional 12 females received 30 mg a.i./kg/day by gavage on GD 6 – 19 (in 0.5% methylcellulose in deionized water).	**Maternal** F: NOAEC 0.010 mg a.i./L (10 mg a.i./m^3); LOAEC 0.020 mg a.i./L (20 mg a.i./m^3) LOAEC based on decreased body weight, gravid uterus weight, and body weight gain; increased absolute reticulocyte counts; and reproductive effects. No treatment-related effects were observed on mortality, clinical signs, food consumption, organ weight, gross and microscopic pathology, pregnancy rate, numbers of corpora lutea/implantation sites/litters, or sex ratio. 0.003 and 0.010 mg a.i./L: No treatment-related effects. 0.020 mg a.i./L: 4% decrease in maternal body weight on GD 20, 11 – 27% decreases in body weight gain from GD 6 to 20, and 20% decrease in gravid uterine weight compared to controls. Mean absolute reticulocyte counts increased by 39% compared to controls. Number of live fetuses/dam decreased 16% compared to controls; 285% increase in post-	MRID 50207106 Herberth (2017) MRID 50207108 Miyata (2017) Acceptable/Guideline

Species	Exposure	Response	Reference
		implantation loss (due to early resorptions) compared to controls. **Portal-of-Entry** F: NOAEC 0.020 mg a.i./L (20 mg a.i./m^3); LOAEC >0.020 mg a.i./L (>20 mg a.i./m^3) Incidence of chronic inflammation was similar between controls and treated animals, and no treatment-related alterations in prevalence, severity, or the histologic character of tissue alterations was observed. **Developmental** F: NOAEC 0.010 mg a.i./L (10 mg a.i./m^3); LOAEC 0.020 mg a.i./L (20 mg a.i./m^3) M: NOAEC 0.010 mg a.i./L (10 mg a.i./m^3); LOAEC 0.020 mg a.i./L (20 mg a.i./m^3) LOAECs based on fetal toxicity (significant increase in early resorptions), a decrease in mean fetal body weights, and visceral and skeletal malformations. No treatment-related external fetal malformations were observed. 0.003 and 0.010 mg a.i./L: No treatment-related effects. 0.020 mg a.i./L: Decrease in mean fetal body weights for live males (11% decrease) and live females (14% decrease) compared to controls and historical controls; increased incidence of	

Species	Exposure	Response	Reference
		visceral malformation (mean 1.3% per litter had interventricular septal defects). Skeletal malformations observed with increased incidence compared to controls included bent ribs (19.2% per litter), bent scapula (13.2% per litter), and decreased ossification of vertebral arches (7.2% per litter) and skull (2.5% per litter).	
Reproduction and Fertility			
Rat, Sprague-Dawley, 44-day-old males and females (30 rats/sex/dose in F0 and F1 generations) F0 M initial body weight: 182 – 241 g F0 F initial body weight: 136 – 184 g	V-53482 (purity: 94.8% a.i.) in diet Dose: 0, 50, 100, 200, or 300 ppm in diet (M: 0, 3.2, 6.3, 12.7, or 18.9 mg a.i./kg/day; F: 0, 3.8, 7.6, 15.1, or 22.7 mg a.i./kg/day) 2-Generation reproductive study. Following 14 days acclimatization, dietary dosing through 83-day premating period, when F0 males and females from the same dose group were mated. F1 males and females from the same dose group were mated following an additional 86-day dietary dosing.	**Parental Systemic** F: NOAEL 15.1 mg a.i./kg/day; LOAEL 22.7 mg a.i./kg/day M: NOAEL 12.7 mg a.i./kg/day; LOAEL 18.9 mg a.i./kg/day LOAELs based on clinical signs of toxicity, increased mortality, liver pathology, and decreased body weight/weight gain and food consumption. <u>50 – 200 ppm</u>: No treatment-related effects. <u>300 ppm</u>: Significantly increased mortality in F1 females (83% increase compared to controls) likely related to hepatotoxicity (3/5 females that died had centrilobular necrosis of the liver; 1/5 females had liver congestion). F0 females had increased incidence of red substance in the vagina likely associated with litter resorption (36% incidence compared to 4% incidence in controls); 3/30 F1 males and 3/30 F1 females	MRID 42684935 Hoberman (1992) Acceptable/Guideline

Species	Exposure	Response	Reference
		were pale (compared to 0/30 control animals). In F0 females, body weight decreased to 90% of control on GD 20; body weight gain decreased to 35% of control on GD 15 – 20, and to 69% of control on GD 0 – 20. In F1 males, body weight decreased to 91% of control from GD 8 through premating. Body weight gain in F1 males decreased to 82 – 93% of control during various premating intervals, and terminal body weight was 94% of controls. Body weight gain in F1 females decreased to 58% and 72% of controls on GD 15 – 20 and 0 – 20, respectively. Relative food consumption decreased in F0 and F1 females during lactation to 65 – 84% of controls (F0 females, days 1 – 14 of lactation) and 78 – 89% of controls (F1 females, days 4 – 7, 7 – 10, and 1 – 14 of lactation). Gross pathology showed increased incidence of yellow livers in F1 females (3/30 compared to 0/30 among controls); these animals also exhibited centrilobular necrosis of liver and bile stasis. **Reproductive** F: NOAEL 7.6 mg a.i./kg/day; LOAEL 15.1 mg a.i./kg/day M: NOAEL 6.3 mg a.i./kg/day; LOAEL 12.7 mg a.i./kg/day	

Species	Exposure	Response	Reference
		LOAELs based on significant decrease in number of liveborn pups and decreased pup body weight. 50 and 100 ppm: No treatment-related effects. 200 ppm: Body weight significantly decreased (by 12%) in F1 offspring; number of live pups/litter decreased in F2 offspring by 18% compared to controls. 300 ppm: F0 females had a significantly decreased gestation index (67%) compared to controls (100%). Number of live pups/litter decreased by 19% and 21% in F1 and F2 offspring, respectively, compared to controls. Both generations exhibited a significantly decreased viability index (11% in F1 offspring and 20% in F2 offspring, respectively) compared to controls. Pup body weight at days 1 and 7 were significantly decreased compared to controls in both generations (17 and 21% in F1 offspring, and 13 and 17% in F2 offspring). F1 offspring had increased incidence of weak pups (incidence data not shown) compared to controls. F1 males had a 22 – 30% decreased mating index though it did not appear dose-related, and increased incidence of atrophied or hypoplastic testes and/or epididymides. Histopathological testicular effects were not assessed at the two	

Species	Exposure	Response	Reference
		mid-doses; therefore, it is unknown if testicular effects occurred at those doses.	

Abbreviations: a.i. = active ingredient; bw = body weight; DER = Data Evaluation Record; DI water = deionized water; F0 = parent generation; F1 = first generation; F = female; g = gram; GD = gestation day; kg = kilogram; LOAEC = lowest-observed-adverse-effect concentration; LOAEL = lowest-observed-adverse-effect level; M = male; mg = milligram; mL = milliliters; MMAD = mass median aerodynamic diameter; NOAEC = no-observed-adverse-effect concentration; NOAEL = no-observed-adverse-effect level; ppm = parts per million

Table A3-6: Carcinogenicity and Combined Carcinogenicity/Chronic Toxicity Studies on Technical Grade Flumioxazin

Species	Exposure	Response	Reference
Carcinogenicity			
Mice, CD-1, 5-week-old males and females (51 mice/sex/dose) M initial body weight: 23 – 30 g F initial body weight: 18 – 24 g	S-53482 Technical (purity: 94.8% a.i.) in diet Dose: 0, 300, 3000, or 7000 ppm (M: 0, 31.1, 314.9, or 754.1 mg a.i./kg/day; F: 0, 36.6, 346.4, or 859.1 mg a.i./kg/day) Administered in diet for 78 weeks.	M: NOAEL 754.1 mg a.i./kg/day; LOAEL >754.1 mg a.i./kg/day F: NOAEL 859.1 mg a.i./kg/day; LOAEL >859.1 mg a.i./kg/day No treatment-related effects were observed on mortality, clinical signs of toxicity, body weight, food consumption, hematological parameters, organ weights, or gross pathology at any dose level. At 3000 ppm, males exhibited increased incidence of malignant lymphoma/leukemia (6/15 treated animals compared to 1/14 controls) and females had increases in pulmonary adenoma (5/51 treated animals compared to 0/50 controls); however, incidence rates are comparable with historical data and not dose-dependent. **No evidence of carcinogenicity.**	MRID 44295018 Seki (1993) Acceptable/Guideline
Combined Carcinogenicity/Chronic Toxicity			
Rats, Crj:CD (SD), 6-week-old males and females (74 rats/sex/dose) M initial body weight: 171 – 225 g	S-53482 Technical (purity: 94.8% a.i.) in diet Doses: 0, 50, 500, and 1000 ppm (M: 0, 1.8, 18.0, and 36.5 mg a.i./kg/day; F: 0, 2.2, 21.8, and 43.6 mg a.i./kg/day)	M: NOAEL 1.8 mg a.i./kg/day; LOAEL 18.0 mg a.i./kg/day F: NOAEL 2.2 mg a.i./kg/day; LOAEL 21.8 mg a.i./kg/day LOAELs based upon increased incidence of chronic nephropathy and extramedullary	MRID 44295028 Seki (1993) Acceptable/Guideline

Species	Exposure	Response	Reference
F initial body weight: 130 – 182 g	Administered in diet for 24 months.	hematopoiesis in males and decreased MCV and MCH in females. No treatment-related effects on mortality, clinical signs, body weight, body weight gain, food and water consumption, clinical chemistry, ophthalmology, urinalysis, gross pathology parameters, or organ weights were observed at any dose at study termination. 50 ppm: No treatment-related effects. 500 ppm: In females, MCV and MCH decreased 7% and 6%, respectively, compared to controls. Increased incidence of extramedullary hematopoiesis (10/33 compared to 1/31 in controls) and chronic nephropathy (26/33 versus 13/31 in controls) in males. 1000 ppm: Erythroblasts per 100 WBC increased significantly in females (2400% compared to controls). Increased incidence of extramedullary hematopoiesis in females (8/10 versus 6/10 in controls) and males (11/33 versus 1/31 in controls). Increased incidence and severity of chronic nephropathy in males (27/33) compared to controls (13/31). **No evidence of carcinogenicity.**	

Species	Exposure	Response	Reference
Rat, Crj:CD(SD), 6-week-old males and females (50 rats/sex/dose) M initial body weight: 171 – 225 g F initial body weight: 130 – 182 g	S-53482 Technical (purity: 94.8% a.i.) in diet Doses: 0, 50, 500, or 1000 ppm in diet (M: 0, 2.1, 20.8, or 42.1 mg/kg/day; F: 0, 2.5, 25.3, or 51.3 mg/kg/day) Administered in diet for 24 months.	M: NOAEL 20.8 mg a.i./kg/day; LOAEL 42.1 mg a.i./kg/day F: NOAEL 25.3 mg a.i./kg/day; LOAEL 51.3 mg a.i./kg/day Based on hematological effects consistent with anemia in males and females. No treatment-related effects on body weight gain. <u>50 and 500 ppm</u>: No toxicologically significant treatment-related effects on males or females. <u>1000 ppm</u>: In males, 3.2% decrease in hemoglobin and 5.2% decrease in MCV at 14 weeks; 4.7 – 5.5% decrease in MCH throughout treatment. In females, 10.6% decrease in hemoglobin at 14 weeks and 8.0 – 9.1% decrease in hemoglobin at 27 and 53 weeks; 6.7% and 6.4% decreases in hematocrit at 14 weeks and 27 weeks, respectively; decreases in MCV, MCH, and MCHC throughout treatment (% not reported); increase in reticulocytes at 14 weeks (1.9% count vs 1.1% in controls); increased erythroblasts/100 WBC at 27 and 53 weeks (4 vs 0 in controls and 19 vs 0 in controls, respectively). Significant increase in male and female relative liver weight.	MRID 42684937 Adachi (1991) Core Supplementary/ Non-guideline

Species	Exposure	Response	Reference
		No evidence of carcinogenicity.	
Gene mutation			
Bacterial reverse gene mutation assay (*Salmonella typhimurium* and *Escherichia coli*)	S-53482 (purity: 94.8% a.i.) in DMSO Doses: 0, 15, 50, 150, 500, 1500, or 5000 µg a.i./plate for preliminary cytotoxicity assay evaluated with and without S9 activation Doses: 0, 50, 100, 200, 500, 1000, or 2000 µg a.i./plate for pre-incubation mutation assays with or without S9 activation.	**Negative** +/-S9 activation in *S. typhimurium* strains TA1535, TA1537, and TA100, and in *E. coli* strain WP2uvrA, for increased frequency of revertant colonies up to cytotoxic and precipitating concentrations (5000 µg a.i./plate). Revertant colonies at that concentration were obscured, and there was no clear evidence of cytotoxicity at 1500 µg a.i./plate. **Equivocal response** in the mutation assays. Increases in revertant colonies of *S. typhimurium* strains TA1538 and TA98 +S9 activation were noted for cytotoxicity and +/-S9 activation for mutagenicity up to precipitating concentration (1000 µg a.i./plate).	MRID 42684938 Kogiso (1989) Acceptable/Guideline
In Vivo/In Vitro Unscheduled DNA Synthesis Assay (Rat Hepatocytes) Rat, Sprague-Dawley, 7 – 8-week-old males (3 rats/dose) M body weight: 222 – 302 g	S-53482 (purity: 94.8% a.i.) in corn oil. Positive control: 50 mg/kg 2-acetylaminofluorene in corn oil Doses in dose-response study: single gavage of 0, 1250, 2500, or 5000 mg a.i./kg (20 mL/kg as a suspension) with cell harvest at 12 hours Doses in time-course study: single gavage of 0 or 5000 mg a.i./kg	**Negative** for inducing unscheduled DNA synthesis in rat hepatocytes. No signs of overt toxicity were reported, though cell viability in hepatocytes recovered 3 and 12 hours after exposure to 5000 mg a.i./kg was significantly decreased compared to controls.	MRID 42684941 Kogiso (1990) Acceptable/Guideline

Species	Exposure	Response	Reference
	with cell harvests at 3, 12, and 24 hours.		
Cytogenetics			
In Vitro Chromosomal Aberration Test (Chinese Hamster Ovary [CHO] cells)	V-53482 (purity: 98.2% a.i.) in DMSO Doses: 0, 30, 100, 200, or 500 µM (0, 11, 35, 70, or 177 µg a.i./mL) with and without S9 activation Without S9, cells exposed for 24 hours. With S9, cells exposed for 6 hours and cultured for an additional 18 hours.	**Negative** for chromosomal aberrations at any dose without S9 (precipitation at ≥200 µM, cytotoxicity at 500 µM). **Positive** for chromosomal aberrations with S9 activation at doses ≥100 µM (primarily chromatid breaks and chromatid exchanges). Precipitation at ≥100 µM and cytotoxicity at 500 µM.	MRID 42684939 Kogsio (1988) Acceptable/Guideline
In Vivo Chromosomal Aberration Test (Rat Bone Marrow cells) Rats, Sprague-Dawley, 7 – 8-week-old males and females (5 rats/sex/group) M body weight: 250 – 302 g F body weight; 149 – 232 g	S-53482 (purity: 94.8% a.i.) in corn oil. Positive control: 40 mg/kg cyclophosphamide (volume of 10 mL/kg). Doses in dose-response study: single gavage dose of 0, 1250, 2500, or 5000 mg a.i./kg (administered at volume of 20 mL/kg) with 24-hour study period Doses in time-course study: single gavage dose of 4400 mg a.i./kg (F) or 5000 mg a.i./kg (M), with 6, 12, 24, and 48-hour sacrifices.	**Negative** for chromosomal aberrations up to 5000 mg a.i./kg (test material was cytotoxic). Ratio of PCEs was significantly lower in males at all dose levels, and in low- and high-dose females.	MRID 42684940 Hara (1990) Acceptable/Guideline

Species	Exposure	Response	Reference
In Vivo Micronucleus Assay Mice, ICR, 8-week-old males (4 mice/dose) Body weight: 33 – 39 g	S-53482 (purity: 98.4% a.i.) in corn oil. Positive control: cyclophosphamide dissolved in saline (80 mg/kg) Dose: 0, 300, 1000, or 5000 mg a.i./kg (at volume assumed to be 20 mL/kg) via intraperitoneal injection; bone marrow cells harvested at 24 hours.	**Negative** for induction of micronuclei in bone marrow cells. No evidence of cytotoxicity or genotoxicity was reported.	MRID 42684942 Hara and Kogiso (1988) Unacceptable (does not meet study guidelines)

Abbreviations: a.i. = active ingredient; CHO = Chinese hamster ovary; DMSO = dimethyl sulfoxide; F = female; g = gram; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; M = male; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; µg = microgram; µM = micromolar; mg = milligram; mL = milliliter; NOAEL = no-observed-adverse-effect level; PCE = polychromatic erythrocytes; ppm = parts per million; WBC = white blood cells

Table A3-7: Acute Eye Irritation, Skin Irritation, and Skin Sensitization Toxicity Studies on Technical Grade Flumioxazin and a Formulated Flumioxazin Product

Species	Exposure	Response	Reference
Acute eye irritation			
Technical Grade Flumioxazin			
Rabbit, New Zealand White, 4-month-old males and females (3 rabbits/sex/dose) M/F initial body weight: 2.60 – 3.13 kg	S-53482 Technical (purity: 94.8% a.i.) 100 mg of test substance was applied to the everted lower eyelid of one eye per animal and held closed for 1 second. The other eye was untreated control. Both eyes were examined for lesions and scored according to the Draize scale for corneal opacity, and iris and conjunctiva redness, chemosis, and discharge at 1, 24, 48, and 72 hours after treatment.	No corneal opacity was observed in any animals. Iris congestion (grade 1) was observed in 2 males but cleared by 24 hours. 6/6 animals exhibited conjunctival redness at 1 hour, and 4/6 animals at 24 hours, but all cleared by 48 hours. Chemosis was observed in all animals at 1 hour but resolved by 24 hours. No other effects were observed. Mean total score was 1.3 at 24 hours and 0 afterwards. The test substance was determined to be minimally irritating and was classified as U.S. EPA Toxicity Category III for primary eye irritation.	MRID 42684917 Nakanishi (1989) Acceptable/Guideline
Rabbit, New Zealand White, young adult males (n = 3) Body weight not reported.	Flumioxazin Technical (purity not reported) 72 mg (0.1 mL) was instilled in each eye. Treated eyes were rinsed with analytical grade water 1 hour after instillation. Study duration not reported.	No corneal opacity or iritis observed. All eyes had a score of 1 for conjunctival redness at 1 hour; resolved by 24 hours. Non-irritant. Classified as U.S. EPA Toxicity Category IV for primary eye irritation.	MRID 50353611 Patil (2016) Acceptable

Species	Exposure	Response	Reference
Formulated Product			
Rabbit, New Zealand White, 12 – 13-week-old females (6 rabbits/dose) F initial body weight: 2.8 – 3 kg	V-53482 50 WDG (purity: 50% a.i.) 50 mg of test substance (equivalent to 25 mg a.i.) was applied to everted lower eyelid of one eye per animal and held closed for 1 second. The other eye was untreated control. Both eyes examined for lesions and scored for corneal opacity, iris, and conjunctiva at 1 hour and 1, 2, 3, 4, and 7 days after treatment.	No corneal opacity or iritis observed. 2 eyes had score of 2 and 4 eyes had score of 1 for conjunctival redness but resolved by 48 hours. All animals had chemosis at 1 hour, and slight discharge at 1 and 24 hours, but resolved by 48 hours. Classified as U.S. EPA Toxicity Category IV for primary eye irritation.	MRID 42684918 Ligget and McRae (1991) Acceptable/Guideline
Acute dermal irritation			
Technical Grade Flumioxazin			
Rabbit, New Zealand White, young adult males (n = 3) Body weight not reported.	Flumioxazin Technical (purity not reported) Test article finely pulverized and moistened with water prior to application to the skin (no further information provided)	No dermal irritation observed at any treated sites. (no further information provided) Non-irritant. Classified as U.S. EPA Toxicity Category IV for primary dermal irritation.	MRID 50353612 Patil (2016) Acceptable
Rabbit, New Zealand White, 4-month-old males and females (3 rabbits/sex/dose) M/F initial body weight: 2.65 – 2.89 kg	S-53482 Technical (purity: 94.8% a.i.) moistened with corn oil 500 mg of test material was applied to 2 shaved dorsal sites on each animal (one site was abraded and one was not) and covered with occlusive surgical tape for 4 hours.	The test material did not induce skin irritation in any animal up to 72 hours post-patch removal. Scores were 0.0 for erythema and edema at all time intervals. Non-irritant. Classified as U.S. EPA Toxicity Category IV for primary dermal irritation.	MRID 42684917 Nakanishi (1989) Acceptable/Guideline

Species	Exposure	Response	Reference
	Dermal irritation was scored for erythema and edema at 4.5, 24, 48, and 72 hours post-patch removal.		
Formulated Product			
Rabbit, New Zealand White, 12 – 13-week-old males (6 rabbits/dose) M initial body weight: 2.7 – 3 kg	V-53482 50 WDG (purity: 50% a.i.) moistened with water 500 mg test material (equivalent to 250 mg a.i.) was applied to clipped 2.5 cm^2 dorsal area on each animal and covered with gauze moistened with 0.5 mL of DI water and a semi-occlusive adhesive dressing for 4 hours Treated sites were washed with water and scored for erythema, eschar formation and edema at 0.5, 24, 48, 72, and 96 hours post-patch removal.	5 of 6 animals showed very slight erythema (score =1) at 0.5 hours, resolved by 24 hours, and no edema at any time. 1 animal showed very slight erythema (score =1) through 72 hours, resolved by 96 hours, and very slight edema (score = 1) through 48 hours, resolved by 72 hours. Slightly irritating. Classified as U.S. EPA Toxicity Category IV for primary dermal irritation.	MRID 42684919 Ligget and McRae (1991) Acceptable/Guideline
Skin sensitization			
Technical Grade Flumioxazin			
Guinea pig, Hartley, 6 – 7-week-old males (20 animals received test substance; 20 animals were negative control; 5 animals were positive control; 5 animals were vehicle control)	S-53482 (purity: 94.8% a.i.) in corn oil. Positive control: 2,4-dinitrochlorobenzene (DNCB; purity 99.95%) in corn oil Guinea Pig Maximization Test.	Treated animals and negative control animals had scores of 0 for erythema and swelling. Positive control animals had scores of 2 – 3 for erythema and swelling. Under the test conditions, the test material is not a dermal sensitizer in male Hartley guinea pigs.	MRID 42684921 Nakanishi (1990) Acceptable/Guideline

Species	Exposure	Response	Reference
Initial body weight: 369 – 490 g	Induction phase: Animals received 50 µL intradermal injections to clipped dorsal skin in their scapular region of Freund's adjuvant at 1:1 with water, 1% test material in corn oil, and 1:1 mixture of 2% test material in Freund's adjuvant and water. One week later, area was re-shaved and a patch with 25% suspension of test material in petrolatum was applied and covered with occlusive surgical tape for 48 hours. One day prior, 10% sodium lauryl sulfate was applied to the area to induce irritation. Challenge phase: Two weeks after induction, a patch with 0.2 g of 25% test material in petrolatum was applied to the clipped right flank (separate from induction site) for 24 hours. Animals were scored for erythema and swelling on scale of 0 – 3 at 24 and 48 hours post-patch removal.		
Guinea pig, English (Hartley), young adult males (n = 32) Body weight not provided	Flumioxazin Technical (purity not reported) Skin Sensitization Study (Buehler Test)	Negative for skin sensitization (no further details provided)	MRID 50353613 Patil (2016) Acceptable

Species	Exposure	Response	Reference
	45% w/v of test substance in analytical grade water, with 0.2% Tween 80 as wetting agent, was used for induction and challenge. Positive control results were acceptable. (no further details provided)		
Formulated Product			
Guinea pig, Dunkin/Hartley, 9 – 10-week-old males (n = 20 for test substance, n = 10 for positive and negative controls) Initial body weight: 435 – 578 g	V-53482 50 WDG (purity: 50% a.i.) in water. Positive control: Formalin Guinea Pig Maximization Test. <u>Induction phase</u>: Animals received 0.1 mL intradermal dose (equivalent to 0.05 mL a.i.) to clipped dorsal skin in their scapular region of Freund's adjuvant at 1:1 with water, 1% w/w test material in irrigation water, and 1% w/w solution of test material in 50:50 mixture of Freund's adjuvant and water. One week later, area was reshaved and a 2 × 4 cm patch with 0.4 mL of test material (equivalent to 0.2 mL a.i.) was applied and covered with occlusive surgical tape for 48 hours.	9 of 10 control animals had no irritation (score = 0); 1 control animal had slight erythema (score = 1) at 24 hours but resolved. 17 of 20 treated animals had no irritation (score = 0), 1 animal had slight erythema (score = 1) at 24 hours (resolved), and 2 animals had inconclusive responses more persistent but not more intense than controls (1 resolved). Positive control animals had strong positive response. Test material is not a dermal sensitizer in male Dunkin/Hartley guinea pigs.	MRID 42684920 Parcell and Denton (1991) Acceptable/Guideline

Species	Exposure	Response	Reference
	Challenge phase: Two weeks after induction, a 2 × 2 cm patch with 0.2 mL of 60% w/w test material in distilled water was applied to clipped anterior flank (separate from induction site) for 24 hours; a patch with 30% w/w test material in distilled water was applied to clipped posterior flank for 24 hours. Animals were scored for erythema and edema on scale of 0 – 3 at 24, 48, and 72 hours post-patch removal.		

Abbreviations: a.i. = active ingredient; cm² = square centimeter; DI = deionized; DNCB = dinitrochlorobenzene; U.S. EPA = U.S. Environmental Protection Agency; F = female; g = gram; kg = kilogram; M = male; µL = microliter; mg = milligram; mL = milliliter; w/v = weight per volume; w/w = weight by weight; WDG = water dispersible granule

Table A3-8: Acute Dermal Exposure Toxicity Studies on Technical Grade Flumioxazin and a Formulated Flumioxazin Product

Species	Exposure	Response	Reference
Acute			
Technical Grade Flumioxazin			
Rats, Sprague-Dawley, 6-week-old males and females (5 rats/sex/dose)	S-53482 (purity: 94.8% a.i.) suspended in 1% methyl cellulose Doses: Single dermal application of 0 or 2000 mg a.i./kg bw (250 mg/mL applied at volume of 8 mL/kg) Applied to shaved 30 cm^2 of dorsal trunk and covered for 24 hours, when dressing was removed and site was wiped with distilled water; 14-day observation period.	M LD_{50}: >2000 mg a.i./kg bw F LD_{50}: >2000 mg a.i./kg bw No mortality or skin irritation in any group. No significant difference in body weight between treated and control animals. Classified as U.S. EPA Toxicity Category III for acute dermal toxicity.	MRID 42684913 Hiromori (1989) Acceptable/Guideline
Rats, Wistar, 20-week-old males and females (10 rats)	Flumioxazin Technical (purity: 98.19 – 98.63% a.i.) ground and then moistened with water Dose: 2000 mg a.i./kg (limit dose) No further details provided.	M LD_{50}: >2000 mg a.i./kg bw F LD_{50}: >2000 mg a.i./kg bw No mortality, clinical signs of toxicity, or dermal irritation observed in any animals tested; no gross pathological alterations observed at necropsy. All animals gained weight. No further details provided. Classified as U.S. EPA Toxicity Category III for acute dermal toxicity.	MRID 50353609 Patil (2016) Acceptable (U.S. EPA noted that age was younger than OCSPP Guideline 870.1200 and OECD Guideline 402, but body weight was within OECD Guideline 402)

Species	Exposure	Response	Reference
Formulated Product			
Rat, Sprague-Dawley, 7 – 10-week-old males and females (5/sex/dose) M initial body weight: 234 – 250 g F initial body weight: 230 – 250 g	V-53482 50 WDG (purity: 50% a.i.) suspended in 114.3% w/v distilled water Dose: Single dermal application of 2000 mg/kg bw (equivalent to 1000 mg a.i./kg; volume of 1.75 mL/kg) (no controls) Applied to shaved 25 cm^2 of dorsal-lumbar region and covered for 24 hours, when dressing was removed and site was washed with warm water; 14-day observation period.	M LD_{50}: >1000 mg a.i./kg bw F LD_{50}: >1000 mg a.i./kg bw No mortality, clinical signs of toxicity, or dermal irritation observed in any animals tested; no gross pathological alterations observed at necropsy. All animals gained weight. Classified as U.S. EPA Toxicity Category III for acute dermal toxicity.	MRID 42684914 Baldrick and Healing (1991) Acceptable/Guideline

Abbreviations: a.i. = active ingredient; bw = body weight; U.S. EPA = U.S. Environmental Protection Agency; F = female; g = gram; kg = kilogram; LD_{50} = median lethal dose; M = male; mg = milligram; mL = milliliters; w/v = weight per volume; WDG = water dispersible granule

Table A3-9: Subchronic Dermal Exposure Toxicity Studies on Technical Grade Flumioxazin

Species	Exposure	Response	Reference
Subchronic			
Rats, Sprague-Dawley, 59-day-old males and females (5 rats/sex/dose) M initial body weight: 264.2 – 299.8 g F initial body weight: 189.5 – 226.4 g	Flumioxazin (purity: 94.8% a.i.) in corn oil Doses: 0, 100, 300, or 1000 mg a.i./kg/day Applied in a 2 mL/kg paste to animals' shaved trunk and covered with gauze for 6 hours/day. After exposure, site was cleaned with distilled water; 21 days of exposure.	M: NOAEL 1000 mg a.i./kg/day; LOAEL >1000 mg a.i./kg/day F: NOAEL 1000 mg a.i./kg/day; LOAEL >1000 mg a.i./kg/day No mortality or clinical signs of toxicity or treatment-related effects on body weight, body weight gain, food consumption, clinical chemistry, organ weights, gross pathology, or histopathology were observed. <u>100 and 300 mg a.i./kg/day</u>: No treatment-related effects. <u>1000 mg a.i./kg/day</u>: Small decreases in hemoglobin (7%) and hematocrit (6%) compared to controls were statistically significant in females, though study DER reviewers did not find the decrease biologically significant.	MRID 44295016 Osheroff (1991) Acceptable/Guideline

Abbreviations: a.i. = active ingredient; DER = Data Evaluation Record; g = gram; F = female; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; M = male; mg = milligram; mL = milliliter; NOAEL = no-observed-adverse-effect level

Table A3-10: Acute Inhalation Toxicity Studies on Technical Grade Flumioxazin and a Formulated Flumioxazin Product

Species	Exposure	Response	Reference
Technical Grade Flumioxazin			
Rats, Crj:CD(SD)(SPF), 7-week-old males and females (5 rats/sex/dose) M initial body weight: 215 – 244 g F initial body weight: 157 – 198 g	S-53482 Technical (purity: 98.3% a.i.) as a fine powder Doses: Whole body exposure to nominal concentrations of 0, 9.56, or 33.03 mg a.i./L (measured concentrations of 0, 1.55, and 3.93 mg a.i./L)[1] for 4 hours 14-Day observation period.	4-Hour LC_{50} not defined due to lack of particle size data. No mortality occurred in any dose group, and no clinical signs of toxicity were noted. No treatment-related effects on body weight gain, gross pathology, or histopathology were observed. All treated animals exhibited bradypnea and decrease of spontaneous activity at both doses. Males exhibited irregular respiration in 4/5 low dose and 3/5 high dose animals during exposure. Females exhibited irregular respiration in 2/5 low dose and 4/5 high dose animals during exposure.	MRID 42684915 Kawaguchi (1990) Core Supplementary with Toxicity Category temporarily undefined
Rats, Wistar, 10-week-old females (6 rats/group) Body weight not reported.	Flumioxazin Technical (purity not reported) as an aerosol Dose: Limit dose of 3.71 mg a.i./L MMAD: 1.38 µ GSD: 2.71 and 2.74 4-Hour exposure and 14-day observation period.	F: LC_{50} >3.71 mg a.i./L No mortality or treatment-related effects on body weight. All treated animals exhibited hypoactivity and ruffled fur from the 4th hour of exposure but recovered by day 2. Classified as U.S. EPA Toxicity Category IV for acute inhalation toxicity.	MRID 50353610 Patil (2016) Acceptable

Species	Exposure	Response	Reference
Formulated Product			
Rat, Sprague-Dawley, 7-week-old males and 9-week-old females (5 rats/sex/dose) M initial body weight: 205 – 224 g F initial body weight: 204 – 217 g	V53482 50 WDG (purity: 50% a.i.) as an aerosol (100 g product in 200 g water) Doses: Whole body exposure to measured concentrations of 0 or 0.094 mg a.i./L (0.19 mg product/L) for 4 hours MMAD: 3.0 µm (SD 2.23 µm) 14-Day observation period.	M: LC_{50} >0.094 mg a.i./L F: LC_{50} >0.094 mg a.i./L No mortality or treatment-related effects on body weight, relative lung weight, or macroscopic findings. During exposure and until day 2 of observation, all treated animals exhibited increased respiratory rate; piloerection was observed until day 1 of observation. Upon histopathological examination, focal degeneration of ventral cartilage of the larynx was observed in ¾ treated males (1 larynx was lost) and 3/5 treated females. Temporary classification as U.S. EPA Toxicity Category I for acute inhalation toxicity due to observed focal degeneration of the ventral cartilage of the larynx.	MRID 42684916 Jackson et al. (1992) Core Supplemental (due to only 1 dose level)

[1]Units were reported as g/m^3, which is equivalent to mg/L.
Abbreviations: a.i. = active ingredient; U.S. EPA = U.S. Environmental Protection Agency; F = female; g = gram; GSD = geometric standard deviation; kg = kilogram; L = liter; LC_{50} = median lethal concentration; M = male; mg = milligram; mL = milliliters; MMAD = mass median aerodynamic diameter; SD = standard deviation; WDG = water dispersible granule; w/v = weight per volume

Appendix 4: Toxicity to Birds

In the following tables, all data attributed to MRID studies were taken from DERs of MRID studies. MRID studies were not available for review.

Table A4-1: Acute Oral and Dietary Toxicity to Birds on Technical Grade Flumioxazin

Species	Exposure	Response	Reference
Acute (Dose-based)			
Bobwhite quail (*Colinus virginianus*), 16-week-old males and females (5 birds/sex/dose) M/F initial body weight: 162 – 214 g	S-53482 (purity: 94.8% a.i.) in corn oil Doses: Single gavage dose of 0, 292, 486, 810, 1350, or 2250 mg a.i./kg bw (volume of 6 mL/kg) Fasted 15 hours prior to dosing; 14-day observation period.	M: LD_{50} >2250 mg a.i./kg bw F: LD_{50} >2250 mg a.i./kg bw NOAEL: 2250 mg a.i./kg bw No mortality or clinical signs of toxicity observed in any dose group. No body weight gain or food consumption differences between treated and control animals.	MRID 42684945 Lloyd et al. (1990) Acceptable/Guideline
Acute (Dietary-based)			
Mallard duck (*Anas platyrhynchos*), 10-day-old birds (10 birds/dose) Initial body weight: 153 – 175 g (birds not sexed due to young age)	S-53482/V-53482 (purity: 94.8% a.i.) in 2% corn oil and diet Dietary concentrations: 0, 562, 1000, 1780, 3160, or 5620 ppm a.i. Doses: 0, 173, 307, 547, 971, or 1728 mg a.i./kg/day (doses calculated by multiplying dietary concentration by food conversion factor[1]) 5-Day exposure period followed by an additional 3 days of observation.	M: LC_{50} >1728 mg a.i./kg/day F: LC_{50} >1728 mg a.i./kg/day NOAEC: 1728 mg a.i./kg/day No mortality or clinical signs of toxicity observed in any dose group. No body weight gain or food consumption differences between treated and control animals.	MRID 42684946 Culotta et al. (1991) Acceptable/Guideline

Species	Exposure	Response	Reference
Bobwhite quail (*Colinus virginianus*), 10-day-old birds (10 birds/dose) Initial body weight: 19 – 21 g (birds not sexed due to young age)	S-53482/V-53482 (purity: 94.8% a.i.) in 2% corn oil and diet Dietary concentrations: 0, 562, 1000, 1780, 3160, or 5620 ppm a.i. Doses: 0, 287, 510, 908, 1611, or 2866 mg a.i./kg/day (doses calculated by multiplying dietary concentration by food conversion factor[2]) 5-Day exposure period followed by an additional 3 days of observation.	M: LC_{50} >2866 mg a.i./kg/day F: LC_{50} >2866 mg a.i./kg/day NOAEC: 2866 mg a.i./kg/day No mortality, clinical signs of toxicity or differences in body weight observed in any dose group compared to control. Data on feed consumption was inconsistent in control and treated groups. Although the DER reports NOAEC of 3160 ppm and LOAEC of 5620 ppm based on reduction in food consumption, this effect is not considered adverse in the absence of decreased body weight. No statistical analysis was reported and individual data were not reported for food consumption.	MRID 42684947 Culotta et al. (1991) Acceptable/Guideline

[1]Average daily food consumption/bird » 84 g; average body weight » 272 g; food conversion factor: 84 g ÷ 272 g = 0.3 g food/g bw. Food consumption was reported as group averages for each treatment group on Days 0 – 5 (exposure) and Days 6 – 8 (observation). Average food consumption was determined as the average of these two rates (66 g/day [Days 0 –5] and 101 g/day [Days 6 – 8]). Body weights were reported as group averages for each treatment group at the beginning of exposure (Day 1), end of exposure (Day 5), and end of observation period (Day 8). To determine an average body weight, the average of Day 1 (167 g), Day 5 (277), and Day 8 (373) weights was taken.
[2]Average daily food consumption/bird » 15 g; average body weight » 30 g; food conversion factor: 15 g ÷ 30 g = 0.51 g food/g bw. Food consumption was reported as group averages for each treatment group on Days 0 – 5 (exposure) and Days 6 –8 (observation). Average food consumption was determined as the average of these two rates (12 g/day [Days 0 – 5] and 19 g/day [Days 6 – 8]). Body weights were reported as group averages for each treatment group at the beginning of exposure (Day 1), end of exposure (Day 5), and end of observation period (Day 8). To determine an average body weight, the average of Day 1 (20 g), Day 5 (31), and Day 8 (38) weights was taken.
Abbreviations: a.i. = active ingredient; bw = body weight; F = female; g = gram; kg = kilogram; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; LOAEC = lowest-observed-adverse-effect concentration; M = male; mg = milligram; NOAEC = no-observed-adverse-effect concentration; NOAEL = no-observed-adverse-effect level; ppm = parts per million

Table A4-2: Chronic Dietary Toxicity to Birds on Technical Grade Flumioxazin

Species	Exposure	Response	Reference
Chronic (Dietary-based)			
Mallard duck (*Anas platyrhynchos*), 18-week-old males and females (16 bird/sex/dose) M average body weight: 1242 g F average body weight: 1123 g	V-53482 (purity: 94.8% a.i.) in acetone and corn oil in diet Dietary concentrations: 0, 100, 250, or 500 ppm a.i. Doses: 0, 13.1, 32.8, or 65.6 mg a.i./kg/day (doses calculated by multiplying dietary concentration by food conversion factor[1]) Dietary exposure 10 weeks prior to egg-laying, followed by 11 additional weeks exposure.	**Reproductive** M/F NOAEL: 32.8 mg a.i./kg/day M/F LOAEL: 65.6 mg a.i./kg/day LOAEL based on reduction in viable embryos and live 3-week embryos. No treatment-related mortality, clinical signs of toxicity, reductions in body weight or food consumption in adult birds. No treatment-related reductions in reproductive parameters (eggs laid, eggs cracked, eggs set, normal hatchlings, 14-day-old survivors and survivor weight, egg shell thickness, or hatchling weight) compared to controls. <u>100 and 250 ppm</u>: No treatment-related effects. <u>500 ppm</u>: Significant reduction in viable embryos and live 3-week embryos (29% and 30%, respectively) compared to controls.	MRID 44295005 Beavers et al. (1994) Acceptable/Guideline

Species	Exposure	Response	Reference
Northern Bobwhite quail (*Colinus virginianus*), 33-week-old males and females (16 bird/sex/dose) M average body weight: 207 g F average body weight: 217 g	V-53482 (purity: 94.8% a.i.) in acetone and corn oil in diet Dietary concentrations: 0, 100, 250, or 500 ppm a.i. Doses: 0, 12.7, 31.8, or 63.6 mg a.i./kg/day (doses calculated by multiplying dietary concentration by food conversion factor[2]) Dietary exposure 10 weeks prior to egg-laying, followed by 11 additional weeks exposure.	**Reproductive** M/F NOAEL: 63.6 mg a.i./kg/day M/F LOAEL: >63.6 mg a.i./kg/day No treatment-related mortality, clinical signs of toxicity, reductions in body weight or food consumption in adult birds, or reductions in any reproductive parameters measured (eggs laid, eggs cracked, eggs set, viable embryos, live 3-week embryos, normal hatchlings, 14-day-old survivors and survivor weight, eggshell thickness, or hatchling weight) compared to controls.	MRID 44295006 Beavers et al. (1994) Classified as Supplemental/Non-guideline (not stated whether the test was conducted with the highest dosage level at or above maximum field residue level)

[1]Average daily food consumption/bird » 155 g; average body weight » 1183 g; food conversion factor: 155 g ÷ 1183 g = 0.13 g food/g bw. Food consumption was reported as the group average for each treatment group; average food consumption was determined as the average of these 4 rates. Body weights were reported as group averages for each treatment group, male and female, at study initiation and termination. Average body weight was derived as the average of these 16 weights.
[2]Average daily food consumption/bird » 27 g; average body weight » 212 g; food conversion factor: 27 g ÷ 212 g = 0.13 g food/g bw. Food consumption was reported as the group average for each treatment group; average food consumption was determined as the average of these 4 rates. Body weights were reported as group averages for each treatment group, male and female, at study initiation and termination. Average body weight was derived as the average of these 16 weights.
Abbreviations: a.i. = active ingredient; F = female; g = gram; kg = kilogram; LOAEL = lowest-observed-adverse-effect level; M = male; mg = milligram; NOAEL = no-observed-adverse-effect level; ppm = parts per million

Appendix 5: Toxicity to Terrestrial Invertebrates

In the following tables, all data attributed to MRID studies were taken from DERs of MRID studies. MRID studies were not available for review.

Table A5-1: Acute Toxicity Technical Grade Flumioxazin to Honey Bees

Species	Exposure	Response	Reference
Acute (Contact)			
Honey bee (*Apis mellifera*), 1- to 6-day-old bees (50 bees/dose)	V-53482 (purity: 94.8% a.i.) in acetone Doses: 0 (negative and solvent control), 14, 23, 38, 63, or 105 µg a.i./bee (volume of 10 mL) Bees dosed with 2 µl test solution on thorax and/or abdomen; 48-hour exposure.	LD_{50} >105 µg a.i./bee NOAEL = 105 µg a.i./bee LOAEL >105 µg a.i./bee No treatment-related mortality or clinical signs of toxicity. Classified as “practically non-toxic”	MRID 42684951 Hoxter et al. (1990) Acceptable/Guideline

Abbreviations: a.i. = active ingredient; LD_{50} = median lethal dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Appendix 6: Toxicity to Terrestrial Plants

In the following tables, all data attributed to MRID studies were taken from DERs of MRID studies. MRID studies were not available for review.

Table A6-1: Seedling Emergence Toxicity Studies on Technical Grade Flumioxazin

Species	Exposure	Response	Reference
Monocots			
Corn (*Zea mays*) Oat (*Avena sativa*) Onion (*Allium cepa*) Ryegrass (*Lolium perenne*) 40 seeds/dose	Flumioxazin Technical (purity: 99.5% a.i.) in 40% acetone/60% DI water Range of application rates tested varied by species from 0.0004 to 0.096 lb a.i./acre with negative and solvent controls (maximum labeled rate: 0.094 lb a.i./acre) Applied to surface soil pre-emergence via spray booth; 21-day observation.	**Most sensitive monocot:** Ryegrass (dry weight) EC_{25}: 0.0037 lb a.i./acre NOAEL: 0.0030 lb a.i./acre Corn (dry weight) EC_{25}: 0.028 lb a.i./acre NOAEL: 0.012 lb a.i./acre Oat (dry weight) EC_{25}: 0.017 lb a.i./acre NOAEL: 0.012 lb a.i./acre Onion (dry weight) EC_{25}: 0.0049 lb a.i./acre NOAEL: 0.0015 lb a.i./acre Signs of toxicity were primarily stunting, leaf desiccation, and plant death.	MRID 44295029 Chetram (1997) Acceptable/Guideline
Dicots			
Cabbage (*Brassica oleracea*) Cucumber (*Cucumis sativus*) Lettuce (*Lactuca sativa*) Radish (*Raphanus sativus*) Soybean (*Glycine max*) Tomato (*Lycopersicon esculentum*) 40 seeds/dose	Flumioxazin Technical (purity: 99.5% a.i.) in 40% acetone/60% DI water Range of application rates tested varied by species from 0.004 to 0.096 lb a.i./acre with negative and solvent controls (maximum labeled rate: 0.094 lb a.i./acre)	**Most sensitive dicot:** Lettuce (dry weight) EC_{25}: 0.0008 lb a.i./acre NOAEL: 0.0004 lb a.i./acre Cabbage (dry weight) EC_{25}: 0.0024 lb a.i./acre NOAEL: 0.0015 lb a.i./acre	MRID 44295029 Chetram (1997) Acceptable/Guideline

Species	Exposure	Response	Reference
	Applied to surface soil pre-emergence via spray booth; 21-day observation.	Cucumber (dry weight) EC_{25}: 0.0056 lb a.i./acre NOAEL: 0.0014 lb a.i./acre Radish (height) EC_{25}: 0.0038 lb a.i./acre NOAEL: 0.0015 lb a.i./acre Soybean (all parameters similar) EC_{25}: >0.096 lb a.i./acre NOAEL: 0.096 lb a.i./acre Tomato (dry weight) EC_{25}: 0.0014 lb a.i./acre NOAEL: 0.0008 lb a.i./acre Signs of toxicity were primarily stunting, leaf desiccation, and plant death.	

Abbreviations: a.i. = active ingredient; DI water = deionized water; EC_{25} = concentration affecting 25% of organisms tested; lb = pound; NOAEL = no-observed-adverse-effect level

Table A6-2: Vegetative Vigor Toxicity Studies on Technical Grade Flumioxazin

Species	Exposure	Response	Reference
Monocots			
Corn (*Zea mays*) Oat (*Avena sativa*) Onion (*Allium cepa*) **Ryegrass (*Lolium perenne*)** **20 plants/dose**	Flumioxazin Technical (purity: 99.5% a.i.) in 40% acetone/60% DI water Range of application rates tested varied by species from 0.00002 to 0.096 lb a.i./acre with negative and solvent controls (maximum labeled rate: 0.094 lb a.i./acre) Applied to plant via spray booth at the 1 – 3 true leaf stage; 21-day observation.	**Most sensitive monocot:** Oat (dry weight) EC_{25}: 0.0071 lb a.i./acre NOAEL: 0.0060 lb a.i./acre Ryegrass (dry weight) EC_{25}: 0.0083 lb a.i./acre NOAEL: 0.0060 lb a.i./acre Corn (dry weight) 4.1 Onion (dry weight) EC_{25}: 0.0081 lb a.i./acre NOAEL: 0.0060 lb a.i./acre Signs of toxicity were primarily stunting, leaf desiccation, chlorosis, and plant death.	MRID 44295030 Chetram (1997) Acceptable/Guideline
Dicots			
Cabbage (*Brassica oleracea*) Cucumber (*Cucumis sativus*) Lettuce (*Lactuca sativa*) Radish (*Raphanus sativus*) Soybean (*Glycine max*) Tomato (*Lycopersicon esculentum*) 20 plants/dose	Flumioxazin Technical (purity: 99.5% a.i.) in 40% acetone/60% DI water Range of application rates tested varied by species from 0.00002 to 0.096 lb a.i./acre with negative and solvent controls (maximum labeled rate: 0.094 lb a.i./acre)	**Most sensitive dicot:** Cucumber (phytotoxicity) EC_{25}: 0.00008 lb a.i./acre NOAEL: 0.00005 lb a.i./acre Cabbage (phytotoxicity) EC_{25}: 0.00041 lb a.i./acre NOAEL: 0.00019 lb a.i./acre Lettuce (dry weight)	MRID 44295030 Chetram (1997) Acceptable/Guideline

Species	Exposure	Response	Reference
	Applied to plant via spray booth at the 1 – 3 true leaf stage; 21-day observation.	EC_{25}: 0.00015 lb a.i./acre NOAEL: 0.00010 lb a.i./acre <u>Radish (phytotoxicity)</u> EC_{25}: 0.00016 lb a.i./acre NOAEL: 0.00005 lb a.i./acre <u>Soybean (dry weight)</u> EC_{25}: 0.00010 lb a.i./acre NOAEL: 0.00005 lb a.i./acre <u>Tomato (phytotoxicity)</u> EC_{25}: 0.00014 lb a.i./acre NOAEL: 0.00010 lb a.i./acre Signs of toxicity were primarily stunting, leaf desiccation, chlorosis, and plant death.	

Abbreviations: a.i. = active ingredient; DI water = deionized water; EC_{25} = concentration affecting 25% of organisms tested; lb = pound; NOAEL = no-observed-adverse-effect level

Table A6-3: Field Studies for Preemergence and Postemergence Applications of Flumioxazin

Species	Exposure	Response	Reference
Cotton (*Gossypium hirsutum*)	Application rate: 70 g a.i./ha (equivalent to 0.062 lb a.i./acre) applied with 0.25% (v/v) nonionic surfactant Preemergence application 10, 8, 6, 5, 4, 3, 2, 1 and 0 prior to planting. Postemergence application: applied at 15 and 30 cm growth stages Soil type: loamy sand (1 – 1.1% OM and 5.5 – 6 pH). Location: North Carolina	Preemergence: approximately 12% plant injury and approximately 4% reduction in fresh weight when applied at immediately before planting, with injury decreasing exponentially with increasing time between application and planting. No visible injury occurred when applied 10 weeks before planting and fresh weight was not affected when applied 5 weeks before planting. Postemergence: No injury to cotton plants at any application stage	Askew et al. (2002)
Cotton (*Gossypium hirsutum*)	Product: Valor SZ herbicide Application rate: 0.03, 0.06, and 0.09 kg a.i./ha (equivalent to 0.027, 0.054 and 0.80 lb a.i./acre, respectively) in 2009, with an additional applications of 0.06 and 0.09 kg a.i./ha in 2010, and 0.09 kg a.i./ha in 2011 Soil types: fine sand (OM <1%), fine sandy loam (OM 2.2%), and sandy clay loam (2% OM) Preemergence application: 30, 20, 15, 10, 5, and 0 days prior to planting	2009: No effect on cotton height assessed 30 and 45 days after planting for any rate or application time; no effects observed on cotton lint yield 2010 – 2011: At 30 days after planting, cotton height was reduced for 0.09 kg a.i./ha applied 10 days (17% decrease), 5 days (12% decrease), and 0 days (23% decrease) before planting; for 0.06 kg/a.i./ha applied on day 0 before planting (32% decrease). At 45 days after planting, cotton height was decreased by 16 and 19% for 0.06 and 0.09 kg/a.i./ha, respectively, applied on day 0 before planting; cotton lint yield decreased by 18% for 0.09 kg a.i./ha when applied 5 before planting days and by 16 and 40% for 0.06 and	Berger et al. (2012)

Species	Exposure	Response	Reference
	Location: Georgia	0.09 kg a.i./ha, respectively, applied on day 0 before planting	
Grain sorghum	Application rate: 0.07 and 0.11 kg a.i./ha (equivalent to 0.062 and 0.098 lb a.i./acre, respectively), applied in water Preemergence application: applied 30, 21, 14, 7, and 0 days prior to planting (2002 – 2004) Location: Texas	No injury to sorghum was observed under for either application rate for any pre-planting timing. Sorghum yield was only affected where annual grasses and broadleaf weeds were not controlled.	Grichar (2006)
Broccoli (*Brassica oleracea*), carrot (*Daucus carota*), head lettuce (*Lactuca sativa*), bulb onion (*Allium cepa*), spinach (*Spinacia oleracea*), and processing tomato (*Lycopersicon esculentum*)	Application rate: 0.063, 0.125, 0.25 kg a.i./acre Preemergence application: days before planting not reported Soil types: fine silty loam (0.8% OM), sandy loam (0.5% OM), loam (2.5% OM) Location: California	None of the crops were tolerant to any application rate of flumioxazin tested (data not shown)	Haar et al. (2002)
Peanut (*Arachis hypogaea*)	Application rate: 71 and 105 g a.i./ha (equivalent to 0.063 and 0.094 lb a.i./acre, respectively) Preemergence application study 1 for growth and yield: applied 0, 2, 4, 6, 8, and 10 days after planting (2001 – 2003)	Study 1: No seedling emergence evident and substantially reduced root length for applications on days 0 – 4 after planting; seedling emergence was observed for application on days 6 and 8 after planting, seedlings were below the soil surface; for application on day 10 after planting, seedlings emerged, with no apparent effects; no effects on peanut yield or peanut stand for any application rate or timing; for applications on	Johnson et al. (2006)

Species	Exposure	Response	Reference
	Preemergence application study 2 for peanut maturity: applied 0, 1, 3, 5, 7, and 10 days after planting. Soil types: loamy sand (0.4% OM), loamy sand (0.2% OM) Location: Georgia	days 8 and 10 after planting, peanut plants were stunted with visual injury. Effects were more pronounced at the higher application rate. Study 2: Application of 105 g a.i./ha reduced the number of mature pods and increased the number of mature pods at all timings.	
Sweetpotato (*Ipomoea batatas*)	Application rate: 36, 72, or 109 g ai/ha (equivalent to 0.032, 0.064, and 0.097 lb a.i./acre, respectively) Preemergence application: applied immediate before transplant of seedlings (2002) Postemergence application: applied immediately after transplant of seedlings (2002 – 2003) Soil type: Fine silty Location: Louisiana	Sweet potato tolerance was measured 9, 18 and 34 days after transplanting. Plant injury: At 9 days (but not 18 days 8% plant injury for all preemergence applications; all postemergence applications produced sweet potato injury (35 – 45%) Plant yield: Plant yield was increased for all preemergence applications due to week control; for postemergence, yield inversely proportional to application rate.	Kelly et al. (2006)
Soybean (*Glycine max*)	Application rate: 142 g a.i./ha (equivalent to 0.13 lb a.i./acre) Preemergence application: applied pre-planting; plants evaluated 1, 2, and 4 weeks after emergence Soil types: clay loam, sandy loam, silt loam, silt, loam	Visible plant injury: 12, 8, and 3% after 1, 2, and 4 weeks after emergence Plant height: no effects Dry weight: no effects Yield: no effects	Mahoney et al. (2014)

Species	Exposure	Response	Reference
	Location: Ontario, Canada (2011 – 2012)		
Soybean (*Glycine max*)	Application rate: 71 and 142 g a.i./ha (equivalent to 0.063 and 0.13 lb a.i./acre) Preemergence application: preplant incorporated and preplant soil Postemergence application: applied at the cotyledon stage Soil type: clay loam Location: Ontario, Canada (2011 – 2013)	Visible injury: 11% injury for preplant soil application; 15 – 18% injury for postemergence application Plant stand: no effects for any application Dry biomass: decreased by 21% for postemergence application Yield: no effects for any application	McNaughton et al. (2014)
Green onion (*Allium cepa*)	Application rate: 56 g a.i./ha (equivalent to 0.05 lb a.i./acre) Postemergence application: applied to 2 – 3 leaf onions Location: South Carolina (2004 – 2005)	Decreased plant height, density, and yield	Norsworthy et al. (2007)
Soybean (*Glycine max*)	Application rate: 74 and 87 g a.i./ha (equivalent to 0.066 and 0.078 lb a.i./acre, respectively) Preemergence application: on day of planting Soil type: clay Location: Mississippi (2001 – 2002)	Visual injury: 14 – 31% Soybean height: decreased 15 – 15% Yield: no effects	Poston et al. (2008)

Species	Exposure	Response	Reference
Cotton (*Gossypium hirsutum*)	Application rate: 71, 105, and 140 g/ha (equivalent to 0.066, 0.094, and 0.124 lb/acre, respectively) Preemergence application: 28, 14, and 7 days before planting; plants assessed 2 and 5 weeks after planting Soil types: loamy sand Location: Lewiston-Woodville, NC (2000 – 2001)	No injury to cotton for any application except 105 g/ha applied 7 days before planting (6% injury). No treatment affected cotton yield. No effect on cotton when treatment was followed by irrigation.	Price et al. (2004)
Sugarcane (*Saccharum* interspecific hybrids)	Application rate: 0.28 kg a.i./ha (equivalent to 0.25 lb a.i./acre) Preemergence and postemergence applications Location: Schriever, LA (2001 – 2002)	Visual injury observed for postemergence but not preemergence application. Reduction in yield for repeated postemergence application	Richard and Dalley (2006)
Sweetpotato (*Ipomoea batatas*)	Application rate: 107 g/ha (equivalent to 0.095 lb a.i./acre) Preemergence application Soil type: sandy loam and sand Location: Wade, NC (2016-2017)	Flumioxazin decreased slip density, length and dry weight.	Smith et al. (2018)
Dry beans (black, cranberry, kidney, and white beans)	Application rate: 52.5, 70, and 140 g ai/ha (equivalent to 0.047, 0.062, and 0.12 lb a.i./acre, respectively)	Preplant soil incorporated did not cause plant injury at any application rate. Preemergence application of 140 g/ha damaged produced up to 34% visual injury and reduced	Soltani et al. (2005)

Species	Exposure	Response	Reference
	Preplant soil incorporated and preemergence applications Location: Exeter, Ontario, Canada (2002 – 2003)	plant height by 23 – 28%, shoot dry weight by 35 – 39% and yield by 20 – 30% in visual damage black beans and white bean. Cranberry and kidney beans were tolerant to all applications.	
Adzuki bean (*Vigna angularis*)	Application rate: 71 and 142 g a.i./ha (equivalent to 0.063 and 0.13 lb a.i./acre, respectively) Preemergence application Location: Exeter, Ontario, Canada (2012 – 2014)	Flumioxazin produced visual crop injury (54 – 84%) and reduced plant stand (78%), shoot dry weight (93%), plant height (42%), and seed yield (24 – 52%)	Soltani et al. (2015)
Soybean (*Glycine max*)	Application rate: 9, 18, and 36 g a.i./ha (equivalent to 0.0071, 0.016, and 0.032 lb a.i./acre, respectively) Preemergence application Alexandria, LA (2016 – 2017)	Visual injury included necrosis and reduce plant height and width. Decreased plant yield was observed	Stephenson et al. (2018)
Soybean (*Glycine max*)	Application rate: 105, 210, and 420 g ai/ha (equivalent to 0.094, 0.18, and 0.37 lb a.i./acre, respectively) Preemergence application Soil type: silt loam Location; Urbana, IL (1998 – 1999)	Emergence counts reduced 19 – 52% Visual injury and stand count reduction were observed	Taylor-Lovell et al. (2001)

Abbreviations: a.i. = active ingredient; ha = hectare; kg = kilogram; lb = pound; OM = organic matter; v/v = volume by volume

Appendix 7: Toxicity to Fish

In the following tables, all data attributed to MRID studies were taken from DERs of MRID studies. MRID studies were not available for review.

Table A7-1: Acute Toxicity of Fish to Technical Grade Flumioxazin and Environmental Metabolites of Flumioxazin

Species	Exposure	Response	Reference
Technical Grade Flumioxazin			
Freshwater: Rainbow trout (*Salmo gairdneri*) (10 fish/concentration) Body weight at test termination: 2.38 ± 0.38 g	S-53482 Technical (purity: 94.8% a.i.) in 1:1 (w/w) DMF and HCO-40 Nominal concentrations: 0 (negative and solvent control), 0.56, 1.0, 1.8, 3.2, or 5.6 mg a.i./L Mean measured concentrations: 0 (negative and solvent control), 0.56, 0.92, 2.0, 2.9, or 5.4 mg a.i./L 96-Hour flow-through test	96-hour LC_{50}: 2.3 mg a.i./L 96-hour NOAEC: 0.92 mg a.i./L 96-hour LOAEC: 2.0 mg a.i./L LOAEC based on mortality and sublethal effects (10/10 fish swimming at surface at 24 and 48 hours; 3/10 fish with on-bottom orientation and 6/10 fish with loss of equilibrium at 72 hours; and 4/10 fish with loss of equilibrium and 2/10 fish with lethargy at 96 hours). Classified as “moderately toxic”	MRID 42684948 Takimoto et al. (1989) Acceptable/Guideline
Freshwater: Bluegill sunfish (*Lepomis macrochirus*) (10 fish/concentration) Body weight at test termination: 1.26 ± 0.16 g	S-53482 Technical (purity: 94.8% a.i.) in 1:1 (w/w) DMF and HCO-40 Nominal concentrations: 0 (negative and solvent control), 3.2, 5.6, 10, 10, or 32 mg a.i./L Mean measured concentrations: 0 (negative and solvent control), 2.1, 3.9, 6.3, 9.4, or 21 mg a.i./L 96-Hour flow-through test	96-hour LC_{50} >21 mg a.i./L 96-hour NOAEC: 3.9 mg a.i./L 96-hour LOAEC: 6.3 mg a.i./L LOAEC based on sublethal effects (3/10 fish swimming at surface at 24 hours; 10/10 fish with abnormal respiration and swimming at surface at 48 hours; 3/10 fish with abnormal respiration at 72 hours). No mortality observed at any concentration.	MRID 42684949 Takimoto et al. (1989) Acceptable/Guideline

Species	Exposure	Response	Reference
		Classified as "slightly toxic" according to U.S. EPA OPP (EPA/OPP, 2003) (toxicity classification not listed in DER).	
Estuarine/marine: Sheepshead minnow (*Cyprinodon variegatus*) (20 fish/concentration) Body weight: 0.28 – 0.62 g	V-53482 Technical (purity: 93.8% a.i.) in acetone Nominal concentrations: 0 (negative and solvent controls), 1.2, 1.9, 3.2, 5.4, or 9 mg a.i./L Mean measured concentrations: 0 (negative and solvent controls), 0.60, 1.1, 1.6, 2.6, or 4.7 mg a.i./L Fasted 48 hours prior to testing; 96-hour flow-through test	96-hour LC_{50} >4.7 mg a.i./L 96-hour NOAEC: 4.7 mg a.i./L 96-hour LOAEC >4.7 mg a.i./L No mortality or clinical signs of toxicity were observed at any concentration tested. Classified as "no more than moderately toxic"	MRID 44295010 Machado (1994) Acceptable/Core Guideline
Flumioxazin Metabolites			
Freshwater: Fathead minnow (*Pimephales promelas*) juveniles (20 fish/ concentration) Initial body weight: 0.13 – 0.35 g	Flumioxazin metabolite 482-HA[1] (purity: 95% a.i.) in laboratory well water (no solvent) Nominal concentrations: 0 (negative control), 2.5, 5, 10, 20, or 40 mg a.i./L Mean measured concentrations: 0 (negative control), 2.3, 4.6, 9, 18, or 36 mg a.i./L 96-Hour test under static renewal conditions	96-hour LC_{50} >36 mg a.i./L 96-hour NOAEC: 36 mg a.i./L 96-hour LOAEC >36 mg a.i./L No mortality or sublethal effects (e.g., lethargy, loss of equilibrium) were observed at any test concentration. Classified as "practically non-toxic"	MRID 49733403 Shaw (2014) Acceptable/Guideline

Species	Exposure	Response	Reference
Freshwater: Fathead minnow (*Pimephales promelas*) juveniles (20 fish/ concentration) Initial body weight: 0.12 – 0.5 g	Flumioxazin metabolite APF[2] (purity: 98.5% a.i.) in laboratory well water (no solvent) Nominal concentrations: 0 (negative control), 2.5, 5, 10, 20, or 40 mg a.i./L Mean measured concentrations: 0 (negative control), 1.5, 3.2, 6.4, 13, or 25 mg a.i./L 96-Hour test under static renewal conditions	96-hour LC_{50} >25 mg a.i./L 96-hour NOAEC: 25 mg a.i./L 96-hour LOAEC >25 mg a.i./L No mortality or sublethal effects (e.g., lethargy, loss of equilibrium) were observed at any test concentration. Classified as "practically non-toxic"	MRID 49733404 Shaw (2014) Acceptable/Guideline
Freshwater: Fathead minnow (*Pimephales promelas*) juveniles (20 fish/ concentration) Initial body weight: 0.23 – 0.5 g	Flumioxazin metabolite THPA-2Na[3] (purity: 99.4% a.i.) in laboratory well water (no solvent) Nominal concentrations: 0 (negative control), 2.5, 5, 10, 20, or 40 mg a.i./L Mean measured concentrations: 0 (negative control), 2.3, 4.8, 9.8, 19, or 38 mg a.i./L 96-Hour test under static renewal conditions	96-hour LC_{50} >38 mg a.i./L 96-hour NOAEC: 38 mg a.i./L 96-hour LOAEC >38 mg a.i./L No mortality or sublethal effects (e.g., lethargy, loss of equilibrium) were observed at any test concentration. Classified as "practically non-toxic"	MRID 49733405 Anonymous (2014) Acceptable/Guideline

[1]**Flumioxazin metabolite 482-HA: chemical formula $C_{19}H_{17}FN_2O_5$.**
[2]Flumioxazin metabolite APF: 6-amino-7-fluoro-4-(2-propynyl)-1,4-benzoxazin-3(2H)-one).
[3]Flumioxazin metabolite THPA: 3,4,5,6-tetrahydrophthalic acid.
Abbreviations: a.i. = active ingredient; DER = Data Evaluation Record; DMF = dimethylformamide; U.S. EPA = U.S. Environmental Protection Agency; g = gram; HCO-40 = polyoxyethylene hydrogenated castor oil; LC_{50} = median lethal concentration; LOAEC = lowest-observed-adverse-effect concentration; mg = milligram; L = liter; NOAEC = no-observed-adverse-effect concentration; OPP = Office of Pesticide Programs; w/w = weight by weight

Table A7-2: Chronic Toxicity of Fish to Technical Grade Flumioxazin and a Formulated Flumioxazin Product

Species	Exposure	Response	Reference
Technical Grade Flumioxazin			
Freshwater: Rainbow trout (*Oncorhynchus mykiss*) (20 fish/concentration) Mean body weight: 1.3 g	S-53482 T.G. (purity: 94.3% a.i.) in DMF Nominal concentrations: 0 (negative and solvent control), 0.25, 0.5, 1, 2, or 4 mg a.i./L Mean measured concentrations: 0 (negative and solvent control), 0.2, 0.37, 0.61, 1.2, or 2.4 mg a.i./L Fasted 48 hours prior to initiation; 21-day flow-through test. Note that starting on day 7, surface film/precipitate was observed in test chambers.	21-day NOAEC: 0.37 mg a.i./L 21-day LOAEC: 0.61 mg a.i./L LOAEC based on 10% mortality and sublethal effects (discoloration, erratic swimming, loss of equilibrium, lying at bottom of aquarium, surfacing, and quiescent fish) observed at test termination. Note that the DER reported a chronic NOAEC of 1.2 mg a.i./L and a LOAEC of 2.4 mg a.i./L. However, at 0.61 mg a.i./L, mortality and sublethal effects were observed as noted. Incidence data on sublethal effects were not reported in the DER.	MRID 44295007 Sword et al. (1992) Supplemental/Non-guideline
Freshwater: Rainbow trout (*Oncorhynchus mykiss*), eggs 8 hours post-fertilization (80 eggs/concentration; 40 post-hatch fish/test chamber)	S-53482 (purity: 98.2% a.i.) in DMF Nominal concentrations: 0 (negative and solvent control), 1, 2, 4, 8, or 16 µg a.i./L Mean measured concentrations: 0 (negative and solvent control), 0.98, 2.0, 3.8, 7.7, or 16 µg a.i./L Early life stage flow-through test (through 64 days post-hatch)	64-day NOAEC: 7.7 µg a.i./L 64-day LOAEC: 16 µg a.i./L 64-day MATC: 11 µg/L LOAEC based on reduced length and weight in 60-day post-hatch trout (5% and 8% reductions, respectively, compared to controls). Percent hatch and post-hatch survival were not significantly affected by treatment, and no sublethal effects (abnormal behavior or appearance) were observed during exposure.	MRID 44295012 Hagino and Miyamoto (1996) Acceptable/Guideline

Species	Exposure	Response	Reference
Freshwater: Fathead minnow (*Pimephales promelas*), embryos <24 hours post-fertilization (200 embryos/ concentration; 120 post-hatch larvae/ concentration)	Flumioxazin T.G. (purity: 100%) in DMF Nominal concentrations: 0 (negative and solvent control), 0.31, 0.63, 1.3, 2.5, or 5.0 µg a.i./L TWA measured concentrations: 0 (negative and solvent control), 0.28, 0.51, 0.99, 2.1, or 4.1 µg a.i./L 159-Day 2-generation life cycle test under flow-through conditions	159-day NOAEC: 0.51 µg a.i./L 159-day LOAEC: 0.99 µg a.i./L LOAEC based on 32% reduction in larval survival at 4 weeks in F1 generation. **F0 generation** No treatment-related effects on time to hatch, hatching success, or growth (total length and wet weight). No effects were observed on secondary sex characteristics in adult fish 17 and 21 weeks post-hatch, or on reproductive endpoints (number of eggs/female per reproductive day, number of spawns/female, and number of eggs/spawn). (Data from 2.1 and 4.1 µg a.i./L treatment groups were excluded from statistical analyses due to significantly reduced survival.) 0.28 – 0.99 µg a.i./L: No effects. 2.1 µg a.i./L: Larvae survival significantly reduced at 4, 8, and 17 weeks post-hatch (20%, 24%, and 24%, respectively, compared to negative control). 4.1 µg a.i./L: Larvae survival significantly reduced at 4, 8, and 17 weeks post-hatch (65%, 73%, and 63%, respectively, compared to negative control).	MRID 49733408 Sayers (2015) Acceptable/Guideline

Species	Exposure	Response	Reference
		F1 generation No treatment-related effects were observed on time to hatch or growth (total length and wet weight). (Growth data from the 3 highest concentration groups were excluded from statistical analyses due to low survival rates.) 0.28 and 0.51 µg a.i./L: No effects. 0.99 µg a.i./L: Larval survival was reduced 32% compared to negative controls at 4 weeks post-hatch. 2.1 µg a.i./L: Larval survival was reduced 69% compared to negative controls at 4 weeks post-hatch. 4.1 µg a.i./L: Hatching success was reduced 13% compared to negative controls, and 4-week post-hatch larval survival was reduced 77% compared to negative controls.	
Freshwater: Fathead minnow (*Pimephales promelas*), 21 – 22-hour-old embryos (120 embryos/ concentration; 80 hatched eggs/concentration)	Flumioxazin T.G. (purity: 99.1% a.i.) in DMF Nominal concentrations (standard lighting scenario: (16-hour light/8-hour dark photoperiod with an intensity range of 540 to 850 lux): 0 (negative and solvent control), 0.25, 0.5, 1, 2, or 4 µg a.i./L	Standard lighting: 32-day NOAEC: 3.3 µg a.i./L 32-day LOAEC: >3.3 µg a.i./L No treatment-related effects on hatching success, live normal fry at hatch, post-hatch larval survival and growth, or sublethal effects (abnormal behavior or appearance).	MRID 49733406 Sayers (2015) Acceptable/Guideline

Species	Exposure	Response	Reference
	Mean measured concentrations (standard lighting scenario): 0 (negative and solvent control), 0.22, 0.51, 0.91, 1.8, or 3.3 µg a.i./L Nominal concentrations (enhanced lighting scenario): 0 (negative and solvent control), 0.063, 0.13, 0.25, 0.5, or 1 µg a.i./L TWA measured concentrations (enhanced lighting scenario: [12-hour light/12-hour dark photoperiod with an intensity range of 1330 to 1728 uW/cm2 (integrated over the wavelengths of interest, 390 to 420 nm)]: 0 (negative and solvent control), 0.045, 0.085, 0.16, 0.35, or 0.78 µg a.i./L 32-Day early life stage flow-through test	Enhanced lighting: 32-day NOAEC: 0.35 µg a.i./L 32-day LOAEC: 0.78 µg a.i./L LOAEC based on reduced hatching success, post-hatch larval survival, and live normal larvae at hatch (7%, 21%, and 20% reductions compared to controls, respectively). No treatment-related effects observed on growth (total length or wet weight) of 4-week post-hatch larvae up to and including the 0.35 µg a.i./L concentration. The highest concentration was excluded from this analysis due to the significant decrease in survival at that level (21% compared to controls).	
Estuarine/marine: Sheepshead minnow (*Cyprinodon variegatus*), 22-hour-old embryos (120 embryos/ concentration; 80 post-hatch larvae/ concentration)	Flumioxazin T.G. (purity: 99.1% a.i.) in DMF Nominal concentrations: 0 (negative and solvent controls), 1.6, 3.1, 6.3, 13, or 25 µg a.i./L	34-day NOAEC: 1.1 µg a.i./L 34-day LOAEC: 1.6 µg a.i./L LOAEC based on 9% reduction in total length compared to controls. No treatment-related effects were observed on time to hatch, hatching success, percent	MRID 49733407 Sayers (2015) Acceptable/Guideline

Species	Exposure	Response	Reference
	TWA measured concentrations: 0 (negative and solvent controls), 1.1, 1.6, 3.3, 6.7, or 10 µg a.i./L 34-Day early life stage flow-through test	live normal larvae at hatch, and post-hatch larval survival. Wet weight was 23% lower than controls at 3.3 µg a.i./L and above.	
Formulated Products			
Bluegill sunfish (*Lepomis macrochirus*), 6 tanks/control, 3 tanks/concentration	Flumioxazin "Clipper" (purity not reported, but the product label reports 51% a.i.) Nominal concentrations: 0, 25, 50, 100, 200, or 400 µg/L (adjusted for a.i., concentrations are 12.8, 25.5, 51, 102, or 204 µg a.i./L) Tanks were under static conditions other than air stones providing aeration. Packets of test substance were added to tanks each week followed by a 3-hour period to allow granules to dissolve prior to fish feeding. 100% water exchange was performed each week, prior to the reapplication of test substance. 6-week study.	6-week NOAEC: 204 µg a.i./L 6-week LOAEC: >204 µg a.i./L No treatment-related effects in average weight gain, percent survival, or feed conversion ratio.	Umphres et al. (2013)

Abbreviations: a.i. = active ingredient; DER = Data Evaluation Record; DMF = dimethylformamide; F1 = first generation; g = gram; L = liter; LOAEC = lowest-observed-adverse-effect concentration; MATC = maximum acceptable toxicant concentration; µg = microgram; mg = milligram; NOAEC = no-observed-adverse-effect concentration; T.G. = technical grade; TWA = time-weighted average

Appendix 8: Toxicity to Aquatic Invertebrates

In the following tables, all data attributed to MRID studies were taken from DERs of MRID studies. MRID studies were not available for review.

Table A8-1: Acute Toxicity of Aquatic Invertebrates to Technical Grade Flumioxazin and an Environmental Metabolite of Flumioxazin

Species	Exposure	Response	Reference
Technical Grade Flumioxazin			
Freshwater: Water flea (*Daphnia magna*) neonates (20 daphnids/ concentration)	S-53482 (purity: 94.7% a.i.) in 1:1 (w/w) DMF and HCO-40 Nominal concentrations: 0 (negative and solvent control), 15.6, 25.9, 43.2, 72, or 120 mg a.i./L Mean measured centrifuged concentrations: 0, 3.74, 5.06, 5.98, 6, or 9.25 mg a.i./L 48-Hour flow-through test Note that precipitate was observed in the test chambers of the 3 highest tested concentrations at the beginning of the test; by 48 hours, precipitate was present in the mixing cells of all treatment groups, clogging the mixing chamber of the 120 mg a.i./L concentration. The presence of precipitate, along with slightly basic conditions, was given as the reason for the considerable difference between nominal and measured concentrations.	48-hour EC_{50}: 5.5 mg a.i./L NOAEC and LOAEC could not be determined due to daphnid immobility at every test concentration, thought to be due in part to the presence of precipitate in the test chambers. Per Amended DER and U.S. EPA statistical analysis of centrifuged mean measured concentration data. The EEB reconsidered the initial evaluation of this study, stating that the difficulty in establishing the EC_{50} was due to the mechanical impact of the precipitate rather than the aquatic toxicity of the chemical in solution. The EEB upgraded the study to "supplemental" from "invalid" because: 1) the unavoidable testing difficulties encountered were handled in a responsible, reasonable and anticipatory manner; 2) testing followed scientifically acceptable techniques and did not significantly deviate from testing protocols; 3) repetition of the study would be unlikely to produce significantly better data; and 4) the test material does not appear to have toxicological characteristics considered serious thus presenting probable high risk to test organisms such as Daphnia.	MRID 42684950 Reed and Swigert (1992) Rated supplemental due to presence of precipitate in test solution (low solubility of test substance) Non-guideline

Species	Exposure	Response	Reference
		Classified as "moderately toxic."	
Estuarine/marine: Eastern oyster (*Crassostrea virginica*) (40 oysters/concentration)	V-53482 Technical (purity: 93.8% a.i.) in acetone Nominal concentrations: 0 (negative and solvent control), 1.2, 1.9, 3.2, 5.4, or 9.0 mg a.i./L Mean measured concentrations: 0 (negative and solvent control), 0.64, 1.0, 1.8, 2.8, or 4.4 mg a.i./L 96-hour flow-through test Note that throughout the exposure period, precipitate was observed in the mixing chamber and in the chemical cell solutions of the 2 highest tested concentrations, although none was observed in the exposure aquaria.	96-hour EC_{50}: 2.4 mg a.i./L 96-hour NOAEC <0.64 mg a.i./L 96-hour LOAEC 0.64 mg a.i./L LOAEC based on significantly reduced shell growth (33 to 65%) at each tested concentration compared to solvent control. No mortality occurred during test at any concentration. At 4.4 mg a.i./L, signs of toxicity observed included reduced feeding, gaped shells, and reduced fecal and pseudofecal production. Classified as "moderately toxic."	MRID 44295008 Dionne (1994) Acceptable/Guideline
Estuarine/marine: Mysid shrimp (*Mysidopsis bahia*), <24 hours old (20 mysids/ concentration)	V-53482 Technical (purity: 94.3% a.i.) in acetone Nominal concentrations: 0 (negative and solvent controls), 0.093, 0.16, 0.26, 0.43, or 0.72 mg a.i./L Mean measured concentrations: 0 (negative and solvent controls),	96-hour LC_{50} = 0.23 mg a.i./L 96-hour NOAEC: 0.10 mg a.i./L 96-hour LOAEC: 0.22 mg a.i./L LOAEC based on mortality and sublethal effects (lethargy). Note that the DER reported a 96-hour NOAEC of 0.072 mg a.i./L and a 96-hour LOAEC of 0.10 mg a.i./L. However, effects	MRID 44295009 Machado (1994) Acceptable/Guideline

Species	Exposure	Response	Reference
	0.053, 0.072, 0.10, 0.22, or 0.39 mg a.i./L 96-Hour flow-through test	observed at 0.10 mg a.i./L were relatively small and toxicologically insignificant. 0.053 and 0.072 mg a.i./L: No mortality or sublethal effects. 0.10 mg a.i./L: 10% mortality; 1/18 surviving mysids exhibited lethargy (not significant). 0.22 mg a.i./L: 30% mortality. 14/14 surviving mysids exhibited lethargy. 0.39 mg a.i./L: 95% mortality; signs of toxicity observed included loss of equilibrium, lethargy, and darkened pigmentation. Classified as "highly toxic."	
Flumioxazin Metabolites			
Freshwater: Water flea (*Daphnia magna*) <24 hours old (20 daphnids/ concentration)	Flumioxazin metabolite 482-HA[1] (purity: 95% a.i.) in fortified well water (no solvent) Nominal concentrations: 0 (negative control), 2.5, 5, 10, 20, or 40 mg a.i./L Mean measured concentrations: 0 (negative control), 2.9, 5.7, 11, 23, or 48 mg a.i./L	48-hour EC_{50} >48 mg a.i./L 48-hour NOAEC: 48 mg a.i./L 48-hour LOAEC >48 mg a.i./L No mortality/immobilization or sublethal effects (e.g., lethargy) were observed at any test concentration. Classified as "practically non-toxic"	MRID 49733402 Shaw (2014) Acceptable/Guideline

Species	Exposure	Response	Reference
	48-Hour test under static renewal conditions.		

[1]Flumioxazin metabolite 482-HA: chemical formula $C_{19}H_{17}FN_2O_5$.

Abbreviations: a.i. = active ingredient; DER = Data Evaluation Record; DMF = dimethylformamide; EC_{50} = median effects concentration; EEB = Ecological Effects Branch; U.S. EPA = U.S. Environmental Protection Agency; HCO-40 = polyoxyethylene hydrogenated castor oil; L = liter; LOAEC = lowest-observed-adverse-effect concentration; mg = milligram; NOAEC = no-observed-adverse-effect concentration; w/w = weight by weight

Table A8-2: Chronic Toxicity of Aquatic Invertebrates to Technical Grade Flumioxazin

Species	Exposure	Response	Reference
Freshwater: Water flea (*Daphnia magna*), 10 – 12 days old (22 daphnids/ concentration)	C-S-53482 (purity: 94.8% a.i.); ^{14}C-S-53482 (purity: 98.5% a.i.) in DMF Nominal concentrations: 0 (negative and solvent controls), 25, 50, 100, 200, or 400 µg a.i./L Mean measured concentrations: 0 (negative and solvent controls), 15, 28, 57, 107, or 205 µg a.i./L 21-Day flow-through test	21-day NOAEC: 28 µg a.i./L 21-day LOAEC: 57 µg a.i./L 21-day MATC: 40 µg a.i./L LOAEC based on reduced reproduction. 15 and 28 µg a.i./L: No effects. 57 µg a.i./L: 5% mortality/immobility; 43% reduction in neonates produced per adult compared to controls. 107 µg a.i./L: 55% mortality; no successful reproduction. 205 µg a.i./L: 73% mortality; no successful reproduction. DER reported NOAECs and LOAECs for daphnid survival and growth (length and dry weight) of 57 and 107 µg a.i./L, respectively. Length and weight at test concentrations of 107 and 205 µg a.i./L were not included in statistical analysis due to the significant mortality in those test chambers.	MRID 44295011 Drottar and Swigert (1994) Acceptable/Guideline

Species	Exposure	Response	Reference
Mysid (*Mysidopsis bahia*) (60 mysids/ concentration)	V-53482 TGAI (purity: 99.5% a.i.) in DMF Nominal concentrations: 0 (negative and solvent controls), 8.1, 16, 33, 65, or 130 µg a.i./L Mean measured concentrations: 0 (negative and solvent controls), 4.3, 7.3, 15, 27, or 55 µg a.i./L 28-Day flow-through test	28-day NOAEC: 15 µg a.i./L 28-day LOAEC: 27 µg a.i./L 28-day MATC: 20 µg a.i./L LOAEC based on impaired reproduction and reduced growth (length and weight) compared to controls. 4.3 – 15 µg a.i./L: No treatment-related effects. 27 µg a.i./L: 18% mortality; 56% reduction in number of young/female per reproductive day compared to controls. 55 µg a.i./L: 40% mortality; 36% reduction in reproductive success compared to controls. The NOAEC/LOAEC for mysid survival was 27/55 µg a.i./L.	MRID 44295013 Sousa (1996) Acceptable/Guideline

Abbreviations: a.i. = active ingredient; DMF = dimethylformamide; L = liter; LOAEC = lowest-observed-adverse-effect concentration; MATC = maximum acceptable toxicant concentration; µg = microgram; NOAEC = no-observed-adverse-effect concentration

Appendix 9: Toxicity to Aquatic Plants

In the following tables, all data attributed to MRID studies were taken from DERs of MRID studies. MRID studies were not available for review.

Table A9-1: Toxicity of Aquatic Vascular Plants to Technical Grade Flumioxazin and Environmental Metabolites of Flumioxazin

Species	Exposure	Response	Reference
Technical Grade Flumioxazin			
Duckweed (*Lemna gibba*), 45 fronds/concentration	[^{14}C] V-53482 (purity: 99.7% a.i.) in acetone Nominal concentrations: 0 (solvent control), 0.064, 0.13, 0.25, 0.5, 1, or 2 µg a.i./L Initial measured concentrations: 0 (solvent control), 0.051, 0.11, 0.22, 0.44, 0.87, or 1.7 µg a.i./L 14-Day test with renewal every 3 days. At the end of the first 3-day renewal period, the measured highest test concentration was 23% of the nominal concentration. As such, toxicity results were based on initial measured concentrations.	Frond Density: 14-day EC_{50}: 0.49 µg a.i./L 14-day NOAEC: 0.22 µg a.i./L 14-day LOAEC: 0.44 µg a.i./L Frond Biomass: 14-day EC_{50}: 0.35 µg a.i./L 14-day NOAEC: 0.22 µg a.i./L 14-day LOAEC: 0.44 µg a.i./L LOAEC based on 54% reduction in average number of fronds compared to controls. Signs of toxicity observed in concentrations of 0.11 µg a.i./L and higher included chlorotic fronds and fronds with reduced root formation or smaller size compared to controls. The DER did not provide incidence data or additional details of these signs of toxicity in the 0.11 µg a.i./L concentration, which was lower than the NOAEC stated in the DER.	MRID 44295035 Hoberg (1996) Acceptable/Guideline
Flumioxazin Metabolites			
Duckweed (*Lemna gibba*), 36 fronds/concentration	Flumioxazin metabolite 482-HA[1] (purity: 98.3%) in DI water (no solvent)	Frond Number: 7-day IC_{05}: 1.055 µg a.i./L 7-day IC_{50}: 7.0 µg a.i./L 7-day NOAEC: 3.94 µg a.i./L 7-day LOAEC: 11.9 µg a.i./L	MRID 49198802 Biester (2011) Acceptable/Guideline

Species	Exposure	Response	Reference
	Nominal concentrations: 0 (negative control), 0.49, 1.5, 4.4, 13, or 40 µg a.i./L Initial measured concentrations: 0 (negative control), 0.515, 1.37, 4.63, 14.3, or 44.2 µg a.i./L Geometric mean measured concentrations: 0 (negative control), 0.391, 0.974, 3.94, 11.9, or 35.2 µg a.i./L 7-Day semi-static test. All 3-day measured test concentrations were 51 – 72% of their initial measured concentrations. DER reported toxicity values for both initial and geometric mean concentrations; toxicity values for geometric mean concentrations are reported here to be most conservative.	LOAEC based on 63% reduction in frond number compared to control. <u>Frond Number Growth Rate</u>: 7-day IC_{05}: 2.052 µg a.i./L 7-day IC_{50}: 19.97 µg a.i./L 7-day NOAEC: 3.94 µg a.i./L 7-day LOAEC: 11.9 µg a.i./L LOAEC based on 33% reduction in frond number growth rate compared to control. <u>Final Biomass</u>: 7-day IC_{05}: 0.9471 µg a.i./L 7-day IC_{50}: 5.8 µg a.i./L 7-day NOAEC: 0.974 µg a.i./L 7-day LOAEC: 3.94 µg a.i./L LOAEC based on 25% reduction in final biomass compared to control. <u>Biomass Growth Rate</u>: 7-day IC_{05}: 2.013 µg a.i./L 7-day IC_{50}: 18.72 µg a.i./L 7-day NOAEC: 3.94 µg a.i./L 7-day LOAEC: 11.9 µg a.i./L LOAEC based on 34% reduction in biomass growth rate compared to control. Signs of toxicity observed in concentrations of 11.9 µg/L or higher included smaller root size and chlorotic fronds.	

Species	Exposure	Response	Reference
Duckweed (*Lemna gibba*), 36 fronds/concentration	Flumioxazin metabolite APF[2] (purity: 98.1%) in sterilized DI water (no solvent) Nominal concentrations: 0 (negative control), 0.26, 0.64, 1.6, 4, or 10 mg a.i./L Initial measured concentrations: 0 (negative control), 0.237, 0.553, 1.48, 2.79, or 10.8 mg a.i./L Geometric mean concentrations: 0 (negative control), 0.233, 0.624, 1.5, 3.08, or 8.88 mg a.i./L 7-Day semi-static test. All 3-day measured test concentrations were 67 – 127% of their initial measured concentrations. DER reported toxicity values for both initial and geometric mean concentrations; toxicity values for geometric mean concentrations are reported here to be most conservative.	<u>Frond Number</u>: 7-day IC_{05}: 2.98 mg a.i./L 7-day IC_{50} >8.88 mg a.i./L 7-day NOAEC: 3.08 mg a.i./L 7-day LOAEC: 8.88 mg a.i./L LOAEC based on 15% reduction in frond number compared to controls. <u>Frond Number Growth Rate</u>: 7-day IC_{05}: 8.403 mg a.i./L 7-day IC_{50} >8.88 mg a.i./L 7-day NOAEC: 3.08 mg a.i./L 7-day LOAEC: 8.88 mg a.i./L LOAEC based on 5% reduction in frond number growth rate compared to controls. <u>Final Biomass</u>: 7-day IC_{05}: Not calculable 7-day IC_{50} >8.88 mg a.i./L 7-day NOAEC: 8.88 mg a.i./L 7-day LOAEC >8.88 mg a.i./L <u>Biomass Growth Rate</u>: 7-day IC_{05}: Not calculable 7-day IC_{50} >8.88 mg a.i./L 7-day NOAEC: 8.88 mg a.i./L 7-day LOAEC >8.88 mg a.i./L No signs of toxicity observed on fronds at any concentration.	MRID 49198804 Biester (2011) Acceptable/Guideline

Species	Exposure	Response	Reference
Duckweed (*Lemna gibba*), 72 fronds/concentration	Flumioxazin metabolite THPA-2Na[3] (purity: 99.3% a.i.) in sterilized DI water (no solvent) Nominal concentrations: 0 (negative control) and 10 mg a.i./L Geometric mean measured concentrations: 0 (negative control) and 10.1 mg a.i./L 7-Day semi-static test.	Frond Number: 7-day IC_{05}: Not calculable 7-day IC_{50} >10.1 mg a.i./L 7-day NOAEC: 10.1 mg a.i./L 7-day LOAEC >10.1 mg a.i./L Frond Number Growth Rate: 7-day IC_{05}: Not calculable 7-day IC_{50} >10.1 mg a.i./L 7-day NOAEC: 10.1 mg a.i./L 7-day LOAEC >10.1 mg a.i./L Final Biomass: 7-day IC_{05}: Not calculable 7-day IC_{50} >10.1 mg a.i./L 7-day NOAEC: 10.1 mg a.i./L 7-day LOAEC >10.1 mg a.i./L Biomass Growth Rate: 7-day IC_{05}: >10.1 mg a.i./L 7-day NOAEC: 10.1 mg a.i./L 7-day LOAEC >10.1 mg a.i./L No treatment-related effects on fronds or signs of toxicity were observed at any concentration tested.	MRID 49198806 Biester (2011) Acceptable/Guideline

[1]**Flumioxazin metabolite 482-HA: chemical formula $C_{19}H_{17}FN_2O_5$**
[2]Flumioxazin metabolite APF: 6-amino-7-fluoro-4-(2-propynyl)-1,4-benzoxazin-3(2H)-one)
[3]Flumioxazin metabolite THPA: 3,4,5,6-tetrahydrophthalic acid
Abbreviations: a.i. = active ingredient; DER = Data Evaluation Record; DI = deionized water; EC_{50} = median effects concentration; IC_{05} = concentration at which 5% of tested organisms are inhibited; IC_{50} = concentration at which 50% of tested organisms are inhibited; L = liter; LOAEC = lowest-observed-adverse-effect concentration; µg = microgram; NOAEC = no-observed-adverse-effect concentration

Table A9-2: Algae Toxicity Studies

Species	Exposure	Response	Reference
Freshwater Green Algae			
Technical Grade Flumioxazin			
Freshwater green algae (*Selenastrum capricornutum*), 3000 cells/mL (3 replicates/concentration)	[^{14}C] V-53482 (purity: 99.7% a.i.) in acetone Nominal concentrations: 0 (solvent control), 0.13, 0.32, 0.8, 2.0, or 5 µg a.i./L Initial measured concentrations: 0 (solvent control), 0.12, 0.33, 0.79, 2.0, or 4.9 µg a.i./L Results based on initial measured concentrations because concentrations at test termination were 13 – 15% of nominal concentrations. 120-Hour test duration under static conditions.	120-hour EC_{50}: 1.02 µg a.i./L 120-hour NOAEC: 0.79 µg a.i./L 120-hour LOAEC: 2 µg a.i./L LOAEC based on 96% reduction in cell density (most sensitive endpoint). Signs of toxicity (bloated cells) observed at 2.0 µg a.i./L.	MRID 44295031 Hoberg (1996) Acceptable/Guideline
Freshwater blue-green alga (*Anabaena flos-aquae*), 10,000 cells/mL (3 replicates/concentration)	[^{14}C] V-53482 (purity: 99.7% a.i.) in acetone Nominal concentrations: 0 (solvent control), 0.024, 0.081, 0.27, 0.9, 3, or 10 µg a.i./L	120-hour EC_{50}: 0.83 µg a.i./L 120-hour NOAEC: 0.022 µg a.i./L 120-hour LOAEC: 0.073 µg a.i./L LOAEC based on 17% reduction in cell density compared to control.	MRID 44295034 Hoberg (1996) Acceptable/Guideline

Species	Exposure	Response	Reference
	Initial measured concentrations: 0 (solvent control), 0.022, 0.073, 0.25, 0.75, 2.8, or 8.7 µg a.i./L Results based on initial measured concentrations because concentrations at test termination were 11 – 13% of nominal concentrations. 120-Hour test duration under static conditions.		
Freshwater diatom (*Navicula pelliculosa*), 10,000 cells/mL (3 replicates/concentration)	[^{14}C] V-53482 (purity: 99.7% a.i.) in acetone Nominal concentrations: 0 (solvent control), 0.048, 0.093, 0.19, 0.38, 0.75, 1.5, or 3 µg a.i./L Initial measured concentrations: 0 (solvent control), 0.042, 0.074, 0.15, 0.31, 0.61, 1.2, or 2.4 µg a.i./L 120-Hour test duration under static conditions. Measured test concentrations at study termination had decreased to 11% of nominal concentrations. Results therefore were based on initial measured concentrations.	120-hour EC_{05}: 0.041 µg a.i./L 120-hour EC_{50}: 1.4 µg a.i./L 120-hour NOAEC <0.042 µg a.i./L 120-hour LOAEC: 0.042 µg a.i./L LOAEC based on significant reductions (8 – 75%) in cell density compared to controls at all tested concentrations. Authors calculated EC_{05} of 0.041 µg a.i./L as a conservative NOAEC.	MRID 44295032 Hoberg (1996) Acceptable/Guideline

Species	Exposure	Response	Reference
Marine diatom (*Skeletonema costatum*), 10,000 cells/mL (3 replicates/concentration)	[^{14}C] V-53482 (purity: 99.7% a.i.) in acetone Nominal concentrations: 0 (solvent control), 0.93, 1.9, 3.8, 7.5, 15, or 30 µg a.i./L Initial measured concentrations: 0 (solvent control), 0.89, 1.9, 3.7, 7.6, 15, or 30 µg a.i./L 120-Hour test duration under static conditions. Highest measured test concentration at study termination had decreased to 6.2 – 6.3% of nominal concentration. Results therefore were based on initial measured concentrations.	120-hour EC_{50}: 19.2 µg a.i./L 120-hour NOAEC: 1.9 µg a.i./L 120-hour LOAEC: 3.7 µg a.i./L LOAEC based on a 24% reduction in cell density compared to controls.	MRID 44295033 Hoberg (1996) Acceptable/Guideline
Flumioxazin Metabolites			
Freshwater green algae (*Selenastrum capricornutum*), 10,000 cells/mL (3 replicates/concentration)	Flumioxazin metabolite 482-HA[1] (purity: 98.3%.) in sterilized DI water (no solvent) Nominal concentrations: 0 (negative control), 0.33, 0.91, 2.6, 7.1, or 20 µg/L Initial mean measured concentrations: 0 (negative	<u>Yield</u> 72-hour IC_{05}: 1.27 µg/L 72-hour IC_{50} >20.2 µg/L 72-hour NOAEC: 7.57 µg/L 72-hour LOAEC: 20.2 µg/L LOAEC based on 38% reduction in biomass compared to control. <u>Growth rate</u> 72-hour IC_{05}: 8.118 µg/L	MRID 49198801 Biester (2010) Supplemental (NOAEC is sound; LC_{50} wasn't achieved within range of concentrations tested, and light regime was higher than recommended, shortening study

Species	Exposure	Response	Reference
	control), 0.385, 0.965, 2.89, 7.57, or 20.2 µg/L 72-Hour test duration under static conditions. Study was intended to be 96 hours, but light regimes were higher than recommended, and test concentrations at 72 hours were 30 – 44% of initial measured concentrations.	72-hour IC_{50} >20.2 µg/L 72-hour NOAEC: 7.57 µg/L 72-hour LOAEC: 20.2 µg/L LOAEC based on 9% reduction in growth rate compared to control. <u>AUC</u> 72-hour IC_{05}: 1.811 µg/L 72-hour IC_{50} >20.2 µg/L 72-hour NOAEC: 2.89 µg/L 72-hour LOAEC: 7.57 µg/L LOAEC based on 22% decrease in area under the cell density growth curve compared to control. No morphological abnormalities or treatment-related phytotoxicity observed at any concentration.	duration from 96 to 72 hours) Non-guideline
Freshwater green algae (*Selenastrum capricornutum*), 10,000 cells/mL (3 replicates/concentration)	Flumioxazin metabolite APF[2] (purity: 98.1%) in sterilized DI water (no solvent) Nominal concentrations: 0 (negative control), 0.26, 0.64, 1.6, 4, or 10 mg/L Initial measured concentrations: 0 (negative control), 0.229, 0.768, 1.74, 2.97, or 10.9 mg/L	<u>Yield</u> 72-hour IC_{05}: 1.42 mg/L 72-hour IC_{50}: 7.187 mg/L 72-hour NOAEC: 2.97 mg/L 72-hour LOAEC: 10.9 mg/L LOAEC based on 68% reduction in cell density compared to control. <u>Growth rate</u> 72-hour IC_{05}: 3.473 mg/L 72-hour IC_{50}: 35.26 mg/L	MRID 49198803 Biester (2011) Acceptable/Guideline

Species	Exposure	Response	Reference
	72-Hour test duration under static conditions. All 72-hour measured concentrations were <LOQ of 0.101 mg/L, so toxicity values were based on initial measured concentrations.	72-hour NOAEC: 2.97 mg/L 72-hour LOAEC: 10.9 mg/L LOAEC based on 21% reduction in growth rate compared to controls. <u>AUC</u> 72-hour IC_{05}: 1.007 mg/L 72-hour IC_{50}: 8.019 mg/L 72-hour NOAEC: 2.97 mg/L 72-hour LOAEC: 10.9 mg/L LOAEC based on 60% decrease in area under the cell density growth curve compared to control. No morphological abnormalities or treatment-related phytotoxicity was observed.	
Freshwater green algae (*Selenastrum capricornutum*), 10,000 cells/mL (6 replicates/concentration)	Flumioxazin metabolite THPA-2Na[3] (purity: 99.3% a.i.) in sterilized DI water (no solvent) Nominal concentrations: 0 (negative control) or 10 mg/L Geometric mean measured concentrations: 0 (negative control) or 9.67 mg/L 72-Hour test duration under static conditions.	<u>Yield</u> 72-hour IC_{05} not calculable 72-hour IC_{50} >9.67 mg/L 72-hour NOAEC: 9.67 mg/L 72-hour LOAEC >9.67 mg/L <u>Growth rate</u> 72-hour IC_{05} not calculable 72-hour IC_{50} >9.67 mg/L 72-hour NOAEC: 9.67 mg/L 72-hour LOAEC >9.67 mg/L	MRID 49198805 Biester (2011) Acceptable/Guideline

Species	Exposure	Response	Reference
		AUC 72-hour IC_{05} not calculable 72-hour IC_{50} >9.67 mg/L 72-hour NOAEC: 9.67 mg/L 72-hour LOAEC >9.67 mg/L No significant reductions in yield, growth rate, or AUC were noted compared to controls; no morphological abnormalities or treatment-related phytotoxicity were observed.	

[1]**Flumioxazin metabolite 482-HA: chemical formula $C_{19}H_{17}FN_2O_5$.**
[2]Flumioxazin metabolite APF: 6-amino-7-fluoro-4-(2-propynyl)-1,4-benzoxazin-3(2H)-one).
[3]Flumioxazin metabolite THPA: 3,4,5,6-tetrahydrophthalic acid.
Abbreviations: a.i. = active ingredient; AUC = area under the curve; DI = deionized water; EC_{05} = concentration that affected 5% of tested organisms; EC_{50} = median effects concentration; IC_{05} = concentration at which 5% of tested organisms are inhibited; IC_{50} = concentration at which 50% of tested organisms are inhibited; L = liter; LOAEC = lowest-observed-adverse-effect concentration; LOQ = limit of quantitation; µg = microgram; mL = milliliter; NOAEC = no-observed-adverse-effect concentration

Appendix 10: Flumioxazin Arial Broadcast Foliar GLEAMS-Driver Modeling Results

The following tables present estimated water concentrations in surface water bodes calculated with GLEAMS-Driver.

Table A10-1: Effective Offsite Application Rate (lb/acre)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	4.74E-05	0.00E+00	5.65E-03	0.00E+00	0.00E+00	1.77E-05	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	4.40E-04	0.00E+00	3.75E-03	0.00E+00	0.00E+00	8.70E-04	0.00E+00	0.00E+00	6.10E-04
Dry and Cold Location	3.89E-02	2.40E-02	7.48E-02	2.60E-02	1.52E-02	5.31E-02	2.99E-04	1.09E-04	1.26E-03
Average Rainfall and Warm Location	2.01E-02	2.25E-03	7.08E-02	4.32E-04	8.35E-07	7.91E-03	5.54E-06	0.00E+00	2.13E-03
Average Rainfall and Temperate Location	1.92E-02	3.69E-03	8.62E-02	7.73E-04	2.10E-04	1.41E-02	8.78E-05	1.42E-05	4.85E-03
Average Rainfall and Cool Location	1.62E-02	5.55E-03	4.03E-02	2.57E-03	1.22E-03	6.80E-03	2.99E-04	1.09E-04	1.26E-03
Wet and Warm Location	1.77E-02	6.62E-03	6.89E-02	5.01E-06	3.16E-08	5.89E-04	5.00E-05	3.41E-07	3.46E-03
Wet and Temperate Location	9.61E-03	1.51E-04	5.11E-02	5.77E-04	1.32E-04	3.86E-03	1.20E-05	2.36E-07	8.59E-04
Wet and Cool Location	2.52E-01	2.02E-01	2.73E-01	2.29E-01	1.38E-01	2.70E-01	2.08E-01	1.39E-01	2.58E-01
Summary									
						Average of Central Values	*3.12E-02*		
						30th Percentile of Lower Bounds	*1.13E-07*		
						Maximum Value	*2.73E-01*		
						Summary of Values[1]	***.0312 (.000000113 – .273)***		

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A10-2: Concentration in Top 12 Inches of Soil (ppm)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	1.74E-01	1.73E-01	1.74E-01	1.59E-01	1.58E-01	1.59E-01	1.59E-01	1.58E-01	1.59E-01
Dry and Temperate Location	1.77E-01	1.76E-01	1.78E-01	1.62E-01	1.61E-01	1.62E-01	1.62E-01	1.61E-01	1.62E-01
Dry and Cold Location	2.47E-01	2.41E-01	2.54E-01	2.28E-01	2.22E-01	2.33E-01	1.67E-01	1.65E-01	1.68E-01
Average Rainfall and Warm Location	1.74E-01	1.72E-01	1.75E-01	1.59E-01	1.58E-01	1.60E-01	1.59E-01	1.58E-01	1.60E-01
Average Rainfall and Temperate Location	1.76E-01	1.74E-01	1.77E-01	1.61E-01	1.60E-01	1.62E-01	1.61E-01	1.60E-01	1.62E-01
Average Rainfall and Cool Location	1.82E-01	1.80E-01	1.84E-01	1.67E-01	1.65E-01	1.68E-01	1.67E-01	1.65E-01	1.68E-01
Wet and Warm Location	1.75E-01	1.72E-01	1.76E-01	2.03E-01	1.99E-01	2.04E-01	1.60E-01	1.58E-01	1.61E-01
Wet and Temperate Location	2.09E-01	2.06E-01	2.10E-01	1.65E-01	1.64E-01	1.65E-01	1.63E-01	1.62E-01	1.64E-01
Wet and Cool Location	1.71E-01	1.50E-01	1.91E-01	1.62E-01	1.45E-01	1.80E-01	1.58E-01	1.39E-01	1.76E-01
Summary									
							Average of Central Values	*1.74E-01*	
							30th Percentile of Lower Bounds	*1.59E-01*	
							Maximum Value	*2.54E-01*	
							Summary of Values[1]	***.174 (0.159 – 0.254)***	

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A10-3: Concentration in Top 36 Inches of Soil (mg/kg)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	5.79E-02	5.77E-02	5.80E-02	5.30E-02	5.28E-02	5.31E-02	5.30E-02	5.28E-02	5.31E-02
Dry and Temperate Location	5.90E-02	5.86E-02	5.92E-02	5.40E-02	5.36E-02	5.41E-02	5.39E-02	5.36E-02	5.41E-02
Dry and Cold Location	8.25E-02	8.03E-02	8.45E-02	7.59E-02	7.41E-02	7.76E-02	5.56E-02	5.50E-02	5.60E-02
Average Rainfall and Warm Location	5.81E-02	5.73E-02	5.82E-02	5.31E-02	5.25E-02	5.32E-02	5.31E-02	5.25E-02	5.32E-02
Average Rainfall and Temperate Location	5.87E-02	5.81E-02	5.90E-02	5.37E-02	5.32E-02	5.39E-02	5.37E-02	5.32E-02	5.39E-02
Average Rainfall and Cool Location	6.08E-02	5.99E-02	6.12E-02	5.56E-02	5.50E-02	5.60E-02	5.56E-02	5.50E-02	5.60E-02
Wet and Warm Location	5.83E-02	5.75E-02	5.86E-02	6.75E-02	6.64E-02	6.79E-02	5.33E-02	5.27E-02	5.36E-02
Wet and Temperate Location	6.97E-02	6.86E-02	7.00E-02	5.49E-02	5.46E-02	5.52E-02	5.50E-02	5.45E-02	5.52E-02
Wet and Cool Location	5.70E-02	5.01E-02	6.37E-02	5.40E-02	4.84E-02	6.00E-02	5.33E-02	4.67E-02	5.97E-02
Summary									
						Average of Central Values	*5.82E-02*		
						30th Percentile of Lower Bounds	*5.30E-02*		
						Maximum Value	*8.45E-02*		
						Summary of Values[1]	***.0582 (0.053 – 0.0845)***		

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A10-4: Maximum Penetration into Soil Column (inches)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	8	4	12	8	4	12	12	4	18
Dry and Temperate Location	12	8	12	12	8	12	12	8	24
Dry and Cold Location	12	8	12	12	8	12	24	18	30
Average Rainfall and Warm Location	12	12	18	18	12	24	24	18	30
Average Rainfall and Temperate Location	12	12	18	18	12	24	24	18	30
Average Rainfall and Cool Location	12	12	18	18	12	24	24	18	30
Wet and Warm Location	18	12	18	36	36	36	30	24	36
Wet and Temperate Location	24	18	30	24	24	30	36	36	36
Wet and Cool Location	18	18	24	30	24	30	36	36	36
Summary									
						Average of Central Values	*19.48*		
						30th Percentile of Lower Bounds	*9.60*		
						Maximum Value	*36.00*		
						Summary of Values[1]	***19.48 (9.6 – 36)***		

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A10-5: Stream, Maximum Peak Concentration in Surface Water (mg/L or ppm)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	1.26E-04	0.00E+00	8.43E-03	0.00E+00	0.00E+00	3.76E-05	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	6.23E-04	0.00E+00	2.68E-03	0.00E+00	0.00E+00	1.32E-03	0.00E+00	0.00E+00	1.36E-03
Dry and Cold Location	3.20E-02	1.74E-02	6.53E-02	2.37E-02	1.32E-02	5.61E-02	1.58E-04	4.78E-05	6.24E-04
Average Rainfall and Warm Location	1.80E-02	3.28E-03	3.67E-02	3.07E-04	7.07E-07	4.87E-03	2.66E-06	0.00E+00	1.20E-03
Average Rainfall and Temperate Location	1.60E-02	5.07E-03	4.84E-02	4.42E-04	1.38E-04	7.91E-03	5.46E-05	8.70E-06	2.13E-03
Average Rainfall and Cool Location	1.28E-02	3.53E-03	3.21E-02	1.02E-03	5.01E-04	2.89E-03	1.58E-04	4.78E-05	6.24E-04
Wet and Warm Location	1.36E-02	4.77E-03	2.98E-02	4.59E-05	2.69E-06	6.78E-04	1.89E-05	1.80E-07	1.07E-03
Wet and Temperate Location	2.21E-02	5.97E-04	6.54E-02	3.18E-04	4.37E-05	2.87E-03	9.45E-06	5.11E-07	6.06E-04
Wet and Cool Location	.071.	6.03E-02	8.28E-02	6.19E-02	4.96E-02	7.59E-02	6.85E-02	5.34E-02	8.85E-02
Summary									
							Average of Central Values	*1.05E-02*	
							30th Percentile of Lower Bounds	*3.12E-07*	
							Maximum Value	*8.85E-02*	
							Summary of Values[1]	***.0105 (.000000312 – 0.0885)***	

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A10-6: Stream, Average Annual Concentration in Surface Water (mg/L or ppm)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	4.80E-07	0.00E+00	3.13E-05	0.00E+00	0.00E+00	1.06E-07	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	3.78E-06	0.00E+00	1.54E-05	0.00E+00	0.00E+00	5.90E-06	0.00E+00	0.00E+00	5.68E-06
Dry and Cold Location	4.02E-04	2.35E-04	6.94E-04	2.80E-04	1.60E-04	4.98E-04	2.15E-06	8.79E-07	9.26E-06
Average Rainfall and Warm Location	1.12E-04	2.59E-05	2.46E-04	9.92E-07	2.06E-09	1.67E-05	9.41E-09	0.00E+00	3.69E-06
Average Rainfall and Temperate Location	1.18E-04	4.04E-05	2.57E-04	5.11E-06	1.90E-06	2.54E-05	6.29E-07	1.23E-07	6.65E-06
Average Rainfall and Cool Location	1.22E-04	6.99E-05	2.22E-04	1.94E-05	1.04E-05	3.88E-05	2.15E-06	8.79E-07	9.26E-06
Wet and Warm Location	1.10E-04	4.64E-05	2.03E-04	6.38E-07	2.18E-08	2.01E-05	8.09E-08	9.10E-10	3.27E-06
Wet and Temperate Location	8.96E-05	3.24E-06	3.13E-04	1.61E-06	3.66E-07	8.75E-06	1.23E-07	7.39E-09	6.35E-06
Wet and Cool Location	1.27E-03	9.13E-04	1.57E-03	9.02E-04	5.64E-04	1.10E-03	7.54E-04	5.40E-04	8.76E-04
Summary									
								Average of Central Values	*1.55E-04*
								30th Percentile of Lower Bounds	*1.37E-09*
								Maximum Value	*1.57E-03*
								Summary of Values[1]	***.000155 (.00000000137 – 0.00157)***

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A10-7: Pond, Maximum Peak Concentration in Surface Water (mg/L or ppm)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	2.53E-05	0.00E+00	2.69E-03	0.00E+00	0.00E+00	9.84E-06	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	1.58E-04	0.00E+00	7.45E-03	0.00E+00	0.00E+00	4.51E-04	0.00E+00	0.00E+00	2.85E-04
Dry and Cold Location	6.75E-03	3.12E-03	1.78E-02	5.11E-03	2.11E-03	1.44E-02	4.58E-05	1.24E-05	2.62E-04
Average Rainfall and Warm Location	6.48E-03	7.80E-04	1.62E-02	1.14E-04	2.06E-07	2.19E-03	1.25E-06	0.00E+00	5.62E-04
Average Rainfall and Temperate Location	5.61E-03	1.13E-03	2.25E-02	1.63E-04	4.41E-05	3.79E-03	1.91E-05	2.58E-06	1.05E-03
Average Rainfall and Cool Location	4.30E-03	8.62E-04	1.22E-02	3.13E-04	1.28E-04	1.57E-03	4.58E-05	1.24E-05	2.62E-04
Wet and Warm Location	3.94E-03	1.23E-03	1.06E-02	4.20E-05	2.16E-06	8.75E-04	8.28E-06	7.22E-08	4.47E-04
Wet and Temperate Location	1.04E-02	1.97E-04	4.48E-02	1.20E-04	1.22E-05	1.24E-03	2.65E-06	1.29E-07	2.67E-04
Wet and Cool Location	1.57E-02	1.20E-02	2.27E-02	1.37E-02	9.95E-03	2.07E-02	1.41E-02	9.32E-03	2.29E-02
Summary									
							Average of Central Values	*3.23E-03*	
							30th Percentile of Lower Bounds	*9.49E-08*	
							Maximum Value	*4.48E-02*	
							Summary of Values[1]	***.00323 (.0000000949 – 0.0448)***	

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A10-8: Pond, Average Annual Concentration in Surface Water (mg/L or ppm)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	1.80E-07	0.00E+00	1.76E-05	0.00E+00	0.00E+00	1.77E-05	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	1.39E-06	0.00E+00	8.89E-06	0.00E+00	0.00E+00	3.19E-06	0.00E+00	0.00E+00	6.10E-04
Dry and Cold Location	1.35E-04	6.81E-05	2.42E-04	9.27E-05	4.39E-05	1.72E-04	9.42E-07	3.55E-07	3.68E-06
Average Rainfall and Warm Location	6.53E-05	1.27E-05	1.45E-04	8.19E-07	1.11E-09	1.52E-05	8.35E-09	0.00E+00	2.87E-06
Average Rainfall and Temperate Location	7.01E-05	2.17E-05	1.69E-04	2.91E-06	9.98E-07	2.15E-05	3.22E-07	6.04E-08	5.64E-06
Average Rainfall and Cool Location	5.81E-05	2.76E-05	1.43E-04	8.43E-06	4.34E-06	1.60E-05	9.42E-07	3.55E-07	3.68E-06
Wet and Warm Location	4.91E-05	2.24E-05	9.80E-05	1.22E-05	4.80E-07	2.46E-04	5.32E-08	6.38E-10	2.41E-06
Wet and Temperate Location	1.76E-03	3.98E-05	8.05E-03	8.69E-07	1.63E-07	6.84E-06	4.77E-08	2.15E-09	2.04E-06
Wet and Cool Location	3.13E-04	2.27E-04	3.81E-04	2.22E-04	1.22E-04	2.84E-04	1.84E-04	1.21E-04	2.23E-04
Summary									
							Average of Central Values	*1.10E-04*	
							30th Percentile of Lower Bounds	*8.27E-10*	
							Maximum Value	*8.05E-03*	
							Summary of Values[1]	***.00011 (.000000000827 – 0.00805)***	

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Appendix 11: Flumioxazin Broadcast Soil GLEAMS-Driver Modeling Results

The following tables present estimated water concentrations in surface water bodes calculated with GLEAMS-Driver.

Table A11-1: Effective Offsite Application Rate (lb/acre)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	6.88E-05	0.00E+00	8.21E-03	0.00E+00	0.00E+00	2.49E-05	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	6.45E-04	0.00E+00	5.50E-03	0.00E+00	0.00E+00	1.23E-03	0.00E+00	0.00E+00	8.70E-04
Dry and Cold Location	5.69E-02	3.52E-02	1.09E-01	3.69E-02	2.15E-02	7.66E-02	3.53E-02	1.87E-02	7.71E-02
Average Rainfall and Warm Location	2.93E-02	3.28E-03	1.25E-01	5.98E-04	1.17E-06	1.58E-02	4.28E-04	1.54E-04	1.80E-03
Average Rainfall and Temperate Location	2.82E-02	5.38E-03	1.06E-01	1.08E-03	2.96E-04	1.98E-02	1.18E-04	1.97E-05	5.41E-03
Average Rainfall and Cool Location	2.37E-02	8.13E-03	5.89E-02	1.28E-05	1.61E-07	7.44E-04	4.28E-04	1.54E-04	1.80E-03
Wet and Warm Location	2.59E-02	9.63E-03	1.01E-01	1.44E-03	2.35E-05	2.04E-02	7.08E-05	4.81E-07	4.75E-03
Wet and Temperate Location	2.23E-02	1.27E-02	8.87E-02	8.14E-04	1.85E-04	5.46E-03	1.69E-05	3.34E-07	1.21E-03
Wet and Cool Location	3.62E-01	2.91E-01	3.90E-01	3.22E-01	1.90E-01	3.80E-01	2.87E-01	1.95E-01	3.64E-01
Summary									
						Average of Central Values	*4.57E-02*		
						30th Percentile of Lower Bounds	*3.93E-07*		
						Maximum Value	*3.90E-01*		
						Summary of Values[1]	***.0457 (0.000000393- .39)***		

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A11-2: Concentration in Top 12 Inches of Soil (ppm)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	2.62E-01	2.62E-01	2.62E-01	2.31E-01	2.31E-01	2.31E-01	2.31E-01	2.31E-01	2.31E-01
Dry and Temperate Location	2.64E-01	2.63E-01	2.64E-01	2.33E-01	2.32E-01	2.34E-01	2.33E-01	2.32E-01	2.33E-01
Dry and Cold Location	3.65E-01	3.55E-01	3.74E-01	3.24E-01	3.16E-01	3.31E-01	3.24E-01	3.15E-01	3.30E-01
Average Rainfall and Warm Location	2.62E-01	2.62E-01	2.62E-01	2.31E-01	2.31E-01	2.31E-01	2.39E-01	2.37E-01	2.40E-01
Average Rainfall and Temperate Location	2.63E-01	2.62E-01	2.63E-01	2.32E-01	2.32E-01	2.33E-01	2.32E-01	2.32E-01	2.32E-01
Average Rainfall and Cool Location	2.70E-01	2.68E-01	2.72E-01	2.32E-01	2.31E-01	2.32E-01	2.39E-01	2.37E-01	2.40E-01
Wet and Warm Location	2.62E-02	2.62E-02	2.62E-02	2.31E-01	2.31E-01	2.31E-01	2.31E-01	2.31E-01	2.31E-01
Wet and Temperate Location	2.67E-01	2.63E-01	2.67E-01	2.35E-01	2.35E-01	2.35E-01	2.33E-01	2.33E-01	2.34E-01
Wet and Cool Location	2.63E-01	2.43E-01	2.89E-01	2.41E-01	2.18E-01	2.61E-01	2.36E-01	2.15E-01	2.58E-01
Summary									
							Average of Central Values	*2.46E-01*	
							30th Percentile of Lower Bounds	*2.31E-01*	
							Maximum Value	*3.74E-01*	
							Summary of Values[1]	***.246 (.231 – .374)***	

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A11-3: Concentration in Top 36 Inches of Soil (mg/kg)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	8.73E-02	8.73E-02	8.73E-02	7.71E-02	7.71E-02	7.71E-02	7.71E-02	7.71E-02	7.71E-02
Dry and Temperate Location	8.79E-02	8.77E-02	8.82E-02	7.77E-02	7.75E-02	7.79E-02	7.76E-02	7.74E-02	7.78E-02
Dry and Cold Location	1.22E-01	1.18E-01	1.25E-01	1.08E-01	1.05E-01	1.10E-01	1.08E-01	1.20E-01	1.80E-01
Average Rainfall and Warm Location	8.73E-02	8.73E-02	8.73E-02	7.71E-02	7.71E-02	7.71E-02	7.96E-02	7.89E-02	8.01E-02
Average Rainfall and Temperate Location	8.76E-02	2.62E-01	2.63E-01	7.74E-02	7.73E-02	7.75E-02	7.74E-02	7.73E-02	7.75E-02
Average Rainfall and Cool Location	9.01E-02	8.93E-02	9.06E-02	7.73E-02	7.72E-02	7.73E-02	7.80E-02	7.89E-02	8.01E-02
Wet and Warm Location	8.73E-02	8.73E-02	8.73E-02	7.71E-02	7.71E-02	7.71E-02	7.71E-02	7.71E-02	7.71E-02
Wet and Temperate Location	8.89E-02	8.78E-02	8.91E-02	7.86E-02	7.84E-02	7.89E-02	7.87E-02	7.84E-02	7.90E-02
Wet and Cool Location	8.78E-02	8.09E-02	9.64E-02	8.04E-02	7.25E-02	8.71E-02	7.99E-02	7.17E-02	8.71E-02
Summary									
							Average of Central Values	*8.48E-02*	
							30th Percentile of Lower Bounds	*7.72E-02*	
							Maximum Value	*2.63E-01*	
							Summary of Values[1]	***.0848 (0.0772 – 0.263)***	

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A11-4: Maximum Penetration into Soil Column (inches)

Site	*Clay*			*Loam*			*Sand*		
	Central	*Lower*	*Upper*	*Central*	*Lower*	*Upper*	*Central*	*Lower*	*Upper*
Dry and Warm Location	8	4	12	8	4	12	12	8	18
Dry and Temperate Location	12	8	12	12	8	18	18	8	24
Dry and Cold Location	12	8	12	12	8	12	18	12	18
Average Rainfall and Warm Location	12	12	18	18	12	24	24	18	30
Average Rainfall and Temperate Location	12	12	18	18	12	24	24	18	36
Average Rainfall and Cool Location	18	12	18	36	30	36	24	18	30
Wet and Warm Location	18	12	18	24	18	24	30	24	36
Wet and Temperate Location	18	18	24	30	24	30	36	36	36
Wet and Cool Location	18	18	24	30	24	36	36	36	36
Summary									
						Average of Central Values	*19.93*		
						30th Percentile of Lower Bounds	*9.60*		
						Maximum Value	*36.00*		
						Summary of Values[1]	***19.93 (9.6 – 36)***		

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A11-5: Stream, Maximum Peak Concentration in Surface Water (mg/L or ppm)

Site	*Clay*			*Loam*			*Sand*		
	Central	*Lower*	*Upper*	*Central*	*Lower*	*Upper*	*Central*	*Lower*	*Upper*
Dry and Warm Location	1.84E-03	0.00E+00	1.23E-02	0.00E+00	0.00E+00	5.28E-05	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	9.11E-04	0.00E+00	3.92E-03	0.00E+00	0.00E+00	1.80E-01	0.00E+00	0.00E+00	1.93E-03
Dry and Cold Location	4.70E-02	2.55E-02	9.58E-02	3.36E-02	1.87E-02	7.69E-02	3.93E-02	1.65E-02	8.51E-02
Average Rainfall and Warm Location	2.61E-02	4.78E-03	6.49E-02	4.30E-04	9.95E-07	8.08E-03	2.24E-04	6.81E-05	8.92E-04
Average Rainfall and Temperate Location	2.34E-02	7.39E-03	6.90E-02	6.20E-04	1.94E-04	1.08E-02	7.62E-05	1.21E-05	2.99E-03
Average Rainfall and Cool Location	1.90E-02	5.17E-03	4.70E-02	2.09E-05	1.39E-06	8.85E-04	2.24E-04	6.81E-05	8.92E-04
Wet and Warm Location	1.98E-02	7.18E-03	4.60E-02	7.27E-04	1.29E-05	8.82E-03	2.67E-05	2.52E-07	1.54E-03
Wet and Temperate Location	1.76E-02	6.44E-03	5.03E-02	4.51E-04	6.18E-05	4.06E-03	1.58E-05	7.25E-07	8.59E-04
Wet and Cool Location	1.11E-01	9.30E-02	1.29E-01	9.31E-02	7.37E-02	1.14E-01	1.09E-01	8.36E-02	1.38E-01
Summary									
						Average of Central Values	*2.02E-02*		
						30th Percentile of Lower Bounds	*8.33E-07*		
						Maximum Value	*1.80E-01*		
						Summary of Values[1]	***.0202 (.000000833 – 0.18)***		

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A11-6: Stream, Average Annual Concentration in Surface Water (mg/L or ppm)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	6.98E-07	0.00E+00	4.54E-05	0.00E+00	0.00E+00	1.48E-07	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	5.53E-06	0.00E+00	2.25E-05	0.00E+00	0.00E+00	8.32E-06	0.00E+00	0.00E+00	8.01E-06
Dry and Cold Location	5.92E-04	3.46E-04	1.02E-03	3.97E-04	2.27E-04	7.09E-04	4.06E-04	2.18E-04	7.24E-04
Average Rainfall and Warm Location	1.63E-04	3.78E-05	3.62E-04	1.39E-06	2.90E-09	2.74E-05	3.06E-06	1.25E-06	1.31E-05
Average Rainfall and Temperate Location	1.72E-04	5.89E-05	3.75E-04	7.17E-06	2.69E-06	3.47E-05	8.81E-07	1.74E-07	9.24E-06
Average Rainfall and Cool Location	1.78E-04	1.02E-04	3.24E-04	2.00E-07	1.43E-08	3.17E-06	3.06E-06	1.25E-06	1.31E-05
Wet and Warm Location	1.62E-04	6.74E-05	2.97E-04	3.29E-06	7.27E-08	3.15E-05	1.15E-07	1.27E-09	4.72E-06
Wet and Temperate Location	1.67E-04	8.86E-05	3.96E-04	2.28E-06	5.08E-07	1.23E-05	2.18E-07	1.09E-08	1.04E-05
Wet and Cool Location	1.88E-03	1.38E-03	2.31E-03	1.30E-03	8.41E-04	1.56E-03	1.08E-03	7.99E-04	1.26E-03
Summary									
							Average of Central Values		*2.42E-04*
							30th Percentile of Lower Bounds		*6.10E-09*
							Maximum Value		*2.31E-03*
							Summary of Values[1]		***.000242 (.0000000061 – 0.00231)***

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A11-7: Pond, Maximum Peak Concentration in Surface Water (mg/L or ppm)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	3.67E-05	0.00E+00	8.21E-03	0.00E+00	0.00E+00	1.38E-05	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	2.31E-04	0.00E+00	1.30E-05	0.00E+00	0.00E+00	6.37E-04	0.00E+00	0.00E+00	4.06E-04
Dry and Cold Location	9.91E-03	4.57E-03	2.61E-02	7.23E-03	3.00E-03	2.04E-02	7.12E-03	3.17E-03	2.21E-02
Average Rainfall and Warm Location	9.42E-03	1.14E-03	2.56E-02	1.63E-04	2.90E-07	3.90E-03	6.52E-05	1.77E-05	3.73E-04
Average Rainfall and Temperate Location	8.17E-03	1.64E-03	3.21E-02	2.31E-04	6.23E-05	5.18E-03	2.70E-05	3.64E-06	1.30E-03
Average Rainfall and Cool Location	6.29E-03	1.26E-03	1.78E-02	1.53E-05	9.16E-07	6.75E-04	6.52E-05	1.77E-05	3.73E-04
Wet and Warm Location	5.72E-03	1.77E-03	1.68E-02	2.84E-04	6.32E-06	4.16E-03	1.18E-05	1.01E-07	6.29E-04
Wet and Temperate Location	4.75E-03	2.10E-03	1.99E-02	1.70E-04	1.70E-05	1.76E-03	5.21E-06	2.55E-07	3.79E-04
Wet and Cool Location	2.37E-02	1.75E-02	3.39E-02	2.02E-02	1.82E-04	4.04E-04	2.12E-02	1.27E-02	3.17E-02
Summary									
						Average of Central Values	*4.63E-03*		
						30th Percentile of Lower Bounds	*2.69E-07*		
						Maximum Value	*3.39E-02*		
						Summary of Values[1]	***.00463 (0.000000269 – 0.0339)***		

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.

Table A11-8: Pond, Average Annual Concentration in Surface Water (mg/L or ppm)

Site	Clay			Loam			Sand		
	Central	Lower	Upper	Central	Lower	Upper	Central	Lower	Upper
Dry and Warm Location	2.62E-07	0.00E+00	2.56E-05	0.00E+00	0.00E+00	7.22E-08	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	2.04E-06	0.00E+00	1.30E-05	0.00E+00	0.00E+00	4.50E-06	0.00E+00	0.00E+00	2.85E-06
Dry and Cold Location	1.98E-04	1.00E-04	3.59E-04	1.31E-04	6.23E-05	2.44E-04	1.28E-04	6.75E-05	2.54E-04
Average Rainfall and Warm Location	9.46E-05	1.82E-05	2.11E-04	1.15E-06	1.56E-08	2.14E-05	1.35E-06	5.04E-07	5.18E-06
Average Rainfall and Temperate Location	1.02E-04	3.17E-05	2.47E-04	4.10E-06	1.41E-06	2.93E-05	4.57E-07	8.52E-08	7.18E-06
Average Rainfall and Cool Location	8.52E-05	4.05E-05	2.09E-04	2.81E-06	2.81E-07	1.21E-04	1.35E-06	5.04E-07	5.18E-06
Wet and Warm Location	7.16E-05	3.24E-05	1.43E-04	1.44E-03	2.35E-05	2.04E-02	7.49E-08	8.93E-10	3.40E-06
Wet and Temperate Location	7.91E-05	3.68E-05	2.21E-04	1.22E-06	2.26E-07	9.65E-06	8.84E-08	3.22E-09	3.46E-06
Wet and Cool Location	4.64E-04	3.33E-04	5.64E-04	3.16E-04	1.82E-04	4.04E-04	2.64E-04	1.83E-04	3.22E-04
Summary									
							Average of Central Values	*1.25E-04*	
							30th Percentile of Lower Bounds	*8.17E-09*	
							Maximum Value	*2.04E-02*	
							Summary of Values[1]	***.000125 (.00000000817 – 0.0204)***	

1 Average of central values followed by an open parenthesis and the lower bound, followed by a dash, followed by the maximum value and a close parenthesis.