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FINAL REPORT

Human Health and Ecological Risk Assessment (HHERA) for Indaziflam

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ATTACHMENT

Attachment 1: Excel Workbook for Indaziflam

EXECUTIVE SUMMARY

The United States Department of Agriculture (USDA) Forest Service (FS) and Bureau of Land Management (BLM) anticipate utilizing the herbicide indaziflam by ground or aerial broadcast application to manage vegetation in areas such as roadsides, utility corridors, hardscapes, and conifer and hardwood production areas, as well as for the release or restoration of desirable vegetation in wildlife management areas, recreational areas, fire rehabilitation areas, natural areas, prairies, non-crop areas, grasslands, and fire breaks. In accordance with FS procedures, a detailed Human Health and Ecological Risk Assessment (HHERA) is required to assess potential human health and ecological effects prior to the use of indaziflam. The purpose of this risk assessment is to estimate the nature and degree of risks associated with the use of indaziflam in FS and BLM vegetation management programs. The HHERA approach follows the general form of previous FS national HHERAs, including previously developed FS risk assessment guidance, as posted on the *FS Forest Health Protection (FHP) Pesticide Management & Coordination website*. This includes the development of both the written HHERA and an accompanying workbook that can be utilized to perform site specific risk analyses for FS and BLM programs based on identified formulations of indaziflam and anticipated program uses. A listing of acronyms, abbreviations and symbols used in this HHERA is provided beginning on page xiv.

Indaziflam is a pre-emergent herbicide that provides broad spectrum control of many weed seedlings through the inhibition of seedling emergence and root development by the inhibition of cellulose biosynthesis in the roots of affected plants. The formulations most likely to be used by the FS and BLM are Esplanade 200 SC and Esplanade F. The labeled application rate for both formulations ranges from 0.046 to 0.091 pound (lb) of active ingredient (a.i.)/acre To provide the most conservative approach to evaluating risks, the calculations used in the Excel workbook that accompanies this risk assessment are based on this maximum application rate of 0.091 lb a.i./acre for various application methods such as backpack, ground broadcast, or aerial application.

The quantitative risk characterization in both 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 divided by a toxicity value that is not likely to be associated with adverse effects. Thus, an HQ of greater than 1 is defined as the level of concern for non-carcinogenic effects. Carcinogenicity has not been observed and therefore cancer risk has not been evaluated. For all non-accidental exposure scenarios, the HQs are linearly related to the application rate. FS risk assessments are based on *Extreme Values* rather than a single value. 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 EPA and other government agencies. 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, and the toxicity values used here are based on U.S. EPA's risk assessments and data evaluation records (DERs). Additionally, an open

literature search was conducted and those studies which contribute to the understanding of indaziflam's environmental fate and toxicity are also presented in the HHERA.

Human Health Risk

As part of the human health risk assessment, risks related to the FS and BLM intended uses of indaziflam were characterized for workers and the general public. Contamination of environmental media may result from spray applications, accidental spills, and other chronic exposures. The exposure scenarios represent dermal, inhalation, and incidental oral exposures of short- and intermediate-term durations. None of the HQs for workers exceed the level of concern based on central estimates of exposures. However, the upper bound estimates of the HQ slightly exceed the level of concern for backpack applications (HQ = 1.8) and aerial applications (HQ = 1.09). Based on the dose-severity relationship, these HQs are relatively modest exceedances in the level of concern and do not raise substantial concern.

Similar to workers, none of the central estimates of HQs exceed the level of concern for members of the general public. The likelihood that individuals from the general public will be exposed to indaziflam depends on the application method and where the pesticide is applied. However, the upper bound HQ value associated with the chronic consumption of contaminated vegetation exceeds the level of concern (HQ = 3). Other exposure scenarios included water consumption, fish consumption, contaminated fruit consumption, direct spray on the body (child and adult) and swimming. The HQ based on consumption of contaminated vegetation is the only HQ value that exceeds the level of concern for the general public. This exceedance does not raise substantial concern based on the ratio of the lowest-observed-adverse-effect level (LOAEL) to no-observed-adverse-effect level (NOAEL) for chronic exposures. Also, undue exposure to indaziflam from the consumption of contaminated fruit or vegetation would not be expected based on FS and BLM intended uses because applications will typically occur in sparsely inhabited areas (rangeland, woodlands, etc.) and unintended application on edible fruits or vegetables is unlikely.

Ecological Risk

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

Terrestrial Organisms. The predominant route of exposure for mammals and birds involves the consumption of contaminated vegetation. The highest HQ values reported for mammals are for the chronic consumption of broadleaf foliage (HQ = 8), tall grass (HQ = 7), and short grass (HQ = 15) by small mammals. For birds, the highest HQ values are associated with the consumption of contaminated broadleaf foliage (HQ = 6), tall grass (HQ = 5), and short grass (HQ = 11) by small birds. The HQs are based on the assumption that 100% of the diet is contaminated using the maximum application rate of 0.091 lb a.i./acre. Thus, exposure levels may be reduced if a lower application rate is considered in a site-specific assessment. All HQ values for accidental exposures are below the level of concern for both mammals and birds.

While indaziflam is an effective herbicide for the control of weed seedlings, it is not exclusively selective and can adversely affect sensitive species of terrestrial plants, including monocots and dicots. For exposure scenarios associated with direct spray (e.g., backpack application), the impact to

sensitive species of dicots, represented by soybeans, will be severe (HQ = 243), and damage to the vegetation will be apparent. Similarly, damage to tolerant species of monocots, represented by ryegrass, may be apparent following direct spray (HQ = 40). Based on estimates of drift using the aerial spray prediction model AgDRIFT, risks to sensitive species (both monocots and dicots) remain above the level of concern downwind from the application site for distances of at least 900 feet for fine droplets and about 500 feet for course droplets downwind following aerial application. For ground application methods, HQs are at or below the level of concern at distances of 300 feet downwind of the application site. Thus, the risks will be greatest with aerial applications and least with other application methods such as backpack spraying.

In runoff scenarios for vegetation, the upper bound HQs for sensitive and tolerant species (represented by oilseed rape and tomato, respectively) are significantly greater than 1 at 587 and 249, respectively indicating that a high level of care is required to prevent unmanaged runoff. Central bound HQs are also above 1 at 73 for sensitive species and 31 for tolerant species, indicating unacceptable risk. If water contaminated with indaziflam is used for irrigation, the upper bound HQ for sensitive species of vegetation is 15. Note that the exposure components of the HQs are based on simulations using the Groundwater Loading Effects of Agricultural Management Systems (GLEAMS) model, and, therefore, may represent estimates of exposure levels that are not applicable to site-specific applications made in FS and BLM programs. GLEAMS-Driver was used in this risk assessment to model peak and longer-term (non-accidental) indaziflam concentrations in surface water. Consequently, site-specific information could reduce the estimates of risks to non-target vegetation. The HQs for non-target vegetation associated with wind erosion of contaminated soil are below the level of concern for sensitive and tolerant species.

In the case of terrestrial invertebrates, all of the HQs are well below 1, and there is no basis for asserting that application of indaziflam will lead to significant or even detectable signs of toxicity to honey bees or herbivorous insects.

Aquatic Organisms. Direct effects on fish and invertebrates are below the level of concern for non-accidental exposures. For accidental exposures, the upper bound HQ for tolerant fish species (HQ = 1.6) exceeds the level of concern. The upper bound HQ for sensitive fish species (HQ = 4) also exceeds the level of concern. Thus, there may be a modest potential for adverse effects in fish following spills of indaziflam that impact surface water bodies and potentially from indirect impacts to aquatic plants. In areas with a higher potential for water contamination, adverse effects in sensitive species of invertebrates cannot be ruled out.

The most substantial non-target impact of indaziflam applications made near surface water will involve effects on aquatic plants, including algae and macrophytes. For non-accidental exposures, the HQs are all below the level of concern, with the exception of the upper bound HQ for sensitive algal species. For accidental exposures, the upper bound HQs are 327 for sensitive species and 0.3 for tolerant species. In the event of a substantial accidental spill that impacts a surface water body, adverse effects on sensitive algae are very likely to occur. However, site-specific information could reduce uncertainty in and refine estimated risks. For example, at sites or in regions where water contamination potential is low due to weather or distance of surface water from the application site, risks to algae should be minimal.

Both non-accidental and accidental exposure scenarios for aquatic macrophytes have HQs above the level of concern. For non-accidental acute exposures, the upper bound HQ is 657 for tolerant species[1]. For longer-term exposures, the upper bound HQ is 12. Based on these HQ values, adverse effects on tolerant species could be evident during acute and chronic exposures. As with the risk characterization for algae, the levels of exposure will depend on site-specific considerations. For accidental exposures, the central HQ is 9,755 (lower = 429 to upper = 85,845) for tolerant species of aquatic macrophytes. These HQ values are far above the level of concern and indicate that severe adverse effects are likely to occur during an event of a substantial accidental spill. In the event of a substantial accidental spill, adverse effects on sensitive algae are likely to occur. Thus, extreme caution should be taken when applying indaziflam to ensure that surface water is not contaminated during application.

No data are available on the toxicity of indaziflam to reptiles or amphibians (terrestrial or aquatic phase). Thus, no risk characterization for these groups of organisms was developed in this HHERA.

Secondary Effects. While the risk characterization for indaziflam focuses on the potential for direct toxic effects, there is potential for secondary effects. Terrestrial applications of any effective herbicide, including indaziflam, 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 may 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 indaziflam or herbicide applications.

[1] Toxicity data for sensitive macrophyte not available, therefore not assessed.

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

a.e.	acid equivalents
AEL	adverse-effect level
AgDRIFT	aerial spray prediction model from ground boom and air-blast applications
AGRICOLA	USDA's National Agricultural Library database
a.i.	active ingredient
ARS	Agricultural Research Service
ASAE	American Society of Agricultural Engineers
ATSDR	Agency for Toxic Substances and Disease Registry
ATV	all-terrain vehicle
BCF	bioconcentration factor
BLM	Bureau of Land Management
BPA	Blanket Purchase Agreement
bw	body weight
CalEPA	California Environmental Protection Agency
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CBI	cellulose biosynthesis inhibitor
CESA	cellulose synthase A
ChemIDPlus	database of chemical names, synonyms, structures
CRD	Crop Reporting Districts
cm	centimeter
DAA	days after application
DAF	dermal adsorption factor
DAT	days after treatment
DER	Data Evaluation Record
DOI	Department of Interior
EDSP	Endocrine Disruptor Screening Program
EFED	Environmental Fate and Effects Division
EPest	estimated pesticide use
EPI-Suite	Estimated Programs Interface Suite™- physical/chemical property and environmental fate estimation program developed by U.S. EPA and Syracuse Research Corp.
EXTOXNET	EXtension TOXicology NETwork
FDAT	fluoroethyldiaminotriazine
FHP	Forest Health Protection
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FS	Forest Service
g	gram
GLEAMS	Groundwater Loading Effects of Agricultural Management Systems
ha	hectare
HED	Health Effects Division
HERO	Health & Environmental Research Online
HHERA	Human Health and Ecological Risk Assessment

HSDB	Hazardous Substances Data Bank
HQ	hazard quotient
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
IUPAC	International Union of Pure and Applied Chemistry
ka	first-order dermal absorption rate coefficient
kd	soil adsorption coefficient
kg	kilogram
Koc	organic carbon-water partition coefficient
Kow	octanol-water partition coefficient
Kp	zero-order dermal absorption rate
L	liter
lb	pound
LC_{50}	lethal concentration, 50% kill
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
LOD	limit of detection
LOQ	limit of quantitation
m	meter
MEI	Most Exposed Individual or Maximum Exposed Individual
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mol	mole
MRID	master record identification number
MW	molecular weight
NAWQA	National Water-Quality Assessment
NEPA	National Environmental Policy Act
NLM	National Library of Medicine
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NRC	National Research Council
OC	organic carbon
OPP	Office of Pesticide Programs
OPPTS	Office of Prevention, Pesticides and Toxic Substances
PC	pesticide chemical
pH	potential hydrogen – scale used to rank relative basicity or acidity
ppm	parts per million
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRZM	U.S. EPA's one-dimensional, finite-difference model that accounts for pesticide and nitrogen fate in the crop root zone
QSAR	quantitative structure activity relationships
RfD	reference dose

SDS	Safety Data Sheet
SERA	Syracuse Environmental Research Associates
TOXLINE	National Library of Medicine's bibliographic toxicology database
UIN	unique identification number
U.S. EPA	U.S. Environmental Protection Agency
USDA	U.S. Department of Agriculture
USGS	U.S. Geological Survey
UTV	utility task vehicle
WCR	water contamination rate
WHO	World Health Organization

COMMON UNIT CONVERSIONS AND ABBREVIATIONS

To convert ...	Into ...	Multiply by ...
acres	hectares (ha)	0.4047
acres	square meters (m^2)	4,047
atmospheres	millimeters of mercury	760
centigrade	Fahrenheit	1.8 °C+32
centimeters	inches	0.3937
cubic meters (m^3)	liters (L)	1,000
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)	1,000
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 ($\mu g/cm^2$)	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

Note: All references to pounds and ounces refer to avoirdupois weights unless otherwise specified.
Source: (SERA 2014a)

CONVERSION OF SCIENTIFIC NOTATION

Scientific Notation	Decimal Equivalent	Verbal Expression
$1x\ 10^{-10}$	0.0000000001	One in ten billion
$1x\ 10^{-9}$	0.000000001	One in one billion
$1x\ 10^{-8}$	0.00000001	One in one hundred million
$1x\ 10^{-7}$	0.0000001	One in ten million
$1x\ 10^{-6}$	0.000001	One in one million
$1x\ 10^{-5}$	0.00001	One in one hundred thousand
$1x\ 10^{-4}$	0.0001	One in ten thousand
$1x\ 10^{-3}$	0.001	One in one thousand
$1x\ 10^{-2}$	0.01	One in one hundred
$1x\ 10^{-1}$	0.1	One in ten
$1x\ 10^{0}$	1	One
$1x\ 10^{1}$	10	Ten
$1x\ 10^{2}$	100	One hundred
$1x\ 10^{3}$	1,000	One thousand
$1x\ 10^{4}$	10,000	Ten thousand
$1x\ 10^{5}$	100,000	One hundred thousand
$1x\ 10^{6}$	1,000,000	One million
$1x\ 10^{7}$	10,000,000	Ten million
$1x\ 10^{8}$	100,000,000	One hundred million
$1x\ 10^{9}$	1,000,000,000	One billion
$1x\ 10^{10}$	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 as the Bureau of Land Management (BLM) is responsible for management of BLM lands. Forest management practices include the implementation of integrated pest and vegetation management programs to protect and maintain forest health. Pesticides are one of the various tools used by the FS and BLM to prevent, control, or manage forest insects, diseases, and invasive plants (USDA/FS 2019). When considering the use of pesticides on forest lands, it is FS and BLM policy that an analysis be conducted to assess potential human health and ecological effects. FS pesticide risk assessments are referred to as Human Health and Ecological Risk Assessments (HHERAs). FS and BLM use HHERAs to evaluate the risks of harm from the use of a particular pesticide to agency personnel, the general public, and the environment. FS also uses data and findings from HHERAs to prepare environmental documents required under the National Environmental Policy Act (NEPA). Additional information on the FS pesticide risk assessment process and a list of completed HHERAs can be accessed on the *FS Forest Health Protection (FHP) Pesticide Management & Coordination website*.

The FS and BLM anticipate utilizing the herbicide indaziflam to manage forest vegetation in areas such as roadsides, utility corridors, hardscapes, and conifer and hardwood production areas, as well as for the release or restoration of desirable vegetation in wildlife management areas, recreational areas, fire rehabilitation areas, natural areas, prairies and fire breaks. The FS and BLM have not conducted previous risk assessments on indaziflam. In accordance with pesticide procedures, the FS and BLM requested the preparation of a HHERA prior to using the herbicide. Kestrel Tellevate LLC, with support from subcontractors BMT Designers & Planners and SRC, Inc. (assessment team), prepared the Indaziflam HHERA. The work was conducted under Blanket Purchase Agreement (BPA) contract #AG-3187-B-17-0008, Call Order 12318718F0358, awarded on July 26, 2018.

1.2. Purpose of this HHERA

The purpose of this risk assessment is to estimate the nature and degree of risks associated with the use of indaziflam in FS and BLM vegetation management programs. Indaziflam is a fluoroalkyltriazine herbicide that controls weeds by inhibiting cellulose biosynthesis in the roots of affected plants (known as a cellulose biosynthesis inhibitor [CBI] herbicide). Indaziflam was registered with the U.S. Environmental Protection Agency (U.S. EPA) Office of Pesticide Programs (OPP) (U.S. EPA/OPP) in 2010 by Bayer Environmental Science and Bayer Advanced for residential and non-residential uses. For commercial property, indaziflam can be used on golf courses, lawns, walkways, cemeteries, evergreen nurseries, and landscaping projects. It works well against crabgrass, goosegrass, kyllinga, bluegrass, doveweed, swinecress, bittercress, and henbit, among many other plants, according to North Carolina State University Turf Research. It has also been registered in Latin America, Asia, and Australia. Indaziflam is sold under the names Alion™, Specticle™, and Esplanade™ (Boyd 2014). At the request of the FS and BLM, this HHERA focuses on the non-residential uses of the two pre-emergent formulations Esplanade 200 SC® and Esplanade F®.

The general framework, approach, and information included in this HHERA are consistent with the 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 indaziflam. It is important to note that the human health and ecological risk assessment is not intended to include summaries or evaluations of all available information on indaziflam. Instead, this document focuses on addressing technical areas and issues of specific importance to the FS and BLM based on FS and BLM intended uses.

In the future, the FS or BLM may 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 helpful only if recommendations for including additional studies specify why and/or how the new or not previously included information would be likely to alter the conclusions reached in the risk assessment.

1.3. HHERA Structure

The HHERA structure 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 indaziflam; (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 U.S. 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. EPA/OPP and the U.S. Department of Interior (DOI), 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.

1.4. Supporting Materials (Excel Workbook)

Exposure and noncarcinogenic hazard estimates are typically expressed as a central tendency estimate along with a range (low and high). Carcinogenicity has not been observed and therefore non-carcinogenic hazards are calculated. 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 a customized Excel® workbook, which is included in Attachment 1. The Excel workbook was generated using the FS risk assessment tool called WorksheetMaker. The tool allows a user to develop pesticide-specific risk assessment Excel workbooks by entering information on a chemical and formulation of interest, including chemical and physical chemical properties, toxicological values, application rates, application volumes, etc. Once an Excel workbook is generated for a chemical and formulation, the Excel 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 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 2016b) includes additional information on WorksheetMaker and the use of Excel workbooks in FS risk assessments.

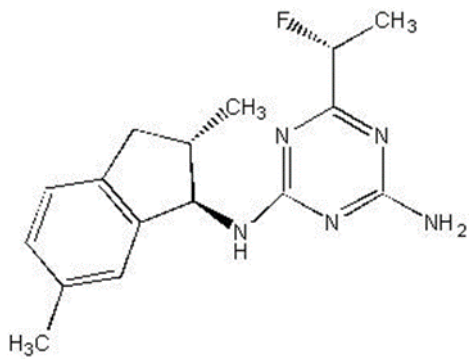
2. CHEMICAL INFORMATION

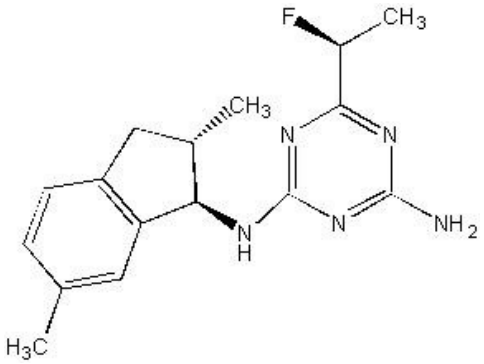
2.1. Chemical Description and Formulations

Indaziflam (N-[(1R,2S)-2,3-dihydro-2,6-dimethyl-1H-inden-1-yl]-6-[(1RS)-1-fluoroethyl]- 1,3,5-triazine-2,4-diamine) is a pre-emergent herbicide. The parent compound, or pure substance, is a mixture of two active diastereoisomers, which are composed of two non-paired stereoisomers (i.e., they differ in their chemical and physical properties) (Garrison 2011). The diastereoisomers are present in the technical grade product as 95-100% isomer A and 0-5% isomer B (U.S. EPA/OPP 2010a). Indaziflam provides broad spectrum control of many weed seedlings through the inhibition of seedling emergence and root development by the inhibition of cellulose biosynthesis in the roots of affected plants. For most effective control, indaziflam should be applied prior to weed germination. Indaziflam has low post-emergent activity, but can be mixed with a herbicide with post-emergent activity (U.S. EPA/OPP 2010c).

Selected chemical and physical properties of indaziflam are summarized in Table 2-1. Additional data are presented in Attachment 1 (Worksheet B01).

Table 2-1: Chemical and Physical Properties of Indaziflam

Parameter	Value	Reference
Common Name	Indaziflam	N/A
Chemical Name (International Union of Pure and Applied Chemistry (IUPAC))	N-[(1R,2S)-2,3-dihydro-2,6-dimethyl-1H-inden-1-yl]-6-[(1RS)-1-fluoroethyl]- 1,3,5-triazine-2,4-diamine	(U.S. EPA/OPP 2010a)
Chemical Abstracts Service (CAS) Registry Number (CASRN)	950782-86-2	(U.S. EPA/OPP 2010a)
U.S. EPA Pesticide Chemical (PC) Code	080818	(U.S. EPA/OPP 2010a)
Structure (Isomer A)		(U.S. EPA/OPP 2010a)

Parameter	Value	Reference
Structure (Isomer B)		(U.S. EPA/OPP 2010a)
Molecular Formula	$C_{16}H_{20}FN_5$	(U.S. EPA/OPP 2010a)
Molecular Weight (MW)	301.36 (g/mol)	Master record identification number (MRID) 47443202 (U.S. EPA/OPP 2010a)
Density (20 °C)	**Pure Substance:** 1.23 g/cm^3 **Technical Substance**: 1.23 g/cm^3	(U.S. EPA/OPP 2010b)
Henry's Law Constant	2.69 x 10^{-6} [Pa x m^3/mol] at 20 °C	(U.S. EPA/OPP 2010b)
Potential Hydrogen (pH) (23 °C)	**Pure Substance:** pH = 6.5 **Technical Substance:** pH = 5.1	MRID 47443202 (U.S. EPA/OPP 2010a)
Vapor Pressure (25 °C)	**Isomer A:** 6.8 x10^{-8} Pa (5.1E-10 mmHg) **Isomer B:** 1.1 x10^{-8} Pa (8.25E-11 mmHg)	MRID 47443202 (U.S. EPA/OPP 2010a)
Water Solubility (20 °C)	**Isomer A:** pH 4: 4.4 mg/L; pH 7: 2.2 mg/L; pH 9: 2.2 mg/L **Isomer B:** pH 4: 1.7 mg/L; pH 7: 1.2 mg/L; pH 9: 1.2 mg/L	MRID 47443202 (U.S. EPA/OPP 2010a)
Dissociation Constant (pK_a)	3.5	(U.S. EPA/OPP 2010b)
Octanol-Water Partition Coefficient (K_{ow})	**Log (K_{ow})** / **K_{ow}** pH 2: 2.0 / pH 2: 100 pH 4, pH 7, pH 9: 2.8 / pH 4, pH 7, pH 9: 631	K_{ow} values based on antilog10 calculation. MRID 47443202 (U.S. EPA/OPP 2010a)
Soil Adsorption Coefficient (K_d)	9.1 mg/L	Value estimated by U.S. EPA using PRZM (U.S. EPA/OPP 2010a)
Soil Organic Carbon (OC) -Water Partition Coefficient (K_{oc})	450 L/(kg$_{oc}$)	Value estimated by U.S. EPA using SCI-GROW (U.S. EPA/OPP 2010a)

1

Parameter	Value				Reference
K_d and K_{oc}	**Soil Texture**	**Organic Carbon %**	**K_d**	**K_{oc}**	Values based on field study data submitted by registrant MRID 47443203; Attachment 2
	Sandy loam	2.0	12.8	640	
	Silt loam	2.4	14.52	605	
	Loam	1.3	8.51	655	
	Loamy sand	1.5	16.41	1094	
	Clay loam	2.3	16.75	728	
Bioconcentration Factor (BCF)	46 and 25 (low dose, 0.3 µg a.i./L, in whole and edible fish, respectively) 65 and 32 (high dose, 3.0 µg a.i./L, in whole and edible fish, respectively)				(U.S. EPA/OPP 2010a)
Photolysis in Water Half-life	3.7 days at pH 7				MRID 47443208 (U.S. EPA/OPP 2010a)
Aquatic Sediment Half-life	**Water-Sand Sediment:** 120 days at pH 7.4-8.6 **Water-Loam Sediment:** 239 days at pH 6.2-6.7				MRID 47443217 (U.S. EPA/OPP 2010a)
Soil Phototransformation Half-life	40.3 days in loamy sand at pH 5.6-6.5, OC 0.7%				MRID 47443209

Bayer is currently the sole registrant of indaziflam, including the trade formulations Esplanade 200 SC (EPA #432-1516) and Esplanade F (EPA #432-1517). The FS anticipates using these two indaziflam formulations for vegetation control programs, as described in Table 2-2. These formulations are intended for pre-emergent use for the control of undesirable vegetation with the re-establishment of desirable perennial grasses, forbs, shrubs, and trees, as permitted by the product label. Indaziflam formulation labels and Safety Data Sheets (SDS) for Esplanade 200 SC and Esplanade F are included in Appendices 1 and 2, respectively. There are several other formulations of indaziflam registered for residential and crop uses (for both pre-emergent and post-emergent applications when combined with other herbicides). Residential and crop uses are not included in this risk assessment; therefore, these formulations are not discussed.

Table 2-2: Indaziflam Formulations and Proposed Uses by the FS

Formulation	Esplanade 200 SC	Esplanade F
U.S. EPA Registration Number	432-1516	432-1517
Active Ingredient	19.05% Indaziflam	19.05 % Indaziflam

Formulation	Esplanade 200 SC	Esplanade F
Use Areas	Managed roadsides, utility corridors, hardscapes (bare ground), and conifer and hardwood production areas. Release or re-establishment of desirable perennial grasses, forbs, shrubs, and trees as permitted by the product label. Non-crop areas such as: parks and open space, wildlife management areas, recreation areas, fire rehabilitation areas, prairies, and fire breaks.	Conifer and hardwood production areas. Release or re-establishment of desirable perennial grasses, forbs, shrubs, and trees as permitted by the product label.
Treatment Type	Pre-emergent application	Pre-emergent application
Application Method	• Backpack • Ground broadcast (ATV/UTV)[1], with boom or boom-less technology), including broadcast applications on rights-of-way • Aerial application via fixed or rotary wing aircraft	• Backpack • Ground broadcast (ATV/UTV)[1], with boom or boom-less technology), including broadcast applications on rights-of-way • Aerial application via rotary wing aircraft
Application Rate	• 3.5 to 7 fl oz of product (0.046 lb to 0.091 lb a.i./acre) [2] • Target rate of 5 fl oz (0.065 lb a.i./acre) for most applications	• 3.5 to 7 fl oz of product (0.046 lb to 0.091 lb a.i./acre) [2] • Target rate of 5 fl oz (0.065 lb a.i./acre) for most applications
Application Volumes	• 10 to 100 gallons/acre for ground application • 5 to 30 gallons/acre for aerial application	• 10 to 100 gallons/acre for ground application • 5 to 30 gallons/acre for aerial application

Note: Information in Table 2-2 was provided by the FS
[1] ATV/UTV = All-Terrain Vehicle/ Utility Task Vehicle
[2] lb a.i./acre = pound of active ingredient/acre

Indaziflam (as Esplanade 200 SC) is expected to receive range and pasture use site registration by U.S. EPA/OPP in 2020-2021. This would increase the usefulness of Esplanade 200 SC for the management of invasive annual grasses, and the restoration of rangeland in the western United States. In August of 2017, Esplanade 200 SC received a Human Health Risk Assessment Emergency Exemption for use on rangeland grasses in Wyoming (U.S. EPA/OPP 2017). However, because the U.S. EPA/OPP registration process for range and pasture site use was not complete at the time the draft HHERA development, risks associated with this use are not addressed.

2.2. Application Methods

As summarized in Table 2-2, the FS anticipates using various methods to apply the indaziflam formulations Esplanade 200 SC and Esplanade F, including ground and aerial broadcast.

2.2.1. Ground Broadcast Application

The most common methods of ground application for indaziflam involve backpack (selective foliar) and boom spray (broadcast foliar) operations. In selective foliar applications, the herbicide sprayer or container is carried by backpack or all-terrain vehicle/utility task vehicle (ATV/UTV), and the herbicide is applied to selected target vegetation. To reduce the likelihood of incidental exposure, application crews should be directed not to walk through treated areas. Typically, a worker is able to treat approximately 0.5 acres/hour with a plausible range of 0.25 to 1.0 acre/hour (SERA 2014a).

Boom spraying is used in rights-of-way management and is applied on either side of the roadway using spray equipment mounted on tractors or trucks. Boom spraying is also used on meadows, open areas, and grasslands. It is estimated that approximately 8 acres can be treated in a 45-minute period (approximately 11 acres/hour). Some special truck mounted spray systems may 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) for rights-of-way treatments (SERA 2014a; USDA/FS 1989).

2.2.2. Aerial Broadcast Application

Aerial broadcast application involves the use of fixed wing aircraft or rotary wing aircraft, such as helicopters. This technique is used in areas that are not accessible by ground or are too large to efficiently cover using ground application methods. For example, steep open areas would be likely candidates for application method. The pesticide is applied using specific spray nozzles and booms that are designed to reduce drifting spray onto non-target areas. For FS risk assessments, it is estimated that approximately 40-100 acres may be treated per hour in aerial applications (SERA 2014a).

According to the indaziflam formulation labels, Esplanade 200 SC may be applied by both fixed and rotary wing aircrafts. Esplanade F may only be applied using rotary wing aircrafts (helicopters). The formulation labels for Esplanade 200 SC and Esplanade F are included in Appendices 1 and 2, respectively.

2.3. Mixing and Application Rates

For indaziflam formulations Esplanade 200 SC and Esplanade F, the labeled application rate for both formulations ranges from 0.046 to 0.091 lb a.i./acre (Table 2-2). The maximum or upper limit of this range, 0.091 lb a.i./acre, is based on the maximum cumulative rate that can be applied in a single year. For most risk assessments, only a single application rate is selected and considered in exposure assessments. Taking the most conservative approach, calculations used in the Excel workbook that accompanies this risk assessment are based on this maximum application rate (Attachment 1). This has been the standard approach used for FS when developing national risk assessments (SERA 2014a). However, the application rate can be modified by users in Worksheet A01 of Attachment 1 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 may 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 indaziflam, the higher the exposure and potential for risk.

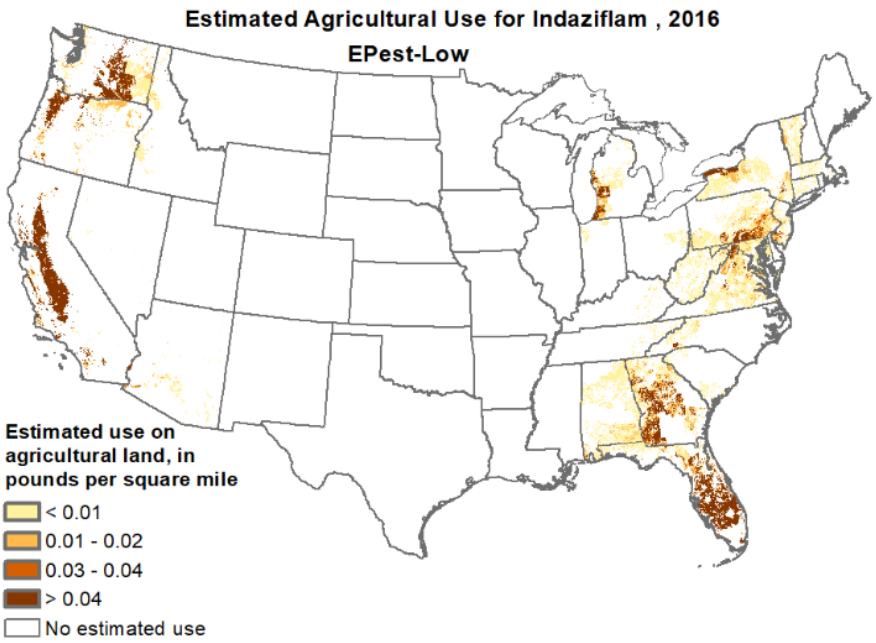
As summarized in Table 2-2, the recommended ground and aerial application volumes for Esplanade 200 SC and Esplanade F range from 5 to 100 gallons/acre. This range of application volumes was obtained from the formulation labels and is used in the Excel workbook as the lower and upper estimates (Attachment 1). The central estimate of the application volume is about 22 gallons/acre, which was derived by calculating the geometric mean of 5 and 100 gallons/acre. The central estimate is also used in this risk assessment to reflect typical or central estimates.

2.4. Use Statistics

FS risk assessments attempt to characterize the use of an herbicide or pesticide in FS programs relative to use in agricultural applications. While the use statistics do not have a direct impact on the FS risk assessments, they can be useful in determining existing exposure conditions and whether FS uses may potentially impact a specific region. FS pesticide use reports up to the year 2004 are available on the *FS FHP Pesticide Management & Coordination website*. As indaziflam is a relatively new herbicide, first registered for use in 2010, usage data are not available from the FS website and database.

Information on agricultural use is compiled by the U.S. Geological Survey (USGS) *National Water-Quality Assessment (NAWQA) Project*, 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 indaziflam is presented in Figure 2-1. These use statistics are for 2016 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 pesticides 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 indaziflam reported by the USGS are for application on crops, including grapes and orchards. The data indicate that approximately 55,000 lbs of indaziflam were used in 2016 and use has steadily increased since registration (USGS 2016).



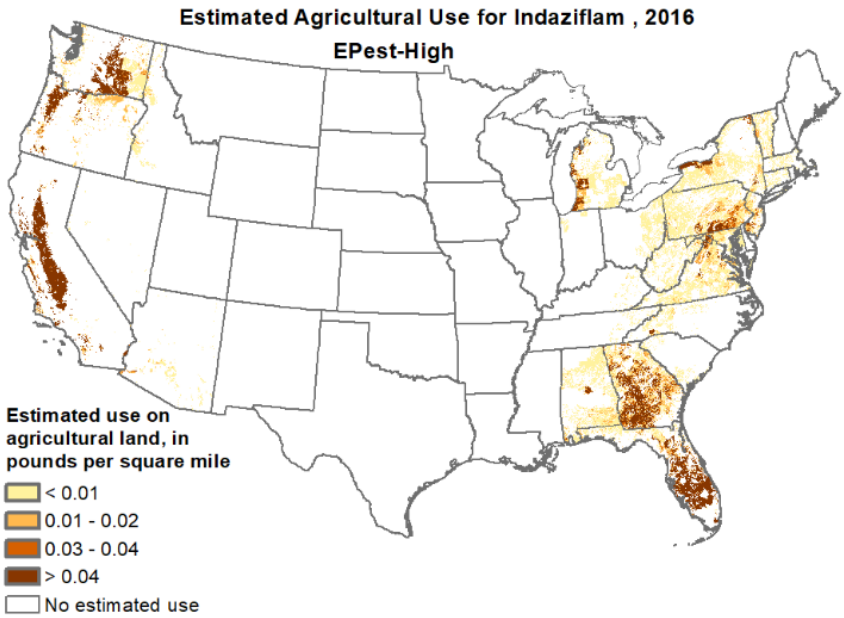


Figure 2-1: USGS EPest-Low and High Agricultural Use Estimates for Indaziflam in 2016.

3. LITERATURE SEARCH AND REVIEW

3.1. Overview

The assessment team conducted a literature search to identify fate and transport, exposure, and toxicity information on indaziflam. 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 provided by Bayer.

3.2. Open Literature

3.2.1. Data Search and Collection

The assessment team conducted a literature search 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. The literature search plan included a list of search terms, potential sources of information (e.g., databases, secondary sources, etc.), and search limits to help define the search strategy and contribute to the effectiveness of the search process. The initial search terms were designed to be broad enough to capture a comprehensive list of relevant records before narrowing the search using other search terms and/or limiting terms. Search terms included the chemical name, synonyms, trade names, and CASRNs. When needed, searches were refined using limiting terms such as the publication date (e.g., 1965 to present) or language (e.g., English).

The assessment team used various databases and internet search tools for the literature search, including but not limited to U.S. EPA's Pesticide Chemical Search, the National Library of Medicine's (NLM's) TOXLINE database, USDA's National Agricultural Library database (AGRICOLA), Thomson Reuters Web of Science database, and Google Scholar. Both peer-reviewed literature and gray literature (i.e., unpublished studies, conference proceedings, theses and dissertations, etc.) were identified during the initial literature search. Table 3-1 includes a list of the search terms and sources that were used.

Table 3-1: Indaziflam Literature Search Methods

Topic Areas	Search Terms/Keywords	Sources/Databases
Physical and chemical properties	• Chemical terms (include CASRNs and synonyms) • Trade names	• U.S. EPA's Pesticide Chemical Search • USDA Agricultural Research Service (ARS) Pesticide Database • NLM Hazardous Substances Data Bank (HSDB) • NLM Toxline • NLM ChemIDPlus • U.S. EPA Estimated Programs Interface Suite™ (EPI-Suite)

Topic Areas	Search Terms/Keywords	Sources/Databases
Use	• Chemical terms (include CASRNs and synonyms) • Trade names	• SDS • Product label • FS National and Regional Reports • USGS NAWQA (Agricultural Pesticide Use)
Fate and transport	• Chemical terms (include CASRNs and synonyms) • Trade names • Narrower keywords: absorb; absorption; accumulation; adsorp; aerob*; anaerob*; analy*; BCF; bioaccumulat*; bioavail*; bioconcentrat*; biodegrad*; fate; groundwater; leach; metaboli*; migrat*; release; surface water; transport; volatil*; water	• U.S. EPA's Pesticide Chemical Search • USDA ARS Pesticide Database • NLM HSDB • NLM Toxline • NLM ChemIDPlus • U.S. EPA EPI-Suite
Exposure	• Chemical terms (include CASRNs and synonyms) • Trade names • Narrower keywords: aquatic; biomoni*; dermal; drinking water; exposure; fish; groundwater; ingestion; inhal*; plants; release; skin; surface water; terrestrial*; water; worker; wildlife	• PubMed • U.S. EPA's Pesticide Chemical Search • U.S. EPA ECOTOX • U.S. EPA Integrated Risk Information System (IRIS) • U.S. EPA Health & Environmental Research Online (HERO) • NLM HSDB • NLM Toxline • USDA AGRICOLA • Web of Science • Science Direct • Agency for Toxic Substances and Disease Registry (ATSDR) database • International Programme on Chemical Safety (IPCS) INCHEM • Google Scholar • Google Books

Topic Areas	Search Terms/Keywords	Sources/Databases
Human health and ecological hazards	• Chemical terms (include CASRNs and synonyms) • Trade names • Narrower keywords: acute; aquatic; cancer; carcinog*; chronic; dermal; disease*; endocrine; endpoint*; epidemiolog*; hazard; ingestion; inhal* immun*; in-vitro; in-vivo; female; fetal; metabolite*; mortality; nervous; oral; reproductive; respiratory; terrestrial; toxic; toxicolog*; vulnerable*; wildlife	• PubMed • U.S. EPA's Pesticide Chemical Search • U.S. EPA ECOTOX • U.S. EPA Integrated Risk Information System (IRIS) • U.S. EPA Health & Environmental Research Online (HERO) • NLM HSDB • NLM Toxline • USDA AGRICOLA • Web of Science • Science Direct • Agency for Toxic Substances and Disease Registry (ATSDR) database • International Programme on Chemical Safety (IPCS) INCHEM • Google Scholar • Google Books

* Truncated terms. An asterisk (*) is placed at the end of a string of characters to search for all terms that being with that string.

Following the database search, the assessment team imported the references into *Zotero*, which is a reference management software used to collect, organize, and share bibliographic data. This included saving the abstracts and full-text articles, which helped facilitate screening and review of the references obtained. Each reference was also assigned a unique identification number (UIN) to help better organize and find the references in Zotero. A total of 315 references were identified through database searching or other sources during the open literature search process. Once duplicates were removed in Zotero, a total of 153 references were retrieved and selected for further evaluation. These references consisted of published articles, technical reports, presentations, conference proceedings, and others.

3.2.2. Data Screening and Review

The assessment team screened the 153 references identified during the literature search for relevance and categorized the references using exclusion criteria developed and submitted to the FS for approval on September 14, 2018. The first step involved screening of the titles and abstracts to determine if the references were relevant to indaziflam. The team also screened titles and abstracts 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 and includes the codes used to document the reasons for excluding studies.

Of the 153 references that were screened, the assessment team selected 124 references for further review prior to including the data in the HHERA. This involved reviewing the full-text articles to determine the quality and acceptability of the references. During this stage, 102 references were excluded because they did not meet the criteria established for indaziflam. The team reviewed and

used 22 open literature studies in the risk assessment that were not reported as registrant study submittals. The studies are referenced throughout the report and included in Section 7.

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 3-1. 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.

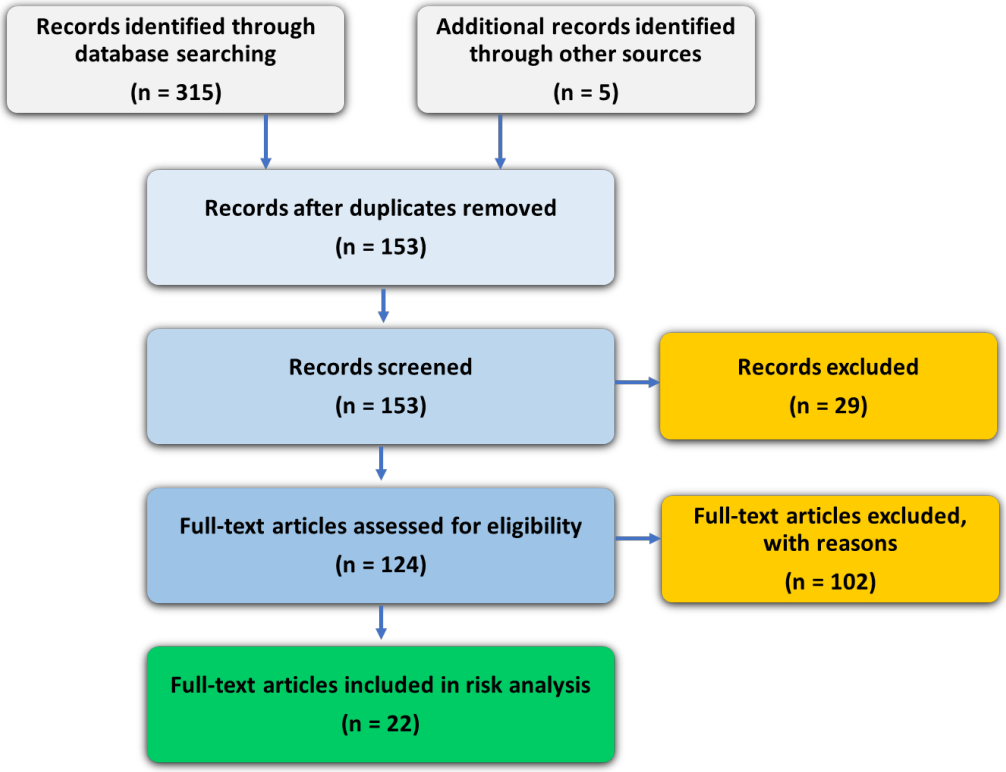


Figure 3-1: Modified PRISMA Flow Diagram for Documenting Literature Search Results

3.3. U.S. EPA Pesticide Risk Assessments and Other Sources

3.3.1. U.S. EPA Pesticide Risk Assessments

FS HHERAs typically rely on risk assessments and summary documents developed by U.S. EPA/OPP during the pesticide registration process. Unless there is a compelling reason to do otherwise, FS risk assessments defer to the most recent assessments developed by the U.S. EPA/OPP. U.S. EPA/OPP evaluates potential human health and ecological impacts based on a wide range of laboratory and field studies, which are mostly prepared and submitted by the registrant.

U.S. EPA/OPP has unrestricted access to studies submitted by registrants in support of pesticide registrations and has a detailed program for evaluating and classifying the quality of these studies. U.S. EPA/OPP records the detailed evaluations of submitted studies as Data Evaluation Records

(DERs). The complexity of DERs vary according to the nature and complexity of the registrant studies, and each DER involves an independent assessment of the study to ensure that U.S. EPA Guidelines[4] are followed and that the results are recorded accurately. In many instances, the U.S. EPA/OPP will reanalyze raw data from the registrant-submitted study as a check of data analyses. In addition, each DER undergoes a series of internal reviews prior to being finalized.

This HHERA is based largely on research studies submitted by the registrant (Bayer Environmental Services) to U.S. EPA/OPP to support the registration of indaziflam in 2010. The DERs prepared by the U.S. EPA/OPP for indaziflam were requested and obtained from a representative at Bayer. Specifically, Bayer provided 148 DERs and two supporting documents for the fate and transport, human health, and ecological studies to support this HHERA.

3.3.2. Other Published Information

The assessment team also searched several other sources of secondary information during the preparation of the indaziflam HHERA. These sources included the World Health Organization (WHO) and California EPA (CalEPA). Both WHO and CalEPA conduct reviews on pesticides and industrial chemicals. The team also searched the EXtension TOXicology NETwork, (EXTOXNET) database, which contains toxicological information on pesticides. EXTOXNET is maintained through a cooperative effort of the University of California-Davis, Oregon State University, Michigan State University, Cornell University, and the University of Idaho. However, these secondary sources did not include information regarding indaziflam.

3.3.3. Citations and References

As a convention for this risk assessment, open literature studies are cited within the text using standard author and date designations. If DERs are referenced and used as the basis of a U.S. EPA/OPP risk assessment, then the unique Master Record Identification (MRID) number designation is included along with the U.S. EPA/OPP risk assessment document citation. An MRID number is assigned to each study submitted by a registrant to U.S. EPA/OPP. The studies submitted by the registrant in support of indaziflam registration are listed in U.S. EPA's fact sheet for indaziflam (U.S. EPA/OPP 2010c).

A full list of references that are cited in this HHERA is provided in the Section 7. This includes open literature studies selected for risk analysis, U.S. EPA/OPP risk assessments, and other relevant reference documents.

[4] Data Evaluation Record Templates for various tests can be found *at https://www.epa.gov/pesticide-registration/oecd-data-evaluation-record-templates* and data requirements are listed at *https://www.epa.gov/pesticide-registration/data-requirements-pesticide-registration*.

4. FATE AND TRANSPORT IN THE ENVIRONMENT

The following sections provide an overview on the fate and transport of indaziflam in the terrestrial and aquatic environments. Fate and transport considerations are critical to understanding potential exposures for both human and ecological receptors. This is not intended to be a comprehensive analysis on fate and transport, but rather, a brief summary of available information that provides context to the FS and BLM for use of indaziflam. The team's primary source of information on fate and transport of indaziflam is U.S. EPA's ecological risk assessment (U.S. EPA/OPP 2010a); however, the open literature was also reviewed. Fate and transport properties, such as half-life and bioconcentration factors, were used in the risk assessment to estimate exposures.

4.1. Terrestrial Environment

Indaziflam is marketed as a pre-emergent herbicide that requires "activation" in the soil column by rain fall (minimum 0.25 inches) so that the chemical becomes incorporated into the soil matrix. Manufacturer's instructions generally instruct users not to reapply the product but every 6 to 12 months. For example, Esplanade 200 SC repeated applications must not additively exceed the maximum label rate (10 fl oz per acre) during any 12-month period It is possible that indaziflam can prevent germination of annual grasses for multiple years if the conditions are favorable such as adequate but not excessive rainfall, higher soil organic content and adequate incorporation of the chemical into the soil matrix following application leading to adsorption on the soil particles. Mobility and persistence of indaziflam in the soil column is influenced by numerous factors including soil type, soil texture (i.e., clay, sand, silt), rainfall, temperature, organic matter content, and soil pH. Indaziflam is classified as a "moderately mobile to mobile" compound in soil (K_{oc} <1000 mL/g organic carbon) (U.S. EPA/OPP 2010a). In aerobic soils, it is moderately persistent (half-lives >150 days), and persistent in anaerobic soil with half-lives greater than one year.

Gonzalez-Delgado et al (2015) reported that indaziflam is a weak acid and anionic at soil pH values of 5.4 and above; however, after further review of the literature and consideration of the structure of indaziflam, the compound is actually a base that exists as a neutral species under most soil conditions (Trigo et al 2014). The dissociation constant (pKa) of 3.5 (see Table 2-1) refers to a protonated species dissociating to a neutral species. An understanding of the anionic (negative charge) or cationic (positive charge) nature of the molecule is important for understanding mobility in soil. Anionic species do not adsorb strongly to soil surfaces and possess higher mobility than neutral species because soil surfaces are generally negatively charged. A speciation diagram of indaziflam clearly indicates that the neutral form is predominant at most soil pH values, but under acidic conditions the protonated species may exist as a conjugate acid, and should therefore adsorb strongly to soil.

Following application, indaziflam is not likely to volatilize, not be transported via atmospheric processes nor be transmitted through the vadose zone (i.e., volatilize) if buried in the subsurface (U.S. EPA/OPP 2010a). Therefore, its dissipation in the environment takes place primarily through degradation into metabolites and leaching through the soil column from surface water infiltration. Esplanade has good photo stability meaning minimal breakdown on the soil surface upon exposure to sunlight. A soil phototransformation half-life of 40.3 days in loamy sand (pH 5.6-6.5, 0.7% organic carbon) has been reported (MRID 47443209).

Field dissipation half-lives were calculated for indaziflam by the registrant and ranged from 9.3 to 69.3 days. These reported half-lives were shorter than half-lives calculated under laboratory conditions (i.e. 36 to 178 days). Thus, these results showed more rapid dissipation of indaziflam under field conditions compared to laboratory degradation studies. The reported indaziflam dissipation half-lives for the total soil profile (0-120 cm) did not significantly differ from the top 15 cm in field and laboratory tests. The percent carryover for indaziflam plus residues of concern from year to year ranged from 0.6 to 17%; total carryover for all residues for the entire profile ranged from 2.2 to 34% (U.S. EPA/OPP 2010a).

In addition, the eight field test sites were sampled and analyzed for indaziflam and its primary known transformation and environmental metabolites (indaziflam-carboxylic acid, triazine-indanone, fluoroethyldiaminotriazine (FDAT), indaziflam-hydroxyethyl, and indaziflam-olefin). For all dissipation studies, the limit of detection (LOD) for parent indaziflam and its transformation products was 0.3 ng/g and the limit of quantitation (LOQ) was 1.5 ng/g. All studies include a substantial number of detections of indaziflam and/or its transformation products at levels between the LOD and the LOQ, which are considered estimated detections. At the end of the study period (545 days post-application), both indaziflam and its major environmental metabolites were detected in the deepest sampled soil strata for all test plots. Other experiments have reported that the leaching depth of indaziflam is positively correlated with the application rate and rainfall amount (Jhala and Singh 2012; Jhala et al. 2012). The primary transformation products detected in the field studies were FDAT, triazine-indanone, and indaziflam-carboxylic acid. These compounds were detected in all field tests and were primarily restricted to the 0-15 cm range. However, the field studies consistently reported detections of FDAT at depths of 60-75 cm, and 45-60 cm (U.S. EPA/OPP 2010a). Several studies found that the major degradants of indaziflam may be more mobile than the parent compounds and may have a greater potential to leach though the soil column (MRID 47743301 and 47743302).

4.2. Aquatic Environment

4.2.1. Surface Water and Sediments

Indaziflam is expected to be persistent in aerobic (half-lives >200 days) and anaerobic (stable) aquatic environments (U.S. EPA/OPP 2010b). However, in clear shallow water, indaziflam is subject to aqueous photolysis, with a measured half-life of <5 days (U.S. EPA/OPP 2010b).

4.2.2. Aquatic Organisms

Compounds in aquatic environments may be concentrated or partitioned from surrounding water into aquatic organisms. Generally, 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 body weight (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.

The U.S. EPA/OPP requires experimentally derived BCFs as part of the registration process for new pesticides. A flow-through bioconcentration study with bluegill sunfish (*Lepomis macrochirus*) was

conducted by the registrant. The fish were exposed to indaziflam for 26 days, followed by a 14-day depuration period. The test results indicated that the fish did not retain indaziflam. BCF values less than 1000 do not trigger further evaluation of bioaccumulative compounds [64 Fed. Reg. 60194-60204 (November 4, 1999)]. The study DER reported BCFs for whole fish, edible, and non-edible fish tissues of 46 L/kg, 25 L/kg, and 79 L/kg, respectively, in low-dose ambient water exposures (0.30 ug/L). Reported BCFs for high-dose ambient water exposures (3.0 ug/L) for whole fish, edible, and non-edible fish tissues are 67 L/kg, 36 L/kg, and 122 L/kg, respectively. Because the reported BCF values for indaziflam are less than 1,000 L/kg, further evaluation of bioaccumulation in fish tissue was not triggered for evaluation by U.S. EPA (U.S. EPA/OPP 2010a).

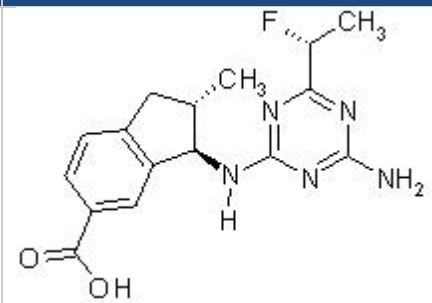
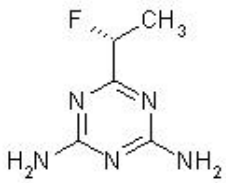
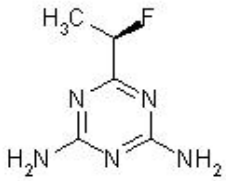
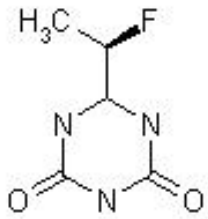
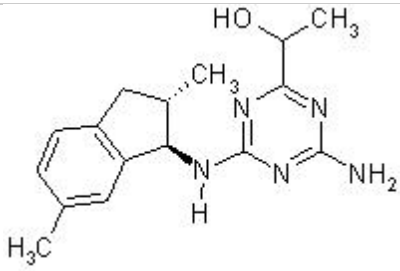
4.3. Environmental Metabolites

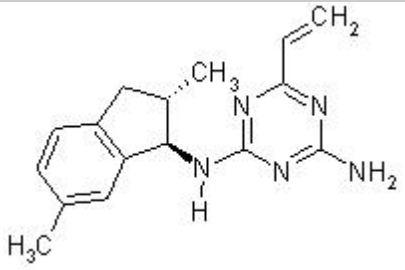
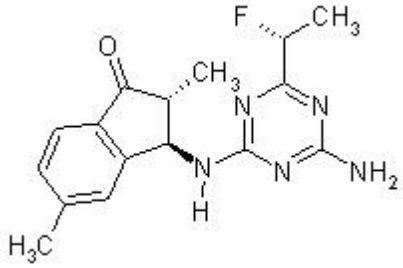
Environmental metabolites refer to compounds that may be formed in the environment by any of several biological or chemical processes, such as the breakdown in soil or water by chemical or biotic forces, or breakdown by sunlight (photolysis). The primary known environmental metabolites of indaziflam include indaziflam-carboxylic acid, FDAT, indaziflam-hydroxyethyl, indaziflam- olefin, and triazine-indanone (U.S. EPA/OPP 2010a). Information, including chemical naming nomenclature and chemical formulas, on these environmental metabolites is presented in Table 4-1.

U.S. EPA performed a preliminary review of the available data on environmental metabolites for purposes of determining residues of concern for drinking water (U.S. EPA/OPP 2010b). U.S. EPA identified the following environmental metabolites of indaziflam to be of concern for drinking water: triazine indanone, indaziflam-carboxylic acid, FDAT, dihydroamino triazine, indaziflam-hydroxyethyl, and indaziflam-olefin (U.S. EPA/OPP 2010b). Except for FDAT, these metabolites are assumed to have comparable toxicity to the parent compound (indaziflam) due to structural similarity (i.e. dual ring). FDAT is not expected to be more toxic than the parent compound based on FDAT's non-neurotoxic mode of action (MRID 47443314) (U.S. EPA/OPP 2010b). In addition, eco-toxicity data submitted to U.S. EPA showed that indaziflam-olefin and indaziflam-hydroxyethyl are similar in toxicity to indaziflam based on studies using duckweed (*Lemna gibba*) and green algae while indaziflam-hydroxyethyl, FDAT, and triazine indanone demonstrate toxicities at magnitudes 2 to 7 times less than that of the parent compound (U.S. EPA/OPP 2010a). Section 6.1.3.4 provides more information on the specific toxicity tests for aquatic plants.

Because the metabolites of indaziflam are not expected to be more toxic than the parent compound, (only comparable or less) risk assessments on the metabolites have not been completed. However, since indaziflam and its metabolites are persistent in terrestrial and aquatic environments, the metabolites could contribute to the herbicidal activity of indaziflam (U.S. EPA/OPP 2010a). According to the registrant, the toxicity of the metabolites of indaziflam to aquatic plants is decreased, as is the herbicidal activity, when compared to the parent compound, indaziflam.

1 **Table 4-1: Major Environmental Metabolites of Indaziflam**

Transformation Product/Code/"Short Name"	Chemical Name and Formula	Chemical Structure
Carboxylic Acid	**IUPAC Name:** (2S,3R)-3-({4-Amino-6-[(1R)-1-fluoroethyl]-1,3,5-triazin-2-yl}amino)-2-methylindane-5-carboxylic acid **Formula:** $C_{16}H_{18}FN_5O_2$	
Diaminotriazine or Fluoroethyl-diaminotriazine (FDAT)	**IUPAC Name:** (R)-6-(1-fluoroethyl)-[1,3,5]triazine-2,4-diamine **Formula:** $C_5H_8FN_5$	 
Fluoroethyl-triazinanedione (ROI1)	**IUPAC Name:** 6-[(1R)-1-fluoroethyl]-1,3,5-triazinane-2,4-dione **Formula:** $C_5H_3FN_3O_2$	
Hydroxyethyl	**IUPAC Name:** 1-{4-Amino-6-[(1R,2S)-2,6-dimethyl-2,3-dihydro-1H-inden-1-ylamino]-1,3,5-triazin-2-yl}ethanol **Formula:** $C_{16}H_{21}N_5O$	

Transformation Product/Code/"Short Name"	Chemical Name and Formula	Chemical Structure
Olefin	**IUPAC Name:** N-[(1R,2S)-2,6-dimethyl-2,3-dihydro-1H-inden-1-yl]-6-vinyl-1,3,5-triazine-2,4-diamine **Formula:** $C_{16}H_{19}N_5$	
Triazine Indanone	**IUPAC Name:** N-[(1R,2S)-2,3-Dihydro-2,6-dimethyl-3-oxo-1H-inden-1-yl]-6-[(1R)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine **Formula:** $C_{16}H_{18}FN_5O$	

1 Source: Modified from (U.S. EPA/OPP 2010a); Table A-1, pp 109-115.

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. Most of the available information on indaziflam is from an extensive set of human health risk assessments completed by U.S. EPA/OPP in 2010 and 2017. These risk assessments are based on original toxicity test reports submitted to U.S. EPA/OPP by the registrant to support the registration of indaziflam. 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 with the results recorded as DERs. In these risk assessments, the U.S. EPA/OPP Health Effects Division (HED) and Environmental Fate and Effects Division (EFED) characterize the toxicology database for indaziflam as complete for the selection of risk assessment endpoints. The toxicology database for indaziflam is also described as having a high degree of scientific quality with toxicity well characterized for developmental, reproductive, immunologic, and neurological effects (U.S. EPA/OPP 2010b).

5.1.2. Mechanism of Action

The mechanism of action refers to the specific biochemical interaction through which a substance produces an effect. The specific mechanism of action of indaziflam in mammals is not discussed in the open literature or U.S. EPA risk assessments. The phytotoxicity of indaziflam is due to inhibition of cellulose biosynthesis (CBI herbicide). Indaziflam acts in plant cells and tissues where cellulose synthesis is actively taking place (germinating weed seeds and developing seedlings); examples include actively growing meristematic tissues, dividing cells, expanding cells, and growing roots. Therefore, fully developed leaves, tissues and plant organs are not or minimally affected by the compound since cell wall formation already has been completed, and no new cellulose synthesis is required (Health Canada 2011).

Cellulose is synthesized at the plasma membrane by large Cellulose Synthase A (CESA) protein complexes that directly release the developing cellulose polymers into the cell wall (Sebastian et al., 2017). While there is limited research on the actual mechanism of action in plants, studies were conducted to determine whether indaziflam has the same mechanism of action as other CBI herbicides, including isoxaben and dichlobenil (Sebastian et al., 2017). Studies on isoxaben and dichlobenil show depletion or immobilization of CESA proteins from the plasma membrane. In contrast, indaziflam has been shown to increase the density of CESA particles at the plasma membrane and reduce CESA particle velocity by approximately 65%, resulting in inhibition of polymerization. In addition, the increase in density results in a decrease in the colocalization between the microtubules and the CESA in the region near the root apical hook (Brabham et al. 2014). Results of these studies confirm that indaziflam inhibits cellulose biosynthesis in plants in a different manner than other CBI herbicides. Indaziflam was also found to be phytotoxic on both monocotyledonous (monocots) and dicotyledonous (dicots) plants, which is unusual because other CBI herbicides are more active on dicots (Sebastian et al., 2017). This herbicidal mechanism of action, however, is specific to plants and not relevant to potential human health effects.

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 indaziflam exposure and provides a general discussion about absorption, metabolism, absorption, and excretion. 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 the breakdown in soil or water or breakdown by sunlight (photolysis). *In vivo* and environmental metabolites are discussed in more detail in SERA 2014a.

Extensive and rapid metabolism of the parent compound provides important toxicokinetic information; however, this does not necessarily indicate a low toxicity substance as the metabolites may be as or more toxic than the parent compound. In addition, a fast metabolism may result in a rapid accumulation of toxic compounds before excretion. This risk assessment accounts for the relationship between toxicity, metabolism, and excretion of the parent compound and metabolites.

No human data on the pharmacokinetics on indaziflam were identified; therefore, pharmacokinetics data obtained from animal studies were used. The U.S. EPA/OPP required a standard metabolism study in rats as part of the pesticide registration process. Two metabolism studies were submitted using indaziflam, including a Tier 1 and Tier 2 metabolism and pharmacokinetics study in rats. Both studies were conducted using Guideline 870.7485 (MRID 47443312 and MRID 47743418) (U.S. EPA/OPP 2010b). The data reviewed below were taken from these studies. Note that use of animal data may add some uncertainty to the human health risk assessment. An *in vivo* dermal absorption study in the rat and *in vitro* dermal absorption studies in the rat and human were submitted to U.S. EPA. The *in-vivo* dermal absorption study (MRID 47743420) was conducted according to Standard Test Guideline 870-7600 and the in vitro studies (MRID 47743419) followed a non-guideline study protocol. In these studies, the total absorbed dose decreased with increasing exposure concentrations of indaziflam indicating saturation of skin penetration with increasing dose. Rat skin was also found to be 3.8 to 10.7 times more permeable than human skin (MRID 47743419). Based on the results of the *in vivo* and *in vitro* dermal absorption tests, an estimated human dermal absorption factor (DAF) of 7.3% was obtained (U.S. EPA/OPP 2010b).

5.1.3.1. Distribution and Metabolism

The U.S. EPA/OPP required a standard metabolism study in rats as part of the pesticide registration process. Two metabolism studies were submitted using indaziflam, including a Tier 1 and Tier 2

metabolism and pharmacokinetics study in rats. Both studies were conducted using Guideline 870.7485 (MRID 47443312 and MRID 47743418) (U.S. EPA/OPP 2010b)).

In the Tier 1 study, male rats were given a single oral dose of either ^{14}C indane-labeled or triazine-labeled indaziflam at 11.5 to 14.98 mg a.i./kg bw (MRID 47443312). Indaziflam absorption was nearly complete (> 90% bioavailability). Radioactivity was found in bile within one-hour postdosing with most (approximately 90% of administered dose) excreted by 24 hours post dose. Measured tissue levels of radioactivity three days after the administered dose were low (0.2%), indicating minimal retention of indaziflam. The highest levels of radioactivity were observed in the gastrointestinal tract, liver, kidney, skin and thyroid (U.S. EPA/OPP 2010b). Excretion was primarily fecal at 62-70% of the administered dose and 35-38% of the administered dose was identified in urine.

Oxidative metabolism was the major pathway for the biotransformation of indaziflam, with the primary metabolite being carboxylic acid. Carboxylic acid was found in urine, bile, and feces. Other metabolites were observed at lower concentrations, but the profile varied among the dose groups. These metabolites included the 3-hydroxyindane acid epimer, diaminotriazine, and 3-ketohydroxymethyl metabolites (U.S. EPA/OPP 2010b).

In the Tier 2 study, rats were administered single gavage doses in three types of studies, including a low dose mass balance study in females and a high dose balance study in males (MRID 47743418). Females were administered ^{14}C-indane-labeled indaziflam at 4.8 mg/kg bw or ^{14}-triazine-labelled indaziflam at 8.8 mg/kg bw) and males were administered ^{14}C-indane-labelled indaziflam at 559 mg/kg bw or ^{14}-triazine-labelled indaziflam at 723 mg/kg bw. A third study of plasma pharmacokinetics administered ^{14}-indane labelled indaziflam at 2.9 and 13.7 mg/kg bw in females and males, respectively, and triazine-labelled indaziflam at 13.2 and 16.3 mg/kg bw in females and males, respectively.

In both studies, absorption of indaziflam was rapid with radioactivity detected in blood within five minutes of administration. Peak blood concentrations were observed between 40 to 60 minutes after dosing and rapidly decreasing thereafter. Females showed slightly higher absorption than males; however, females were given a high dose. Excretion was also rapid with greater than 87% excreted within 24 hours. Excreted indaziflam was equally distributed between urine and feces in females. Radioactivity was not retained at significant levels in tissues. As with the Tier 1 study, carboxylic acid[5] was the major metabolite in both high dose males and low dose females. The metabolite was found in urine and feces. Other metabolites present at > 5% of administered dose included 3-hydroxyindane acid and dihydroxy in low dose females and hydroxyethyl acid in the high dose males (U.S. EPA/OPP 2010b).

Results of the Tier 1 and Tier 2 studies demonstrate that oral bioavailability of indaziflam is high and excretion is rapid. The primary metabolite is carboxylic acid, which is considered to have comparable toxicity to the parent compound due to its similar structure (i.e. dual ring). Other compounds were identified as major metabolites and assumed to have comparable toxicity to indaziflam. These

[5] See Section 4.3 for complete chemical names and formulas for metabolites.

metabolites include 3-hydroxyindane acid, 3-hydroxyindane acid epimer, dihydroxy, and hydroxyethyl acid (U.S. EPA/OPP 2010b).

5.1.3.2. Dermal Absorption

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 on 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 dermal absorption 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}).

Details regarding the derivation of the K_a and K_p rates for indaziflam are provided in the subsections below. For additional information on the dermal exposure scenarios and absorption rates used by the FS, see SERA 2014a.

5.1.3.2.1. First-Order Dermal Absorption

The registrant submitted an *in vivo* dermal absorption study in rats and *in vitro* dermal absorption studies in rats and humans to U.S. EPA/OPP. Based on data from these studies, U.S. EPA/OPP (2010b) estimated a DAF of 7.3% for short- and intermediate-term exposures. For long-term exposures, U.S. EPA noted that this scenario was not required given that "exposure is seasonal; long-term occupational exposure scenarios are not anticipated" (U.S. EPA/OPP 2010b). It is important to note that the absorption factor referenced by U.S. EPA is not a first-order dermal absorption rate coefficient. It refers to the percent absorbed over a workday, which is typically 8 hours. If considering a first-order absorption, an absorption factor of 7.3% is equivalent to a first-order dermal absorption rate coefficient of about 0.0095 hour^{-1} [ln(1-0.0.73) ÷ 8 hours ≈ 0.009475 hour^{-1}].

As discussed in SERA 2014a, FS risk assessments typically use quantitative structure activity relationships (QSAR) for estimating dermal absorption rate coefficients. The QSAR method is based exclusively on dermal absorption data from studies in humans involving numerous chemicals. As detailed in Worksheet B03b of Attachment 1, the QSAR method yields estimated dermal absorption rate coefficients for indaziflam of about 0.0028 (95% Confidence Interval: 0.0014 to 0.0058) hour^{-1}using a K_{ow} value of 631 and a molecular weight of 301.36 g/mole. These rates are used to estimate dermal exposures for workers and the general public.

5.1.3.2.2. Zero-Order Dermal Absorption

Exposure scenarios involving the assumption of zero-order dermal absorption require an estimate of dermal permeability (K_p) in units of cm/hour. No experimental data were found on the dermal permeability rate of indaziflam. In the absence of experimental data, FS risk assessments use a QSAR algorithm developed by U.S. EPA (SERA 2014a). The U.S. EPA algorithm is derived from an analysis of 95 organic compounds with K_{ow} values ranging from 0.0056 to 309,000 and molecular weights ranging from 30 to 770 g/mole (U.S. EPA/ORD 2007). These ranges of K_{ow} values and molecular weights encompass the estimates of the corresponding values for indaziflam. As detailed in Worksheet B03a of Attachment 1, the estimated dermal permeability (K_p) is approximately 0.0025 (95% Confidence Interval: 0.0017 to 0.0038) cm/hour.

5.1.3.3. Excretion

Excretion rates are typically not used quantitatively in FS risk assessments. However, excretion half-lives 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 half-life (T_{50}) [$k = \ln(2) \div T_{50}$]. 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 Nth dose ($X_{N\ Dose}$) relative to the body burden immediately following the first 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-lives are most appropriate for estimating steady-state body burdens.

Based on the studies discussed in Section 5.1.3.1, approximately 87-90% of the administered dose was eliminated within 24 hours after dosing (U.S. EPA/OPP 2010b). Using a first-order approximation, these excretion patterns correspond to elimination rates (k) of about 2 day^{-1} [$-\ln(1 - 0.87) \div 1$ day ≈ 2.040 day^{-1}] to 2.3 day^{-1}. Substituting the lower rate coefficient into the equation above, the estimated plateau for indaziflam (parent compound and metabolites) is approximately 1.16 [$1 \div (1 - e^{-2}) \approx 1.156$]. Therefore, over very prolonged periods of exposure, the maximum increase in the body burden for indaziflam should be no more than a factor of approximately 1.16 (i.e., there is virtually no increased body burden over the long term).

5.1.4. Acute Oral Toxicity

Acute oral toxicity studies are used to evaluate the adverse effects of a substance following oral administration of a single dose or multiple doses in a short period of time (typically 14 days or less). The results of acute oral toxicity studies are reported as time-specific LD_{50} (median lethal dose) values, which is the dose, given all at once, that causes death to 50% of a group of test animals. .

These values are expressed in terms of weight of test substance per unit weight of test animal (mg/kg) and are used by U.S. EPA/OPP to categorize potential risks. Specifically, U.S. EPA/OPP uses a toxicity category ranking system for responses ranging from Category I (most severe response) to Category IV (least severe response). For acute oral toxicity, Category I refers to compounds with oral LD_{50} values of ≤50 mg/kg, while Category IV refers to compounds with oral LD_{50} values of > 5,000 mg/kg. 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).

As part of the registration process for indaziflam, two acute oral toxicity studies were submitted by the registrant to U.S. EPA/OPP, and results from this study are presented on Table 5-1 (MRID 47443280 and MRID 47443281). Appendix 2, Table A2-1 provides additional information about these studies.

Both studies identify an LD_{50} value > 2,000 mg/kg for female rats. This value is lower than the LD_{50} values of > 5,000 mg/kg bw for rats that are listed in the SDSs for Esplanade 200 SC and Esplanade F. In these studies, the LD_{50} valued reported is greater than the highest dose tested. Based on this acute oral LD_{50} value, U.S. EPA classified indaziflam as Category III in rats for technical grade indaziflam, which is "relatively nontoxic" according to the classification system used by U.S. EPA/OPP.

Table 5-1: Acute Oral Toxicity Studies for Indaziflam

Test Species	Test Substance	Result	Toxicity Category	Reference
Rats	AE 1170437 94.5% a.i.	LD_{50} > 2,000 mg/kg bw	III	MRID 47443280
Rats	AE 1170437 95.7% a.i.	LD_{50} > 2,000 mg/kg bw	III	MRID 47443281

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 over a longer period of time. In addition, some repeated dose studies are designed to detect specific toxic endpoints, such as reproductive and neurological effects (SERA 2016a). 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. This HHERA uses NOAEL and LOAEL values as determined by U.S. EPA/OPP to quantify risk.

Subchronic oral toxicity studies for indaziflam are available in rats (MRID 47443287), mice (MRID 47443288), and dogs (MRID 47443289). These studies were submitted to U.S. EPA/OPP in support of the registration of indaziflam and were conducted in accordance with U.S. EPA Standard Testing Guideline 870.3100 for rodents and 870.3150 for non-rodents. Standard chronic toxicity studies are also available in rats (MRID 47443296) and dogs (MRID 47443294 for the main study and MRID 47443295 for the dietary stability), which were conducted in accordance with the U.S. EPA Standard Testing Guideline 870.4100a for rodents and 870.4100b for non-rodents (U.S. EPA/OPP 2010b).

These studies are discussed below, and additional details of the studies are provided in Appendix 2, Table 2-2.

For the subchronic dietary study in rats, (MRID 47443287) rats were exposed for 90 days to technical grade indaziflam (98.7% a.i.) at doses of 0, 14, 338, and 689 mg a.i./kg bw/day for male and doses of 0, 16, 410 and 806 mg a.i./kg bw/day for female for 90 days. For males, a LOAEL of 338 mg a.i./kg bw/day for males was identified based on increased thyroid stimulating hormone (TSH) at week 3 (but not at week 13) and diffuse thyroid follicular cell hypertrophy at week 13; the NOAEL value was 14 mg a.i./kg bw/day. For females, a LOAEL of 806 mg a.i./kg bw/day was identified based on mortality in one rat (sacrificed *in extremis* with clinical signs, decreased motor activity, and gastric red foci), and marginally decreased body weights (also in males), and decreased food consumption in surviving females; the NOAEL value was 410 mg a.i./kg bw/day(U.S. EPA/OPP 2010b).

In the subchronic dietary study in mice (MRID 47443288), male and female mice (10 mice/sex/dose) were exposed to technical grade indaziflam (96.5% a.i.) at doses of 0, 19, 91, and 218 mg a.i./kg bw/day for males and doses of 0, 23, 118, and 256 mg a.i./kg bw/day for females for 90 days. A LOAEL of 218 mg a.i./kg bw/day for males and 256 mg a.i./kg bw/day for females was observed based on increased mortality, wasted appearance (females), hunched posture in both sexes, and decreased body weight, body weight gain, and food consumption in both sexes; the corresponding NOAELs were 91 mg a.i./kg bw/day for males and 118 mg a.i./kg bw/day for females. One mortality occurred in a female rat at 1,200 ppm (256 mg/kg/day). The cause of death could not be clearly determined; however, the animal had a wasted appearance and mortality was presumed to be due to treatment (U.S. EPA/OPP 2010b).

In the subchronic study in dogs (*Cannis familiarus*), a LOAEL was observed at 15 mg a.i./kg bw/day for axonal degeneration in the brain, spinal cord, and sciatic nerve for both males and females following exposure to technical grade indaziflam (94.5-99.4% a.i.) at doses of 0, 7.5, 15, and 30 mg/kg/day by oral gavage for at least 90 days (MRID 47443288).A NOAEL of 7.5 mg a.i./kg bw/day was observed in both males and females. The study identified at 30 mg a.i./kg/day, three dogs experienced seizures on days 15, 22, and 35 of the study, and were sacrificed on the day the seizures were observed. By day 36, all remaining group animals were sacrificed. Decreased body weight gain and neuropathology were observed (U.S. EPA/OPP 2010b).

For the chronic study, rats (70 rats/sex/dose) were exposed to technical grade indaziflam (93.1%) in the diet for up to 24 months (MRID 47443296). The dietary concentrations were 0, 300, 3,000, or 10,000 ppm, which is equivalent to 0, 14, 136, 474 mg a.i./kg bw/day for males and 0, 19, 185, or 589 mg a.i./kg bw/day for females. A LOAEL of 474 mg a.i./kg bw/day was identified for males based on decreased body weight, weight gain, and food consumption. Thyroid effects were also observed and included transiently increased TSH and colloid alternation in follicular cells. A LOAEL of 185 mg a.i./kg bw/day was identified for females based on increased mortality, clinical signs of toxicity, mydriasis, and absence of papillary reflex (U.S. EPA/OPP 2010b). The NOAEL was observed for males at 136 mg a.i./kg bw/day and females at 19 mg a.i./kg bw/day.

For the chronic study, dogs were exposed to technical grade indaziflam (94.5%) in the diet for at least 12 months (MRID 47443294 and MRID 47443295). In addition to conducting the chronic toxicity study, a neurological examination was performed monthly from months 7 through 11 and

just prior to termination. Dietary concentrations were 0, 60, 225, or 450 ppm, with associated daily doses of 0, 2, 6, or 12 mg a.i./kg bw/day for males and 0, 2, 7, or 11 mg a.i./kg bw/day for females. LOAEL values of 6 and 7 mg a.i./kg bw/day were identified for males and females, respectively, based on axonal degeneration of nerve fibers in the brain, spinal cord, and sciatic nerve in both sexes, with a corresponding NOAEL of 2 mg a.i./kg bw/day for both sexes (U.S. EPA/OPP 2010b). A NOAEL of 2 mg a.i./kg bw/day was identified for both sexes. In the highest dose group of 12 and 11 mg a.i./kg bw/day in males and females, respectively, decreased body weight was observed early in the study (U.S. EPA/OPP 2010b).

For studies that provide separate NOAELs and LOAELs for males and females, the NOAELs and LOAELs are presented as the arithmetic average of the values for males and females, with all values rounded to the nearest tenth. This averaging is consistent with previous FS risk assessments (SERA 2014a). Based on the toxicity values summarized in Table 5-2 from subchronic and chronic oral toxicity studies, dogs appear to be more sensitive than either rats or mice. Based on subchronic LOAELs, dogs appear to be more sensitive than rats by a factor of about 38 (572 mg/kg bw/day ÷ 15 mg/kg bw/day ≈ 38.13). For chronic LOAELs, dogs are more sensitive than rats by a factor of about 50 (329.5 mg/kg bw/day ÷ 6.5 mg/kg bw/day ≈ 50.69).

Table 5-2: Subchronic and Chronic Oral Toxicity Studies for Indaziflam

Test Species	NOAEL Male	NOAEL Female	NOAEL Average	LOAEL Male	LOAEL Female	LOAEL Average	Reference
Subchronic Rats	14	410	212	338	806	572	MRID 47443287
Subchronic Mice	91	118	104.5	218	256	237	MRID 47443288
Subchronic Dogs	7.5	7.5	7.5	15	15	15	MRID 47443289
Chronic Rats	136	19	77.5	474	185	329.5	MRID 47443296
Chronic Dogs	2	2	2	6	7	6.5	MRID 47443294 (Main Study) MRID 47443295 (Dietary Stability)

Note: NOAEL and LOAEL are measured in mg a.i./kg bw/day.

5.1.6. Effects on the Nervous System

Exposure to any chemical may cause gross signs of toxicity, which 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).

Three neurotoxicity studies for indaziflam using rats were submitted to U.S. EPA/OPP by the registrant and were classified as "acceptable" (U.S. EPA/OPP 2010b). Of the submitted neurotoxicity studies, one is an acute neurotoxicity screening battery, one is a subchronic neurotoxicity screening battery, and the third is a developmental neurotoxicity study. Each are described in the following subsections.

Based on the studies submitted and evaluated by U.S. EPA during the registration process, the nervous system is the primary target system for indaziflam in rats and dogs. As described in Section 5.1.5, neuropathology in the dog was the most sensitive effect with degenerative effects observed in the brain, spinal cord, and sciatic nerve following both subchronic and chronic oral exposure. In the rat, histopathology of the brain and pituitary *pars nervosa* were observed following chronic exposure. Clinical signs of neurotoxicity were also observed in both species. In the acute neurotoxicity study, decreased motor activity was observed in the rat. The acute neurotoxicity study in rats was selected as the most appropriate endpoint for acute oral toxicity for U.S. EPA's risk assessment (U.S. EPA/OPP 2010b). Table 5-3 summarizes the NOAELs and LOAELs for the studies described below. Appendix 2, Table A2-3 provides additional information about these studies.

Table 5-3: Acute, Subchronic, and Developmental Neurotoxicity Studies for Indaziflam

Test Species	NOAEL Male	NOAEL Female	NOAEL Average	LOAEL Male	LOAEL Female	LOAEL Average	Reference
Acute Rats	50	50	50	100	100	100	MRID 47443310
Subchronic Rats	243.6	306.9	275.3	585.7	580.9	583.3	MRID 474433309
Developmental Rats – Maternal	--	83.8	83.8	--	432	432	MRID 47443311
Developmental Rats - Offspring	83.8	83.8	83.8	432	432	432	MRID 47443311

Note: NOAEL and LOAEL are measured in mg a.i./kg bw/day.

5.1.6.1. Acute Screening Battery

An acute neurotoxicity battery was completed for rats according to Standard Testing Guideline 870.6200a (MRID 47443310). Rats were exposed to indaziflam (93.14% a.i.) at concentrations of 0, 50, 100, and 2,000 mg/kg in corn oil via gavage. Rats were given a single dose and observed for 14 to 15 days. The LOAEL was established at 100 mg a.i./kg bw. Neurotoxic effects observed at 100 mg a.i./kg bw included decreased motor and locomotor activity in females. The NOAEL was established at 50 mg a.i./kg bw. The lower NOAEL and LOAEL observed in the acute study compared to the subchronic study is likely due to gavage versus dietary exposure routes (U.S. EPA/OPP 2010b).

5.1.6.2. Subchronic Screening Battery

A subchronic neurotoxicity screening battery was completed in rats according to Standard Testing Guideline 870.6200b (MRID 47443309). Rats were exposed to indaziflam (93.14% a.i.) at concentrations of 0, 200, 4,000, or 8,000 (male)/10,000 (female) ppm in the diet for 13 weeks. These dietary exposures are equivalent to doses of 0, 12.2, 243.6, or 585.7 mg a.i./kg bw/day for males and 0, 15.1, 306.9, and 580.9 mg a.i./kg bw/day for females. The LOAELs of 585.7 mg a.i./kg bw/day for males and 580.9 mg a.i./kg bw/day for females are based on decreased total session motor and locomotor activity in females, clinical effects observed in both sexes (tremors, repetitive chewing

motion, and perianal and lacrimal staining), decreased body weights in females, and cumulative body weight gain in both sexes. The NOAEL dose for males was 243.6 mg a.i./kg bw/day and 306.9 mg a.i./kg bw/day for females (U.S. EPA/OPP 2010b).

5.1.6.3. Developmental Neurotoxicity

A study was conducted to examine the developmental neurotoxicity in female rats (MRID 47443311). Pregnant rats were exposed to indaziflam (93.14% a.i.) in the diet at concentrations of 0, 150, 1,000, or 7,000ppm. The highest test diet concentration of 7,000 ppm was reduced to 4,000 ppm during the study. These exposure concentrations in the diet correspond to respective, average daily doses of 0, 13, 83.8 or 432 mg a.i./kg/day. The maternal LOAEL was 432 mg a.i./kg/day and the NOAEL was 83.8 mg a.i./kg/day. The maternal LOAEL is based on clinical signs of toxicity, including coarse tremors, dilated pupils, dilated pupils unresponsive to penlight, nasal staining, and repetitive chewing movements. Effects on body weight, body weight gain and food consumption were only observed in the 7,000/4,000 ppm group. Body weights were decreased on gestation day (GD) 13 and 20 (-7 to 13%), resulting in a decreased cumulative body weight gain (GD 0-20) of 42%. Effect on food consumption is unclear due to excessive feed spillage at the high dose during the first week of treatment followed by a change in feeders. Food consumption was similar to controls during GD 13-20. The offspring LOAEL was 432 mg a.i./kg/day and the NOAEL was 83.8 mg a.i./kg/day. The LOAEL is based on decreased body weights in both sexes and decreased motor activity in male pups. No other treatment-related effects were noted in the offspring (U.S. EPA/OPP 2010b).

5.1.7. Effects on the Immune System

An immunotoxicity study for indaziflam in rats was submitted by the registrant (MRID 47443313). As part of this study, rats were administered 0, 300, 3,000, 6,000 (females), or 10,000(later reduced to 6,000) (males) ppm of indaziflam (93.12% a.i. technical grade) in the diet. The study was conducted for 29 days for males and 30 days for females. Males initially receiving 10,000 ppm displayed severe body weight loss compared to controls. As a result, the dose for this group was reduced to 6,000 ppm on day 16. Immunotoxicity was not observed at doses up to 528 a.i./kg bw/day for males and 737.9 mg a.i./kg bw/day for females; therefore, a LOAEL was for immunotoxicity was not identified. This made establishing a LOAEL for immunotoxicity not plausible. The NOAELs for immunotoxicity for indaziflam to rats was identified as 528 and 737.9 mg a.i./kg bw/day for males and females, respectively (U.S. EPA/OPP 2010b). The immunotoxicity study is summarized in Table 5-4 and discussed in further detail in Appendix 2, Table A2-4.

Although there was no evidence of immunotoxicity, clinical signs of toxicity were observed in rats during the immunotoxicity study. These effects included tremors, abnormal gait, pallor, and hunched back, and decreased body weight and weight gain in males and females. In addition, there was one mortality of a male rat in the study that was sacrificed *in extremis* with clinical signs. A LOAEL was identified for systemic toxicity at 528 and 737.9 mg a.i./kg bw/day based on the observed clinical signs of toxicity in both males and female respectively; NOAEL values were 258.8 and 334.2 mg a.i./kg bw/day for males and females, respectively. The immunotoxicity study is summarized in Table 5-4 and discussed in further detail in Appendix 2, Table A2-4.

Table 5-4: Subchronic Immunotoxicity Toxicity Studies for Indaziflam

Test Species	NOAEL Male	NOAEL Female	NOAEL Average	LOAEL Male	LOAEL Female	LOAEL Average	Reference
Immunotoxicity: Rats	528	737.9	633	N/A	N/A	N/A	MRID 47443313
Systematic Toxicity: Rats	258.8	334.2	296.5	528	737.9	633	MRID 47443313

Note: NOAEL and LOAEL are measured in mg a.i./kg bw/day.

5.1.8. Effects on the Endocrine System

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 between the dose and 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 where 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 9 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). Indaziflam 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. Section 5.1.5 and Table A2-2 provide more information on thyroid effects, including increase in thyroid stimulating hormone levels.

5.1.9. Reproductive and Developmental Effects

Three studies are available that examine the potential reproductive and developmental toxicity of indaziflam. These studies were submitted by the registrant to U.S. EPA/OPP for evaluation and were judged by U.S. EPA/OPP to be “acceptable.” Two of the studies were performed to evaluate prenatal development in rats (MRID 47443291) and rabbits (MRID 47443292) using Standard Testing Guidelines 870.3700a for rodents and 870.3700b for non-rodents. The other study focused on evaluating reproductive effects in rats over multiple generations (MRID 47443293) and was conducted in accordance with the Testing Guideline 870-3800. Each of these reproductive and developmental tests with indaziflam are discussed in the subsections below. A summary of the NOAELs and LOAELs is presented in Table 5-5 and discussed in detail in Appendix 2, Table A2-5.

Table 5-5: Reproductive and Developmental Toxicity Studies for Indaziflam

Test Species	NOAEL Male	NOAEL Female	NOAEL Average	LOAEL Male	LOAEL Female	LOAEL Average	Reference
Prenatal Development: Rats - Maternal	--	25	25	--	200	200	MRID 47443291
Prenatal Development: Rats – Fetal Developmental	25	25	25	200	200	200	MRID 47443291
Prenatal Development: Rabbits - Maternal	--	25	25	--	60	60	MRID 47443292
Prenatal Development: Rabbits – Fetal Developmental	60	60	60	> 60	> 60	> 60	MRID 47443292
Reproduction and Fertility: Rats - Parental	69.3	85.2	77.3	560.1	656.2	608.2	MRID 47443293
Reproduction and Fertility: Rats - Offspring	69.3	85.2	77.3	317.6	355.2	336.4	MRID 47443293
Reproduction and Fertility: Rats – Reproduction	69.3	85.2	77.3	317.6	355.2	336.4	MRID 47443293

Note: NOAEL and LOAEL are measured in mg a.i./kg bw/day.

5.1.9.1. Prenatal Developmental Effects

In one prenatal developmental study, rats were exposed daily to indaziflam (94.5% a.i.) by oral gavage during gestational days 6 to 20 at doses of 0, 10, 25, or 200 mg a.i./kg bw/day in 0.5% aqueous methylcellulose (MRID 47443291). No adverse effects were observed in the maternal rats at 25 mg a.i./kg bw/day. A maternal LOAEL of 200 mg a.i./kg bw/day was identified based on decreased body weight gain and food consumption. Decreased fetal body weights were observed at doses of 200 mg a.i./kg bw/day and higher. These results establish a developmental NOAEL and LOAEL of 25 and 200 mg a.i./kg bw/day for the rat, respectively (U.S. EPA/OPP 2010b, 2010c).

The second prenatal developmental study was conducted in rabbits. In this study, rabbits were exposed daily to indaziflam by oral gavage during gestational days 6 to 28 at doses of 0, 10, 25, or 60 mg a.i./kg bw/day in 0.5% aqueous methylcellulose (MRID 47443292). No adverse effects were observed in the maternal rabbits at 25 mg a.i./kg bw/day. Decreased maternal body weight gain, food consumption, and macroscopic changes in the liver were observed in the maternal rabbits at

the highest doses administered of 60 mg a.i./kg bw/day, which establishes a LOAEL of 60 mg a.i./kg bw/day. These results establish a developmental NOAEL and LOAEL of 25 and 60 mg a.i./kg bw/day for rabbits, respectively (U.S. EPA/OPP 2010b, 2010c).

5.1.9.2. Reproduction and Fertility Effects

Only one study on reproduction and fertility effects was identified in U.S. EPA documents (MRID 47443293). In this study, rats were exposed to 0, 150, 1,000, or 8,000 ppm in diet for two consecutive generations. The highest dietary exposure of 8,000 ppm was reduced to 4,000 ppm at 5 to 17 days postweaning due to severe toxicity. For males, the average parental (F1 generation) consumption of indaziflam from the diet was reported as doses of 0, 10.4, 69.3 or 560.1 (P)/317.6 (F1) mg a.i./kg bw/day (due to the reduction in dietary concentration of indaziflam). For females, the average parental (F1 generation) consumption of indaziflam from the diet was reported as doses of 0, 12.9, 85.2, or 656.2 (P)/355.2 (F1) mg a.i./kg bw/day (due to the dietary concentration reduction of indaziflam) (U.S. EPA/OPP 2010b).

The parental LOAEL was reported as 560.1 and 656.2 mg a.i./kg bw/day for males and females, respectively. The LOAEL is based on coarse tremors in females, decreased body weights and body weight gains, and food consumption in both sexes. Effects on the kidneys were also observed in males and included tubular degeneration/regeneration, as well as increased kidney weights. Based on this study, a NOAEL for parental toxicity was identified at 69 and 85 mg a.i./kg bw/day in males and females, respectively.

For the offspring toxicity, the LOAEL was reported as 317.6 and 355.2 mg a.i./kg bw/day in males and females, respectively, based on clinical signs of toxicity, and decreased body weights and body weight gains. Clinical signs of toxicity included perianal effects, urine or nasal staining, diarrhea or soft stool, distended abdomen, weakness, tremors, myoclonus, increased activity and reactivity, and decreased pup body weights throughout postnatal period. A NOAEL of 69 and 85 mg a.i./kg bw/day was observed in males and females, respectively.

In terms of reproductive and fertility effects, there were no effects observed on estrous cycle duration or periodicity, follicle counts, or the mating, fertility, and gestation indices. The only effect on reproductive parameters was delayed sexual maturation in males and females. NOAELs for effects on reproduction are 69.3 and 85.2 mg a.i./kg bw/day for males and females (parents), respectively. These values are based on the male and female parental (F1) doses. The LOAELs for reproductive effects are 317.6 and 355.2 mg a.i./kg bw/day for males and females, respectively, based on delayed sexual maturation (% pups reaching criterion was unaffected) (U.S. EPA/OPP 2010b).

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 bioassays on mammals. When applicable, quantitative estimates of carcinogenic potency are typically based on mammalian bioassays.

No epidemiology studies specific to indaziflam were identified. Two acceptable carcinogenic bioassays were submitted by the registrant to U.S. EPA/OPP, which consisted of two-year dietary

studies using rats (MRID 47743417) and mice (MRID 47743416). In both two-year dietary studies, there was no evidence of carcinogenicity in rats or mice. Appendix 2 Table A2-6 contains detailed summaries of these studies.

Male and female rats were exposed to indaziflam in the diet at concentrations of 0, 300, 3,000, or 10,000 ppm (equivalent to 0, 12, 118, 414 mg/kg bw/day for males and 0, 17, 167, and 452 mg/kg bw/day for females). At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. There was no evidence of carcinogenicity. The observed NOAEL was 12 and 17 mg a.i./kg bw/day for male and female rats, respectively. The observed LOAEL was equal to 118 and 167 mg a.i./kg bw/day for male and female rats, respectively. The LOAEL was based on decreased body weight/weight gain and signs of neurotoxicity in both sexes. In females, renal and liver toxicity were also observed. In males, liver toxicity, atrophic seminal vesicles, thyroid colloid alteration, and a transient increase in TSH in males (MRID 47743417) (U.S. EPA/OPP 2010b).

In the mouse bioassay, male and female mice were exposed to indaziflam in the diet at concentrations of 0, 50, 250, or 1,000 ppm (equivalent to 0, 6.8, 34, 142 mg/kg bw/day for males and 0, 8.4, 42, and 168 mg/kg bw/day for females). At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. There was no evidence of carcinogenicity. Decreased body weight, decrease weight gain, and decreased food consumption were reported in both sexes. The observed NOAELs were 34 and 42 mg a.i./kg bw/day for male and female mice, respectively. The observed LOAELs were equal to 142 and 168 mg a.i./kg bw/day for male and female mice, respectively. The LOAEL is based on increased incidence of wasted appearance in females; decreased body weight, body weight gains and food consumption in both males and females; and indications of renal toxicity and hepatotoxicity in males; and stomach and ovarian toxicity in females (MRID 47743416) (U.S. EPA/OPP 2010b).

A summary of the NOAELs and LOAELs from the carcinogenic studies is presented in Table 5-6. In addition, three acceptable gene mutation studies and two cytogenetics studies were submitted by the registrant to U.S. EPA as part of the registration process. These studies are described in Appendix 2, Table A2-6. Results from these genotoxicity studies (reverse gene mutation in bacteria, forward gene mutation in mammalian cells, and in vitro and in vivo chromosomal aberration assays) were negative and indicate that indaziflam is not genotoxic. Based on the lack of evidence of carcinogenicity or genotoxicity, HED classified indaziflam as “not likely to be carcinogenic to humans” (U.S. EPA/OPP 2010b).

Table 5-6: Carcinogenic Toxicity Studies for Indaziflam

Test Species	NOAEL Male	NOAEL Female	NOAEL Average	LOAEL Male	LOAEL Female	LOAEL Average	Reference
Carcinogenicity: Mice	34	42	38	142	168	155	MRID 47743416
Combined Carcinogenicity/ Chronic Toxicity: Rats	12	17	14.5	118	167	142.5	MRID 47743417

Note: endpoints are based on non-cancer effects.
Note: NOAEL and LOAEL are measured in mg a.i./kg bw/day.

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 5-7 summarizes the irritation and sensitization tests. Additional information is provided in Appendix 2, Table A2-7 and summarized in the following subsections.

Table 5-7: Acute Eye Irritation, Skin Irritation, and Skin Sensitization Toxicity Studies for Indaziflam

Test Species	Study Type	Result	Toxicity Category	Reference
Rabbit	Acute eye irritation	Non-irritant	IV	MRID 47743605
Rabbit	Acute dermal irritation	Non-irritant	IV	MRID 47743606
Guinea Pig	Skin sensitization	Not a sensitizer (Buehler method)	N/A	MRID 47743607

5.1.11.1. Eye Irritation

Only one study on eye irritation was identified in U.S. EPA documents (MRID 47743605). This study indicates that indaziflam does not cause eye irritation in rabbits based on the lack of corneal opacity or iritis observed during the study. Conjunctival redness was observed in one rabbit at 24 and 48 hours. However, all ocular irritation was resolved by the end of the 72-hour study. The U.S. EPA used this study to classify indaziflam as Category IV (non-irritant) for eye irritation (U.S. EPA/OPP 2010b). This classification is consistent with the notation on eye irritation in the SDSs for Esplanade 200 SC and Esplanade F.

5.1.11.2. Skin Irritation

As with eye irritation, only one study is available on dermal irritation in rabbits (MRID 47743606). This study was conducted over 72 hours and no signs of irritation were observed during the test. Based on this information, U.S. EPA classified indaziflam as a non-irritant to skin (Category IV) (U.S. EPA/OPP 2010b). This classification is consistent with the notation on skin irritation in the SDSs for Esplanade 200 SC and Esplanade F.

5.1.11.3. Skin Sensitization

A single study is available on skin sensitization in guinea pigs following exposure to indaziflam (MRID 47743607). In this study, the Buehler epicutaneous patch test (Buehler 1965) was performed on 30 female guinea pigs to determine if indaziflam (as BCS-AA10717 SC 500 G) exhibits skin-sensitizing properties. Doses for the induction and challenge treatments were selected based on results from the range-finding study, which revealed no skin effects at the concentrations tests (0, 25%, 50%, 100%) at any time point assessed (30 and 54 hours). Thus, indaziflam, under the Buehler test, was considered not to be a dermal sensitizer and labeling for indaziflam was not required.

5.1.12. Systematic Toxic Effects from Dermal Exposure

5.1.12.1. Acute Dermal Toxicity

Two acute dermal toxicity studies were conducted in rats exposed to indaziflam as AE 1170437 (MRID 47443282) and AE 1170437 SC 500 g/l (MRID 47743603). No clinical signs or dermal irritation were observed at the limit dose of 2,000 mg/kg bw. Mortality was not observed. Based on the observed LD_{50} being greater than 2,000 mg/kg in both studies, indaziflam was classified as Toxicity Category III for acute dermal toxicity. The acute dermal toxicity studies are summarized in Table 5-8 and additional information is presented in Appendix 2 Table A2-8. These acute dermal studies are considered "acceptable" by U.S. EPA and satisfy the guideline requirement for an acute dermal study (Office of Prevention, Pesticides and Toxic Substances (OPPTS) 870.1200 guideline).

Table 5-8: Acute Dermal Exposure Toxicity Studies for Indaziflam

Test Species	Study Type	Result	Toxicity Category	Reference
Rat	Acute dermal	LD_{50} > 2,000 mg/kg	III	MRID 47743603
Rat	Acute dermal	LD_{50} > 2,000 mg/kg	III	MRID 47443282

5.1.12.2. Subchronic Dermal Toxicity

A 28-day *in vivo* dermal toxicity study was identified and conducted according to Standard Test Guideline 870.3200 (MRID 47443290). In this study, rats were exposed to 0, 40, 200, or 1,000 mg of indaziflam (90.32% a.i.) /kg bw/day for five days per week for four weeks. No mortality or signs of systematic effects were observed during the study. Some indication of local irritation was observed at all doses in females, but the findings were transient (generally observed between days 3 and 7) and were observed in only one sex. The study investigator and reviewer did not consider these findings adverse. Therefore, a LOAEL could not be identified from the study results (> 1,000 mg a.i./kg bw/day). The NOAEL was identified as 1,000 mg a.i./kg bw/day., U.S. EPA waived the requirements for a chronic dermal toxicity study. The subchronic dermal toxicity study is summarized in Table 5-9 and additional details are provided in Appendix 2 Table A2-9.

Table 5-9: Subchronic Dermal Exposure Toxicity Studies for Indaziflam

Test Species	Study Type	NOAEL (mg a.i./kg bw/day)	LOAEL (mg a.i./kg bw/day)	Reference
Rat	Subchronic (28-day dermal)	1,000	Not determined (> 1,000)	MRID 47443290

5.1.13. Inhalation Exposures

Two acute inhalation toxicity studies were identified and reviewed by EPA for indaziflam, which are summarized in Table 5-10.

For one of the studies (MRID 47743604), two groups of adult rats were exposed via the inhalation route to either water or indaziflam (as AE 1170437 SC 500 g/L). The test group was exposed to a mean maximum attainable aerosol concentration of 1.937 mg/L (nose only) for 4 hours. Animals were observed for 14 days. Following exposure, mortality did not occur at the maximum technically feasible concentration of 1.937 mg/L and gross-pathological examinations indicated no observed necropsy findings. There were some transient clinical signs observed after exposure, but all rats were without signs after Day 3. Based on the lethal concentration, 50% kill (LC_{50}) of > 1.937 mg/L, U.S. EPA classified indaziflam as Category III (U.S. EPA/OPP 2010b).

In the second rat inhalation acute toxicity test (MRID 47443283), five rats per sex were exposed (nose-only) via the inhalation route to aerosolized indaziflam (as AE 1170437, 94.5%) for 4 hours at a concentration of 2.3 mg/L. The test animals were observed for mortality and clinical signs of toxicity several times on the day of exposure and at least once daily thereafter for the remainder of the 14-day study period. All test animals survived and exceeded their initial body weights by the end of the study. The LC_{50} is reported as > 2.3 mg/L and was classified by U.S. EPA as Category IV for acute inhalation toxicity (U.S. EPA/OPP 2010b). Category IV is the lowest (i.e. least toxic) category used by U.S. EPA/OPP in the classification of responses from acute toxicity studies. U.S. EPA waived the requirements for a chronic inhalation toxicity study.

No other inhalation studies on indaziflam were submitted to U.S. EPA or found in the open literature.

Table 5-10: Acute Inhalation Toxicity Studies for Indaziflam

Test Species	Study Type	Result	Toxicity Category	Reference
Rat	Acute inhalation	LC_{50} > 1.937 mg/L	III	MRID 47743604
Rat	Acute inhalation	LC_{50} > 2.3 mg/L	IV	MRID 47443283

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 may be substantial. For example, some adjuvants used in glyphosate formulations may be as toxic as or more toxic than glyphosate itself, based on the FS risk assessment on glyphosate (SERA 2011). In the case of indaziflam, the formulation labels for Esplanade 200 SC and Esplanade F do not recommend the use of adjuvants.

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 (U.S. EPA 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) may suggest non-toxicity, some inerts are toxic, and the U.S. EPA/OPP now uses the term other ingredients rather than inerts (U.S. EPA 2019). For purposes of this report, the discussion below uses the term *other ingredients* to refer to any substance other than the active ingredient.

The Esplanade 200 SC and Esplanade F formulation labels and SDSs do not identify other ingredients in the formulation. 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. Appendices 1 and 2 include the indaziflam formulation labels and SDSs for both Esplanade 200 SC and Esplanade F, respectively. There are no known adverse effects associated with other ingredients in these two indaziflam formulations.

5.1.15. Impurities

Information regarding the impurities in technical grade indaziflam or relevant commercial formulations was not found. Impurities are not discussed in the open literature or the recent risk assessments by U.S. EPA (U.S. EPA/OPP 2010c, 2017). 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 indaziflam with other compounds were not identified in the available studies submitted to U.S. EPA/OPP, nor the open literature. Consequently, there is no basis for inferring toxicological interactions of indaziflam with other agents.

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 may occur during any type of application.

The following subsections describe the exposure scenarios and associated doses for workers and the general public. The team assessed exposures for indaziflam using an Excel workbook that includes detailed calculations for quantitative exposures and risks for various receptors. The Excel workbook for Esplanade 200 SC and Esplanade F was generated using the FS risk assessment tool called Worksheet Maker and is included in Attachment 1. The Excel workbook is important in providing an exposure dose for each exposure scenario, which is then compared to dose-response values to calculate HQs. In FS HHERAs, the methodology and results of calculations are provided in the Excel workbook with the intention of keeping the text simpler in the report. The assessment team conducted all exposure assessments for indaziflam assuming a single application rate of 0.091 lb a.i./acre. The FS may modify the assumptions and inputs to better represent a specific site in future risk assessment.

5.2.1. Workers

The assessment team evaluated worker exposures for the three application methods described in Section 2.2, which include backpack spray, broadcast ground spray, and aerial spray. Exposure estimates are discussed below and summarized in and Table 5-15. Dermal exposure is the predominant route of exposure for pesticide applicators (Ecobichon 1998; van Hemmen 1992). 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

General exposures for workers are calculated as the amount of a.i. handled by a worker in a single day multiplied by the worker exposure rate (in units of mg/kg bw per lb handled) (SERA 2014). The worker exposure rates used for estimating worker exposure doses are summarized below and were derived by incorporating the most recent approach described in the *Reassessment of Worker Exposure Rates* guidance document developed by SERA (SERA 2014b). This involved selecting one of the reference chemicals listed in Table 14 of SERA 2014b for each application method. Reference chemicals are based directly on worker studies and are used for estimating workers exposures for pesticides on which no data are available. Once a reference chemical is selected, the worker exposure rates are estimated from the first-order dermal absorption rate coefficient for the pesticide of concern (ka_P), the first-order dermal absorption rate coefficient for the reference pesticide (ka_{Ref}), and the worker exposure rate for the reference chemical ($ExpRt_{Ref}$). In this case, the pesticide of concern is indaziflam. See Equation 22 and Section 4.1.6 in SERA 2014b for additional information.

Three reference chemicals with corresponding worker exposure rates are available for backpack directed foliar application with differing first-order dermal absorption rate coefficients (k_a values): glyphosate (k_a = 0.00041 hour^{-1}), 2,4-D (k_a = 0.00066 hour^{-1}), and triclopyr BEE (k_a = 0.0031 hour^{-1}). As shown in Worksheet B03b of Attachment 1, the first-order dermal absorption rate coefficient for indaziflam is 0.0028, which is comparable to the rate coefficient for triclopyr BEE. Therefore, triclopyr BEE is used as the reference chemical for directed foliar applications in order to minimize extrapolation. The calculated worker exposures rates for directed foliar applications of indaziflam are provided in Table 5-11 and are used in Worksheet C01a (Attachment 1) to estimate exposures for workers involved in backpack spray application.

Only one reference chemical is available for ground broadcast and aerial applications, which is 2,4-D. The first-order dermal absorption rate coefficient for 2,4-D is 0.00066 $hour^{-1}$, which is below the corresponding value for indaziflam. Thus, the worker exposure rates for these application methods are adjusted upward by a factor of approximately 4 [0.0028 $hour^{-1}$ ÷ 0.00066 $hour^{-1}$= 4.24]. As discussed in SERA 2014b, the adjustment factor for differences in dermal absorption is optional for ground broadcast and aerial applications because of the limited data supporting such an adjustment. In the case of indaziflam, the adjustment factor is used in this risk assessment as a conservative approach given the greater dermal absorption rate of indaziflam relative to 2,4-D. Calculated worker exposures rates are provided in Table 5-12 and Table 5-13, which are used in Worksheets C01b and C01c (Attachment 1) to estimate exposures for workers involved in ground broadcast and aerial applications.

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. These values are presented in Worksheets C01a, CO1b, and C01c (Attachment 1) 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 being based on working 6 hours per day with 1 hour at each end of the work day spent in activities that do not involve herbicide exposure. The upper end of the range, 8 hours per day, is based on an extended (10-hour) work day, allowing for 1 hour at each end of the work day to be spent in activities that do not involve herbicide exposure (SERA 2014a).

Table 5-11: Derivation of Worker Exposure Rates for Backpack Directed Foliar

Parameter	Chemical	Value	Reference
First-order dermal absorption rate coefficient ($hour^{-1}$) [ka_{Ref}]	Reference Chemical (Triclopyr BEE)	0.0031	SERA 2014b, Table 14
Worker Exposure Rate: Central	Reference Chemical (Triclopyr BEE)	0.01	SERA 2014b, Table 14
Worker Exposure Rate: Lower 95% Prediction Bound	Reference Chemical (Triclopyr BEE)	0.002	SERA 2014b, Table 14
Worker Exposure Rate: Upper 95% Prediction Bound	Reference Chemical (Triclopyr BEE)	0.06	SERA 2014b, Table 14
First-order dermal absorption rate coefficient ($hour^{-1}$) [ka_p]	Subject Chemical (Indaziflam)	0.0028	Attachment 1, Worksheet B03b
Ratio of the k_a values (ka_P ÷ ka_{Ref})	Subject Chemical (Indaziflam)	0.903225806	Calculated according to SERA 2014b, Equation 22
Worker Exposure Rate[1]: Central	Subject Chemical (Indaziflam)	**0.009**	Calculated according to SERA 2014b, Equation 22

Parameter	Chemical	Value	Reference
Worker Exposure Rate[1]: Lower 95% Prediction Bound	Subject Chemical (Indaziflam)	**0.002**	Calculated according to SERA 2014b, Equation 22
Worker Exposure Rate[1]: Upper 95% Prediction Bound	Subject Chemical (Indaziflam)	**0.05**	Calculated according to SERA 2014b, Equation 22

[1] Worker exposure rate included in Attachment 1 Worksheet C01a (rounded to one significant digit)
Note: Worker exposure rate is measured in mg/kg bw per lb.

Table 5-12: Derivation of Worker Exposure Rates for Ground Broadcast

Parameter	Chemical	Value	Reference
First-order dermal absorption rate coefficient (hour^{-1}) [ka_{Ref}]	Reference Chemical (2,4-D)	0.00066	SERA 2014b, Table 14
Worker Exposure Rate: Central	Reference Chemical (2,4-D)	0.0001	SERA 2014b, Table 14
Worker Exposure Rate: Lower 95% Confidence Bound	Reference Chemical (2,4-D)	0.00004	SERA 2014b, Table 14
Worker Exposure Rate: Upper 95% Confidence Bound	Reference Chemical (2,4-D)	0.0002	SERA 2014b, Table 14
First-order dermal absorption rate coefficient (hour^{-1}) [ka_p]	Subject Chemical (Indaziflam)	0.0028	Attachment 1, Worksheet B03b
Ratio of the k_a values ($ka_P \div ka_{Ref}$)	Subject Chemical (Indaziflam)	4.242424242	Calculated according to SERA 2014b, Equation 22
Worker Exposure Rate[1]: Central	Subject Chemical (Indaziflam)	**0.0004**	Calculated according to SERA 2014b, Equation 22
Worker Exposure Rate[1]: Lower 95% Confidence Bound	Subject Chemical (Indaziflam)	**0.0002**	Calculated according to SERA 2014b, Equation 22
Worker Exposure Rate[1]: Upper 95% Confidence Bound	Subject Chemical (Indaziflam)	**0.001**	Calculated according to SERA 2014b, Equation 22

[1] Worker exposure rate included in Attachment 1 Worksheet C01b (rounded to one significant digit)
Note: Worker exposure rate is measured in mg/kg bw per lb.

Table 5-13: Derivation of Worker Exposure Rates for Aerial Broadcast

Parameter	Chemical	Value	Reference
First-order dermal absorption rate coefficient (hour^{-1}) [ka_{Ref}]	Reference Chemical (2,4-D)	0.00066	SERA 2014b, Table 14
Worker Exposure Rate: Central	Reference Chemical (2,4-D)	0.00002	SERA 2014b, Table 14
Worker Exposure Rate: Lower 95% Confidence Bound	Reference Chemical (2,4-D)	0.000006	SERA 2014b, Table 14
Worker Exposure Rate: Upper 95% Confidence Bound	Reference Chemical (2,4-D)	0.00007	SERA 2014b, Table 14
First-order dermal absorption rate coefficient (hour^{-1}) [ka_p]	Subject Chemical (Indaziflam)	0.0028	Attachment 1, Worksheet B03b
Ratio of the k_a values ($ka_P \div ka_{Ref}$)	Subject Chemical (Indaziflam)	4.242424242	Calculated according to SERA 2014b, Equation 22
Worker Exposure Rate[1]**: Central**	Subject Chemical (Indaziflam)	**0.0001**	Calculated according to SERA 2014b, Equation 22
Worker Exposure Rate[1]**: Lower 95% Confidence Bound**	Subject Chemical (Indaziflam)	**0.00003**	Calculated according to SERA 2014b, Equation 22
Worker Exposure Rate[1]**: Upper 95% Confidence Bound**	Subject Chemical (Indaziflam)	**0.0003**	Calculated according to SERA 2014b, Equation 22

[1] Worker exposure rate included in Attachment 1 Worksheet C01c (rounded to one significant digit).
Note: Worker exposure rate is measured in mg/kg bw per lb.

As shown in Table 5-14, 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. The calculations used to estimate the exposure doses in workers are presented in Worksheets C01a (backpack spray), C01b (ground broadcast spray), and C01c (aerial spray) of Attachment 1. As summarized in Table 5-14 and the Excel worksheets, the central estimates of exposure for workers are approximately 0.004 mg/kg/day for backpack, ground broadcast, and aerial applications. Upper estimates are approximately 0.04 mg/kg/day for backpack application, 0.02 mg/kg/day for ground broadcast application, and 0.02 mg/kg/day for aerial application.

Table 5-14: General Worker Exposure Doses

Scenario	Dose: Central	Dose: Lower[1]	Dose: Upper[1]	Detail Worksheet
Backpack Application	3.58E-03	2.73E-04	3.64E-02	C01a
Ground Broadcast Application	4.08E-03	1.20E-03	1.53E-02	C01b
Aerial Application	4.46E-03	6.55E-04	2.18E-02	C01c

[1] The lower and upper dose represent the 95% confidence interval.
Dose is measured in mg a.i./kg bw/day or mg a.i./kg bw/event.

5.2.1.2. Accidental/Incidental Worker Exposures

Dermal exposure is the predominant route of exposure for pesticide applicators (Ecobichon 1998; van Hemmen 1992). 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 indaziflam include the following:

1. Direct Contact to Surface Area of Hands for 1 Minute (Attachment 1, Worksheet C02a)
2. Direct Contact to Surface Area of Hands for 1 Hour (Worksheet C02b)
3. Accidental Spill on Hands for 1 Hour (Worksheet C03a)
4. Accidental Spill on Lower Legs for 1 Hour (Worksheet C03b)

For the first two exposure scenarios involving direct contact with indaziflam, the scenarios evaluated include either immersion of the hands in a field solution for 1 minute or wearing pesticide contaminated gloves for 1 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 may 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 absorption 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 0.091 lb a.i./acre, the estimated concentrations in a field solution are 0.50 mg/mL with a range of 0.11 to 2.2 mg/mL for both Esplanade 200 SC and Esplanade F (Worksheet A01).

The accidental dermal exposure scenarios for workers consist of spilling indaziflam onto the hands (Worksheet C03a) and spilling a solution of indaziflam onto the lower legs for 1 hour (Worksheet C03b). These dermal exposures are described as "second order" in that some (but not all) of the indaziflam solution adheres to the skin. The absorbed dose is then calculated as the product of the amount of indaziflam 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 (Attachment 1).

The direct contact and accidental spill scenarios are detailed in Worksheets C02a (contaminated gloves, 1-minute exposure), C02b (contaminated gloves, 1-hour exposure), C03a (spill on hands, 1-hour exposure), and C03b (spill on lower legs, 1-hour exposure). The calculated exposure doses for workers to indaziflam (central, lower, and upper estimates) associated with accidental/incidental exposure scenarios are reported in Table 5-15 and Worksheet E01.

Table 5-15: Accidental/Incidental Worker Exposure Doses

Scenario	Dose: Central	Dose: Lower[1]	Dose: Upper[1]	Detail Worksheet
Direct Contact to Surface Area of Hands for 1 Minute	2.59E-04	3.88E-05	1.73E-03	C02a
Direct Contact to Surface Area of Hands for 1 Hour	1.56E-02	2.33E-03	1.04E-01	C02b
Accidental Spill on Hands for 1 Hour	1.39E-04	1.53E-05	1.27E-03	C03a
Accidental Spill on Lower Legs for 1 Hour	3.49E-04	3.84E-05	3.17E-03	C03b

[1] The lower and upper dose represent the 95% confidence interval.
Dose is measured in mg a.i./kg bw/day or mg a.i./kg bw/event.

5.2.2. General Public

5.2.2.1. General Considerations

The likelihood that individuals from the general public will be exposed to indaziflam depends on the application method and where the pesticide is applied. The FS and BLM may apply indaziflam along roadsides, power lines, pipelines, and rights-of-way. Although some of these applications may 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 Attachment 1. In addition, details about the assumptions and calculations for the general public exposure scenarios are provided in Worksheets D01 through D10. For indaziflam, 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.

As discussed in SERA 2014a, FS risk assessments are based on *Extreme Values* rather than a single value. 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 estimate 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, this is a strong indication that the pesticide cannot be used in a manner that will lead to acceptable risk (SERA 2014a).

The general public exposure scenarios for indaziflam are summarized in Table 5-16 and Worksheet E03 of Attachment 1. The accidental exposure scenarios for the general public assume that an individual is exposed to indaziflam during or shortly after direct spray application or an accidental spill. Non-accidental exposures involve dermal contact with contaminated vegetation and the consumption of contaminated fruit, vegetation, water, or fish. Potential risks associated with swimming in 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 each of 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 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. Indaziflam is designed to be applied to pre-emergent vegetation and not on fruits or post-emergent edible vegetation making ingestion of fruits and vegetations a highly unlikely scenario.

Table 5-16: General Public Exposure Doses

Scenario	Exposure Type	Receptor	Dose: Central	Dose: Lower[1]	Dose: Upper[1]	Detail Worksheet
Direct spray of child, whole body	Accidental Acute	Child	6.13E-03	6.75E-04	5.58E-02	D01a
Direct spray of woman, feet and lower legs	Accidental Acute	Adult Female	5.75E-04	6.33E-05	5.24E-03	D01b
Water consumption (spill)	Accidental Acute	Child	1.72E-02	4.62E-04	2.27E-01	D05
Fish consumption (spill)	Accidental Acute	Adult Male	8.69E-03	3.82E-04	7.65E-02	D08a
Fish consumption (spill)	Accidental Acute	Subsistence Populations	4.55E-02	2.00E-03	4.01E-01	D08b
Vegetation contact, shorts and T-shirt	Non-Accidental Acute	Adult Female	5.98E-04	3.04E-04	1.20E-03	D02
Contaminated fruit consumption	Non-Accidental Acute	Adult Female	1.07E-03	4.89E-04	1.70E-02	D03a

Scenario	Exposure Type	Receptor	Dose: Central	Dose: Lower[1]	Dose: Upper[1]	Detail Worksheet
Contaminated vegetation consumption	Non-Accidental Acute	Adult Female	1.47E-02	1.02E-03	1.23E-01	D03b
Swimming, one hour	Non-Accidental Acute	Adult Female	1.28E-06	1.03E-09	1.24E-05	D10
Water consumption	Non-Accidental Acute	Child	1.82E-04	1.31E-07	1.74E-03	D06
Fish consumption	Non-Accidental Acute	Adult Male	9.20E-05	1.09E-07	5.85E-04	D09c
Fish consumption	Non-Accidental Acute	Subsistence Populations	4.82E-04	5.69E-07	3.07E-03	D09d
Contaminated fruit consumption	Chronic/ Longer Term	Adult Female	4.99E-04	2.28E-04	7.92E-03	D04a
Contaminated vegetation consumption	Chronic/ Longer Term	Adult Female	6.88E-03	4.78E-04	5.73E-02	D04b
Water consumption	Chronic/ Longer Term	Adult Male	8.47E-07	5.18E-10	6.35E-06	D07
Fish consumption	Chronic/ Longer Term	Adult Male	1.35E-07	1.19E-10	8.47E-07	D09a
Fish consumption	Chronic/ Longer Term	Subsistence Populations	1.18E-06	1.03E-09	7.37E-06	D09b

[1] The lower and upper dose represent the 95% confidence interval.
Dose is measured in mg a.i./kg bw/day or mg a.i./kg bw/event.

5.2.2.2. Dermal Exposure from Direct Spray

The assessment ream evaluated two direct spray scenarios, one for a young child and the other for a young woman. The scenarios are modeled in a manner similar to accidental spills for workers in that it is assumed that the individual is sprayed with an indaziflam solution and that the amount of solution remaining on the skin is absorbed by first-order kinetics (SERA 2014a). For the young child scenario, it is assumed that a naked child is sprayed directly during a ground broadcast application and that the child is completely covered with 100% of the surface area of the body exposed. As discussed in SERA 2014a, 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.

The exposure scenario for a young woman sprayed accidentally with indaziflam is less extreme compared to the child. In this scenario, it is assumed that the lower legs and feet are accidentally sprayed with indaziflam. A young woman, rather than an adult male, is used in this risk assessment in an effort to be conservative given that a young woman would typically be subject to a higher dose than a standard adult male based on body weight. The assumptions and calculation of doses associated with these exposure scenarios are reported in Worksheets D01a (young child) and D01b (young woman) of Attachment 1. The resulting doses are reported in Table 5-16.

5.2.2.3. Dermal Exposure from Contaminated Vegetation

For this exposure scenario**,** it is assumed that indaziflam is sprayed onto vegetation and that a young woman 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 indaziflam 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 indaziflam. However, because dermal transfer rates are reasonably consistent for numerous pesticides, as discussed in SERA 2014a, the dermal transfer rates are used as defined in Worksheet D02 (Attachment 1). For this risk assessment, a default dislodgeable residue rate of 0.1 of the indaziflam 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 D02and the resulting doses are reported in Table 5-16.

5.2.2.4. Contaminated Water

In order to estimate exposure doses for human receptors to indaziflam, it is necessary to estimate or provide measurements of indaziflam in environmental media. Contamination of environmental media may result from spray applications, accidental spills, and other chronic exposures. The following subsections describe how indaziflam 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

Indaziflam concentrations in the surface water of a small pond are estimated for accidental spill exposure scenarios (Attachment 1, Worksheet D05). In this scenario, it is assumed that a young child consumes contaminated water shortly after an accidental spill of indaziflam into a small pond. Given that the scenario is based on the assumption that exposure occurs shortly after the spill, no degradation is considered 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 (1,000 m^2) and a depth of one meter, resulting in a pond volume of 1,000 m^3 or 1,000,000 liters. This is standard assumption in FS risk assessments (SERA 2014a).

For applications involving liquid formulations, a spill volume 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 indaziflam in the hypothetical small pond ranges from 0.0083 to 1.67 mg/L, with a central estimate of approximately 0.19 mg/L. The resulting doses are reported in Table 5-16 and Worksheet D05.

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 (Attachment 1, Worksheet B04c) and a small stream (Worksheet B04d). The concentrations of indaziflam 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) indaziflam 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* developed by SERA (SERA 2007b).

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 Cligen, which is a climate generator program developed and maintained by the USDA/ARS (USDA/NSERL 2019). For As summarized in Table 5-17, 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, 2007b). For this national risk assessment, climate simulations producing 24 years of climate data were used in the GLEAMS-Driver calculations. For future site-specific modeling using GLEAMS-Driver when actual application locations, methods, rates, and site characteristics are known, FS recommends generating climate data files from Cligen using 1000-year simulations.

Table 5-17: 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 [1]	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

[1] 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 5-18. For each location, simulations were conducted using clay (high runoff, low leaching potential), loam (moderate runoff, 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 indaziflam 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 an application rate of 0.091 lb a.i./acre. This adjustment is shown in Attachment 1 Worksheet B04a, where the application rate is multiplied by the water contamination rates to estimate the expected concentrations of indaziflam.

Table 5-18: Input Parameters for Fields and Waterbodies 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 [1]	Code[2]	Clay	Loam	Sand
Percent clay (w/w/):	CLAY	50%	20%	5%
Percent silt (w/w/):	SILT	30%	35%	5%
Percent sand (w/w/):	N/A	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

[1] From Knisel and Davis (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.
[2] Codes used in documentation for GLEAMS (Knisel and Davis 2000) and GLEAMS-Driver (SERA 2007a).

The chemical-specific inputs that were used in GLEAMS-Driver are provided in Table 5-19. The inputs are based on the environmental fate studies submitted to U.S. EPA by the registrant, the parameters used by U.S. EPA's EFED (U.S. EPA/OPP 2010a), and the standard values for GLEAMS modeling recommended by Knisel and Davis (2000). These inputs are shown as ranges or confidence intervals.

Table 5-19: Chemical- Specific Parameters Used in GLEAMS-Driver Modeling

Parameter	Values	Note
Half-Lives (Days)	--	--
Aquatic Sediment	120 (sand) 239 (loam and clay)	Value used by U.S. EPA/OPP (U.S. EPA/OPP 2010a).
Foliar	35	Value used by U.S. EPA/OPP (U.S. EPA/OPP 2010a) based on the work of Willis and McDowell (1987)
Soil	40.3	Value used by U.S. EPA/OPP (U.S. EPA/OPP 2010a).
Water	3.7	Value used by U.S. EPA/OPP (U.S. EPA/OPP 2010a).

Parameter	Values	Note
Soil Koc (mL/g)	450	Value used by U.S. EPA/OPP in SciGrow modeling (U.S. EPA/OPP 2010a). Indaziflam is moderately mobile to mobile (Koc's < 1000 mL/g oc) based on the FAO Soil Mobility Classification Guidance.
Sediment Kd (mL/g)	9.1	Value used by U.S. EPA/OPP in PRZM/EXAMS modeling (U.S. EPA/OPP 2010a).
Water Solubility (mg/L)	1.2	Value used by U.S. EPA/OPP in PRZM/EXAMS modeling (U.S. EPA/OPP 2010a).
Foliar Washoff Fraction (unitless)	0.65	Data for foliar washoff of indaziflam are not available. A value of 0.65 is used based on other pesticides in Knisel and Davis (2000) with comparable water solubility, including Ethanox [1.1 mg/L]; Haipen [1.4 mg/L]. Lower values are plausible; however, the use of 0.65 is conservative in that it will increase pesticide concentrations in water.
Fraction Applied to Foliage (unitless)	0.5	A foliar fraction of 0.5 is used in GLEAMS-driver by default for liquid formulations.
Coefficient of Transformation (unitless)	1	A default value of 1 is used when metabolites are not being modeled.
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	N/A

The results of the modeled concentrations of indaziflam in surface water are summarized in Table 5-20 and include an average of central values, a lower bound (25th percent of lower bounds), and an upper bound (maximum value). In addition, the outputs of the GLEAMS-Driver simulations are provided in Appendix 9, which include the off-site application rate, indaziflam concentrations in the top 12 and 36 inches of soil, maximum penetration into the soil column, and peak and longer-term indaziflam concentrations in a small pond and stream. In general, the results of the small stream provide the highest estimates of indaziflam in surface water. The specific concentrations of indaziflam in surface water used in the exposure assessment are discussed in Section 5.2.2.4.5.

Table 5-20: Summary of Modeled Concentrations in Surface Water

Scenario/Source	Peak Concentrations: Soil Type	Peak Concentrations: Concentration[1]	Long-Term Average Concentrations: Soil Type	Long-Term Average Concentrations: Concentration[1]
Pond[2]	**Clay**	16.62 (1.28 – 52.90)	**Clay**	0.63 (0.08 – 1.83)
Pond[2]	**Loam**	7.16 (0.01 – 43.90)	**Loam**	0.24 (0 – 1.23)
Pond[2]	**Sand**	5.65 (0 – 40.30)	**Sand**	0.19 (0 – 1.17)

Scenario/Source	Peak Concentrations: Soil Type	Peak Concentrations: Concentration[1]	Long-Term Average Concentrations: Soil Type	Long-Term Average Concentrations: Concentration[1]
Pond[2]	**Average**	9.81 (0.01 – 52.90)	**Average**	0.35 (0 – 1.83)
Stream[3]	**Clay**	35.28 (3.94 – 135)	**Clay**	0.52 (0.05 – 2.52)
Stream[3]	**Loam**	16.08 (0.01 – 115)	**Loam**	0.26 (0 – 1.7)
Stream[3]	**Sand**	14.21 (0 – 113)	**Sand**	0.20 (0 – 1.32)
Stream[3]	**Average**	21.86 (0.03 – 135)	**Average**	0.32 (0 – 2.52)

[1] Average of central estimates (95% upper and lower bound).
Note: Concentrations measured in ppb or µg/L per lb/acre.
[2] See Appendix 9, Tables 7 and 8.
[3] See Appendix 9, Tables 5 and 6.

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 indaziflam.

5.2.2.4.5. Concentrations in Water Used for Risk Assessment

The modeled surface water concentrations used in this risk assessment for indaziflam are summarized in Table 5-21. 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 of Attachment 1 and are adjusted based on an application rate of 0.091 lb a.i./acre as shown in Worksheet B04a.

In an effort to be conservative, the highest estimates of indaziflam concentrations in surface water shown in Table 5-20 were used in the risk assessment HQ calculations. The results of the small stream provide the highest estimates of indaziflam in surface water, with exception of two of the longer-term WCRs for a small pond, central and lower bound values. For example, the average peak WCR values are 0.0098 (0.000014 - 0.053) mg a.i./L per lb/acre for a small pond (Table 7 in Appendix 9) and 0.022 (0.000026 - 0.14) mg a.i./L per lb/acre for a small stream (Table 5 in Appendix 9). The average longer-term WCR values are 0.00035 (0.00000035 - 0.0018) mg a.i./L per lb/acre for a small pond (Table 8 in Appendix 9) and 0.00033 (0.00000011 - 0.0025) mg a.i./L per lb/acre for a small stream (Table 6 in Appendix 9). The WCR values used in the risk assessment are summarized in Table 5-21 and are rounded to two significant places. The table includes the estimated concentrations for both the stream and pond scenarios. The higher concentrations used for HQ calculations (worst case) are highlighted in bold and noted by footnote 2. FS staff should use the concentrations for future modeling appropriate to their site-specific conditions.

Table 5-21: Concentrations in Surface Water Used in this Risk Assessment

Estimate	Peak WCR [1] (mg a.i./L per lb a.i./acre)	Longer-term WCR [1] (mg a.i./L per lb a.i./acre)
Stream Central	**0.022**[2]	0.00033
Stream Lower	**0.000026**[2]	0.00000011
Stream Upper	**0.14**[2]	**0.0025**[2]
Pond Central	0.0098	**0.00035**[2]
Pond Lower	0.000014	**0.00000035**[2]
Pond Upper	0.053	0.0018

[1] 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 workbook that accompanies this risk assessment.
[2] Higher concentration estimates used in HQ risk calculations.

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. As discussed in Section 4.2.2, 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 (Attachment 1 Worksheets D08a and D08b), acute exposures based on expected peak concentrations of indaziflam in water (Worksheets D09c and D09d), and chronic exposures based on estimates of longer-term concentrations in water (Worksheets D09a and D09b).

This accidental spill scenario assumes that an adult male consumes fish from a small pond shortly after an accidental spill of indaziflam into the pond. The amount of indaziflam in edible fish tissue consumed by the adult male is based on a study of bioconcentration of indaziflam in bluegill. The calculation of indaziflam doses associated with fish consumption are provided in Attachment 1 Worksheet D08a and are also reported in Table 5-16. 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 indaziflam in edible fish tissue is based on use of the lower measured BCF in edible fish tissues. The calculation of indaziflam 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 5-16 also includes a summary of the doses calculated for fish consumption.

Experimental BCFs are required by the U.S. EPA/OPP as part of the registration process. A flow through bioconcentration study with bluegill sunfish (*Lepomis macrochirus*) exposed to indaziflam for 26 days with a 14-day depuration period demonstrated that indaziflam does not bioaccumulate (MRID 47443237). BCFs from the study are reported at 46 and 25 for whole fish and edible, respectively, in low-dose samples (0.30 µg/L) and 65 and 32, respectively, for high-dose samples (3.0 µg /L). However, BCF values less than 1,000 typically do not trigger further evaluation of bioaccumulative compounds (U.S. EPA/OPP 2010a). These BCFs are used for estimating exposures for consumption of fish in general public exposure scenarios. The consideration of bioaccumulation of indaziflam in fish tissues and subsequent exposures for the public by ingestion is considered as extremely conservative and unlikely.

5.2.2.6. Dermal Exposure from Swimming in Contaminated Water

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

To assess potential risks associated with swimming in contaminated water, an exposure scenario was developed using a young woman swimming in surface water for 1 hour (Attachment 1, Worksheet D10). The 1-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 2-hour exposure would lead to an HQ that is twice as high as the associated exposure period of 1 hour. In the case of indaziflam, the upper bound HQ is 0.00002, which is well below the level of concern.

5.2.2.7. Oral Exposure from Contaminated Vegetation

FS risk assessments include standard exposure scenarios for the acute and longer-term/chronic consumption of contaminated vegetation if a pesticide may be applied to vegetation. Two sets of exposure scenarios are considered: one for the consumption of contaminated fruit and the other for the contaminated vegetation. These scenarios are presented in Attachment 1 Worksheets D03a (fruit) and D03b (vegetation) for acute exposure and Worksheets D04a (fruit) and D04b (vegetation) for chronic exposure.

As discussed in SERA 2014a, the initial pesticide concentration on fruit and vegetation is estimated using the empirical relationships between application rate and concentration on different types of vegetation. 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 5-22 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. 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 5-22: Estimated Residue Rates in Food Items

Food Item	Central	Lower	Upper
Broadcast Liquid Applications: Short grass	85	30	240
Broadcast Liquid Applications: Tall grass	36	12	110
Broadcast Liquid Applications: Broadleaf/forage plants and small insects	45	15	135
Broadcast Liquid Applications: Fruits, pods, seeds, and large insects	7	3.2	15

Broadcast liquid applications measured in mg/kg wet weight per lb/acre applied.

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). Experimental half-lives for indaziflam on fruit or broadleaf vegetation are not reported in the available literature. For short and tall grasses, residue decline data submitted in support of the Section 18 exemption showed a half-life of 5.4 days for indaziflam and its metabolite FDAT (U.S. EPA/OPP 2017). For this risk assessment, a conservative foliar dissipation half-life of 35 days was used based on the work of Willis and McDowell (1987), which is consistent with the value used in the GLEAMS-Driver modeling.

As summarized in Table 5-16 and Worksheet E03 of Attachment 1, the estimated acute exposures are approximately 0.0011 (0.00049 to 0.017) mg a.i./kg bw/day for the consumption of contaminated fruit and 0.015 (0.0010 to 0.12) mg a.i./kg bw/day for the consumption of contaminated vegetation. The estimated chronic exposures are 0.00049 (0.00023 to 0.0079) mg a.i./kg bw/day for the consumption of contaminated fruit and 0.0069 (0.00048 to 0.057) mg a.i./kg bw/day for contaminated vegetation.

U.S. EPA dietary exposure data were also found and discussed in U.S. EPA's risk assessment. However, the approach taken by U.S. EPA is different in that the exposure assessments are based on dietary surveys (i.e. amounts of different commodities consumed by individuals) and tolerance limits on those commodities (SERA 2016a). Based on the U.S. EPA's 2017 human health risk assessment in support of the Section 18 exemption (U.S. EPA/OPP 2017), the acute dietary dose for indaziflam ranges from approximately 0.0039 to 0.015 mg a.i./kg bw/day across various population subgroups. The estimated upper bound acute dietary dose from U.S. EPA is a factor of 8 below the upper bound of the acute dose of 0.12 mg a.i./kg bw/day (Worksheet D03b) [0.12 ÷ 0.015 mg a.i./kg bw/day ≈ 8]. For chronic dietary exposures, U.S. EPA estimated a dose of 0.0043 to 0.0015 mg a.i./kg bw/day. The

upper bound of the range from U.S. EPA is about factor of 5 below the upper bound of the chronic exposures of 0.0079 mg a.i./kg bw/day (Worksheet D04b) [0.0.0079 ÷ 0.0015 mg a.i./kg bw/day ≈ 5.266]. The higher estimates in the current risk assessment are expected given the different methods used in the U.S. EPA risk assessment. This is because U.S. EPA risk assessments use a tolerance approach while FS risk assessments use a direct deposition-based approach. Thus, FS risk assessments are likely to be more conservative and consistent with the concern for the MEI.

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 such as reference doses (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 toxicity values used in the human health risk assessment unless there is a compelling reason to differ. For indaziflam, the acute and chronic RfDs are based on the most recent U.S. EPA human health risk assessment (U.S. EPA/OPP 2010b) and are adopted without modification. The available data on the toxicity of indaziflam to mammals is complete. The observed neurotoxic effects in rats and dogs serve as the basis for the risk assessment since all endpoints were associated with neurotoxic effects observed in mammalian toxicity studies. The proposed use pattern is 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 were not assessed. Table 5-23 summarizes the toxicity values used for human health used in this risk assessment.

Table 5-23: Toxicity Values Used in the Human Health Risk Assessment

Element	Exposure	Derivation of RfD	Reference
NOAEL Dose	Acute (Single Exposure)	50 mg a.i./kg bw/day	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)
LOAEL Dose	Acute (Single Exposure)	100 mg a.i./kg bw/day	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)
LOAEL Effects	Acute (Single Exposure)	Decreased motor and locomotor activity in females	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)
Species/Sex	Acute (Single Exposure)	Rats/females	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)
Uncertainty Factor	Acute (Single Exposure)	100 (10X interspecies extrapolation, 10X intraspecies variability)	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)
Acute RfD	Acute (Single Exposure)	0.50 mg a.i./kg bw/day	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)
Target Population	Acute (Single Exposure)	All populations	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)

Element	Exposure	Derivation of RfD	Reference
NOAEL Dose	Chronic (Lifetime Exposure)	2 mg a.i./kg bw/day	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)
LOAEL Dose	Chronic (Lifetime Exposure)	6 mg a.i./kg bw/day (males) 7 mg a.i./kg bw/day (females)	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)
LOAEL Effects	Chronic (Lifetime Exposure)	Nerve fiber degeneration in the brain, spinal cord, and sciatic nerve in males and females	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)
Species/Sex	Chronic (Lifetime Exposure)	Dogs/males and females	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)
Uncertainty Factor	Chronic (Lifetime Exposure)	100 (10X interspecies extrapolation, 10X intraspecies variability)	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)
Chronic RfD	Chronic (Lifetime Exposure)	0.02 mg a.i./kg bw/day	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)
Target Population	Chronic (Lifetime Exposure)	All populations	Table 3.5.13, page 20 (U.S. EPA/OPP 2010b)

5.3.2. Acute RfD

U.S. EPA/OPP established an acute RfD for indaziflam of 0.50 mg a.i/kg bw/day for all populations (including infants, children and females). This acute RfD is based on the NOAEL of 50 mg a.i./kg bw/day from the acute neurotoxicity study in rats (MRID 47443310) and an uncertainty factor of 100 [50 mg a.i./kg bw/day ÷ 100]. The uncertainty factor is based on 10X for interspecies extrapolation and 10X for intraspecies variability. In this study, decreased motor and locomotor activity was observed in females at the LOAEL of 100 mg a.i./kg bw/day. The endpoint is protective of the decreases in maternal body weight gains seen within the first three days of exposure in the developmental rat (25/200 mg/kg/day, NOAEL/LOAEL) and rabbit (25/60 mg/kg/day, NOAEL/LOAEL) toxicity studies, but which were considered questionable as an endpoint due to variability in the data. No other acute effects were observed in the database. The endpoint is also protective of potential developmental effects, based on the lack of observed increased pre- and/or postnatal susceptibility and higher LOAELs observed in developmental, reproductive, neurotoxicity, developmental neurotoxicity and immunotoxicity studies. Although the rat developmental toxicity NOAEL was lower (25 mg/kg/day), the neurotoxicity NOAEL of 50 mg/kg is considered protective because the rat developmental LOAEL (7-9% decrease in fetal body weight) was significantly greater (200 mg/kg/day) and the effects were relatively mild at that dose and unlikely to occur after a single dose (U.S. EPA/OPP 2010b).

5.3.3. Chronic RfD

U.S. EPA/OPP established a chronic RfD for indaziflam of 0.02 mg a.i./kg bw/day for all populations. This chronic RfD is based on the NOAEL of 2.0 mg a.i./kg bw/day from the chronic toxicity study in dogs (MRID 47443294) and an uncertainty factor of 100 [2 mg a.i./kg bw/day ÷ 100]. In this study, nerve fiber degeneration in the brain, spinal cord, and sciatic nerve was observed at the LOAEL of 6 and 7 mg a.i./kg bw/day in males and females, respectively (U.S. EPA/OPP 2010b). As discussed in 5.1.5 and shown on Table 5-2, dogs appear to be more sensitive than rats or mice based on the LOAELs (average LOAEL for the rat = 77.5 mg a.i./kg bw/day).

5.3.4. Surrogate RfD for Occupational Exposures

RfDs are not derived by U.S. EPA for occupational exposures. Instead, U.S. EPA identifies a longer-term NOAEL from an animal study and recommends a level of concern. U.S. EPA typically uses the same longer-term toxicity value used to derive the chronic RfD when establishing the level of concern. However, for indaziflam, U.S. EPA derived separate estimates for dermal and inhalation exposures based on the subchronic toxicity study in dogs.

5.3.5. Dose-Severity Relationships

For some risk assessments, the dose-severity relationships are evaluated to help further characterize potential risks in exposure scenarios where the doses exceed the RfDs. In the case of indaziflam, this is important because two of the general exposure scenarios for workers are modestly above the chronic RfD (Section 5.4.2.1).

As part of this analysis, a comparison of LOAELs to NOAELs can be conducted to evaluate potential concerns for exceedances in the RfDs. The ratios of the LOAEL to the corresponding NOAEL are 2 for the acute RfD [100 mg a.i./kg bw/day ÷ 50 mg a.i./kg bw/day = 2] and 3 for the chronic RfD [6 mg a.i./kg bw/day ÷ 2 mg a.i./kg bw/day = 3]. While these ratios might not reflect dose-severity responses in human populations, they are the most objective basis for assessing exposure scenarios with doses exceeding the RfDs.

Another factor to consider in dose-severity relationships is the uncertainty factor of 100 used in the derivation of both acute and chronic RfDs. A comparison of LOAELs to NOAELs does not consider the impact of uncertainty factors, which are intended to be protective (SERA 2014a).

5.4. Risk Characterization

5.4.1. Overview

The quantitative risk characterization for human health is based on the HQ approach. As discussed in SERA 2014a, the HQ is defined as the estimated exposure divided by a toxicity value that is likely not to be associated with adverse effects, such as an RfD. If the HQ is equal to or less than 1, then no adverse effects are anticipated as a result of the exposure. When an HQ is greater than 1, then the exposure exceeds the level of concern (i.e. adverse effects are possible).

The toxicity values used in the human health risk assessment include an acute RfD of 0.50 mg a.i/kg bw/day and a chronic RfD of 0.02 mg a.i./kg bw/day for all populations (Section 5.3.1). The quantitative risk characterization for workers is provided in Worksheet E02 and the risk

characterization for the general public is summarized in Worksheet E04 of Attachment 1. All HQs are based on the application rate of 0.091 a.i./acre.

5.4.2. Workers

5.4.2.1. General Exposures

None of the HQs exceed the level of concern based on central estimates of exposures. However, the upper bound estimates of the HQ exceed the level of concern for backpack applications (HQ = 1.8) and aerial applications (HQ = 1.09). The exposure assessments developed in FS risk assessments are based on 16 *Extreme Values* rather than a single value. Extreme value exposure assessments, as the name implies, bracket the most plausible estimate of exposure (referred to statistically as the central or maximum likelihood estimate) with lower and upper bounds of credible exposure levels. The upper bound estimate is designed to characterize the extreme, but still plausible upper limit of exposure (SERA, 2014a). Based on the ratio of the LOAEL to NOAEL discussed in Section 5.3.5 and the conservative nature of the upper bound exposure estimates, these HQs are relatively modest exceedances in the level of concern and do not raise substantial concern. The HQs for workers are summarized in Worksheet E02 of Attachment 1.

5.4.2.2. Accidental Exposures

All HQ values for worker accidental exposures are below the level of concern (maximum HQ = 0.2). The HQs are summarized in Worksheet E02 of Attachment 1.

5.4.3. General Public

The upper bound HQ value associated with the chronic consumption of contaminated vegetation by the general public is the only HQ that exceeds the level of concern (HQ = 3). As discussed in the Dose-Severity Relationships section (Section 5.3.5), the interpretation of the HQs must also consider the uncertainties in the exposure assessment. While an HQ of 3 is above the level of concern, this exceedance does not raise substantial concern based on the ratio of the LOAEL to NOAEL for chronic exposures. Additionally, the RfD includes an uncertainty factor of 100, so that the RfD is 100x lower than the NOAEL. The upper bound exposure estimates are also intended to reflect extremely conservative estimates. Indaziflam is designed to be applied to pre-emergent vegetation and not on fruits or post-emergent edible vegetation making consumption of indaziflam on fruits and vegetations a highly unlikely scenario. The HQs for members of the general public are summarized in Worksheet E02 of Attachment 1.

5.4.4. Sensitive Subgroups

For exposures to almost any chemical, there is particular concern for children, women who are pregnant or may become pregnant, the elderly, or individuals with health issues. There are no reports in the literature suggesting subgroups that may be unusually sensitive to indaziflam. However, sensitive subpopulations could include those with underlying neurological disorders and although there is a lack of literature, the sensitivity of this subpopulation cannot be quantified.

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 may 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. For indaziflam, U.S. EPA noted the following regarding cumulative effects (U.S. EPA/OPP 2010b):

> *Unlike other pesticides for which U.S. EPA has followed a cumulative risk approach based on a common mechanism of toxicity, U.S. EPA has not made a common mechanism of toxicity finding for indaziflam or its metabolite FDAT and any other substances, and indaziflam does not appear to produce a toxic metabolite produced by other substances. Therefore, for the purposes of this risk assessment, U.S. EPA has not assumed that indaziflam or its metabolite FDAT has a common mechanism of toxicity with other substances.*

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 indaziflam. Therefore, the potential for cumulative effects associated with exposures to indaziflam 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 indaziflam to ecological receptors through a review of the available toxicological literature. The primary source of information on receptors is taken from the most recent U.S. EPA risk assessment (U.S. EPA/OPP 2010a). As discussed in Section 5.1.1, the U.S. EPA risk assessment is based on original toxicity test reports submitted to U.S. EPA/OPP by the registrant to support the registration of indaziflam (Bayer).

Based on acute studies, U.S. EPA classified indaziflam as “practically non-toxic” to mammals, birds, honey bees, and earthworms. However, subacute effects were observed in earthworms and chronic effects were observed in mammals and birds. In aquatic organisms, indaziflam is categorized as “highly toxic” to freshwater and estuarine/marine fish, “moderately toxic to highly toxic” to estuarine invertebrates, and “slightly toxic to moderately toxic” to freshwater invertebrates on an acute exposure basis. The U.S. EPA does not have a classification scheme for effects on plants. Both monocots and dicots in general appear more sensitive to exposures in seedling emergence testing than those from vegetative vigor testing for both formulations. This is consistent with indaziflam’s mode of action as a pre-emergent herbicide. No data are available on the toxicity of indaziflam to reptiles or amphibians.

6.1.2. Terrestrial Organisms

6.1.2.1. Mammals

As summarized in the human health risk assessment (Section 5), several standard toxicity studies are available for mammals exposed to indaziflam. The mammalian studies are discussed in Section 5.1 and Appendix 2 of this document and were used to identify potential toxic effects in mammalian wildlife. This discussion from Section 5.1 is not repeated here. Selection of the mammalian dose-response values used in the ecological risk assessment for indaziflam are 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 differences in toxicity among species. However, for the acute oral toxicity studies described in Section 5.1.4 and Table 5-1, toxicity values are available only in rats. Thus, potential differences across species cannot be determined. Regardless, EPA found indaziflam to be “practically non-toxic” on an acute basis. Subchronic and chronic oral toxicity studies are summarized in Section 5.1.5 and Table 5-2. Subchronic and chronic studies conducted in dogs, rats, and mice show that dogs are the most sensitive species. For subchronic studies, the lowest LOAEL values in dogs, rats, and mice were 15, 572, and 237 mg a.i./kg bw/day, respectively; for chronic studies, the lowest LOAEL values in dogs and rats were 6.5 and 329.5 mg a.i./kg bw/day, respectively. U.S. EPA/OPP selected the male NOAEL of 69.3 mg a.i./kg bw/day to assess chronic risk of indaziflam to mammals. A 2-generation reproduction study in rats yielded LOAEL values for paternal male and female toxicity of 560.1 and 656.2 mg a.i./kg bw/day, respectively, and a LOAEL of 317.6 and 355.2 mg a.i./kg bw/day in males and females, respectively.

Based on these results, U.S. EPA/OPP selected the 2-generaltion reproduction study in rats as the critical study and used the NOAEL of 69.3 mg a.i./kg bw/day for toxicity to male parents and offspring to assess chronic risk of indaziflam to mammals. However, because the most sensitive effect observed in chronic studies for indaziflam is neurotoxic effects in dogs, the chronic neurotoxicity study in dogs serves as the basis for the dose-response the ecological risk assessments described in this report. Therefore, the chronic effects analysis for indaziflam in this assessment differs from the approach used by U.S. EPA.

6.1.2.2. Birds

Toxicity studies that describe the hazard potential of indaziflam to birds include acute oral studies, acute dietary exposure studies, and chronic reproductive studies. The available acute oral, acute dietary, and chronic reproductive studies are summarized in Table 6-1 and discussed in the following subsections. Additional information is provided in Appendix 3, Table A3-1.

Table 6-1: Acute and Chronic Toxicity of Indaziflam to Birds

Species	Study Type	Exposure Duration	Result	Reference
Northern bobwhite quail	Acute (Dose-based)	14-day single oral dose	LD_{50} > 2,000 mg a.i./kg bw NOAEL: 2,000 mg a.i./kg bw	MRID 47443240 (Acceptable)
Zebra finch	Acute (Dose-based)	14-day single oral dose	LD_{50} > 2,000 mg a.i./kg bw	MRID 47743306 (Acceptable)
Northern bobwhite quail	Acute (Dietary-based)	8-day dietary	LC_{50}: > 5,007 mg a.i./kg diet NOAEC: 5,007 mg a.i./kg diet	MRID 47443241 (Acceptable)
Mallard duck	Acute (Dietary-based)	8-day dietary	LC_{50}: > 5,215 mg a.i./kg diet LOAEC: 5,215 mg a.i./kg diet NOAEC: 2,518 mg a.i./kg diet	MRID 47443242 (Acceptable)
Northern bobwhite quail	Chronic (Dietary-based)	*ca.* 23-week avian reproduction study	LOAEC: > 1,023 mg a.i./kg diet NOAEC: 1,023 mg a.i./kg diet	MRID 47443243 (Acceptable)
Mallard duck	Chronic (Dietary-based)	*ca.* 22-week avian reproduction study	LOAEC: 95 mg a.i./kg diet NOAEC: < 95 mg a.i./kg diet	MRID 47443244 (Supplemental)
Mallard duck	Chronic (Dietary-based)	*ca.* 6-week avian reproduction study	LOAEC: 44 mg a.i./kg diet	MRID 47443244 (Supplemental)

Species	Study Type	Exposure Duration	Result	Reference
			NOAEC: < 44 mg a.i./kg diet	

6.1.2.2.1. Acute Oral Toxicity

Two acute oral toxicity studies exposing indaziflam to avian species were submitted by the registrant to U.S. EPA/OPP for evaluation. This includes one study with northern bobwhite quail (*Colinus virginianus*) (MRID 47443240) and one with the zebra finch (*Poephila guttata*) (MRID 47743306).

Northern bobwhite quail (10 birds/dose/16 weeks old) were exposed to a single dose (0 (control), 500, 1000, and 2000 mg a.i./kg bw) of technical grade indaziflam (90.3% a.i.) by gelatin capsule and observed for 14 days post exposure. Similarly, zebra finches were exposed to a single oral dose (0 (control) and 2000 mg a.i./kg bw) of technical grade indaziflam (90.3% a.i.) by gavage dosing and observed for 14 days post exposure.

In the bobwhite study, no treatment-related mortality occurred during the study. In zebra finch, one mortality was observed; gross necropsy demonstrated that death was related to intestinal and respiratory problems. There was insufficient evidence to determine whether or not this mortality and/or intestinal and respiratory problems were treatment-related. Observed clinical signs of toxicity in the treatment zebra finch study group included slightly ruffled to ruffled appearance, reduced reaction to stimuli (i.e. sound and movement), wing droop, and lethargy (see Appendix 3, Table A3-1 for details). Based on these observations, the oral LD_{50} was identified at > 2,000 mg a.i./kg bw as was the NOAEL based on sublethal effects was > 2,000 mg a.i./kg bw (U.S. EPA/OPP 2010a) for both studies. As result, U.S. EPA classified indaziflam as "practically non-toxic" to bobwhite quail and zebra finch when administered a single oral dose.

6.1.2.2.2. Acute Dietary Toxicity

Two acute dietary studies evaluated the toxicity of indaziflam on northern bobwhite quail (*C. virginianus*) (MRID 47443241) and mallard ducks (*Anas platyrhynchos)* (MRID 47443242). Juvenile northern bobwhite quail (10 birds/dose 10-days old) and mallard ducks (10 birds/dose eight days old) were exposed for eight days to indaziflam in the diet at 0, 313, 625, 1250, 2500 and 5000 mg a.i./kg. There were no adverse effects observed in the quail during the study based on the lack of treatment-related mortality, clinical signs of toxicity, effects on body weight or food consumption, or gross pathological changes. Based on this observation, the LC_{50} was identified as > 5,007 mg a.i./kg diet and the NOAEC as 5,007 mg a.i./kg diet for the quail (U.S. EPA/OPP 2010a).

In mallards, no mortality was observed, yielding an LC_{50} of > 5,125 mg a.i./kg for indaziflam in the diet (U.S. EPA/OPP 2010a). Based upon (apparent transient) treatment-related reductions in body weight and food consumption at the 5,125 mg ai/kg diet level, the 8-day NOAEC was 2,518 mg ai/kg diet was determined. The study authors reported that the effect on body weight and feed consumption at the 5,125 mg a.i./kg diet level may be recoverable since body weight gain and food consumption were slightly higher (although not statistically significant) once the birds were offered untreated food in the recovery phase.

As with the acute gavage studies, results of these studies demonstrate that indaziflam is "practically non-toxic" to juvenile quail and mallard ducks on an acute dietary exposure basis (U.S. EPA/OPP 2010a).

6.1.2.2.3. Chronic Reproductive Toxicity

Chronic reproductive toxicity studies in northern bobwhite quail (MRID 47443243) and mallard ducks (MRID 47443244 - primary and supplemental studies) were submitted by the registrant to U.S. EPA/OPP. Results of the one-generation reproductive toxicity study in quail was judged to be "acceptable" meeting the OPPTS 850.2300 guideline standards for an avian reproductive study.

Results of the 23-week study in quail (18 pairs/dose level) showed that there were no treatment related effects to either adults or offspring following exposure to indaziflam (90.3% a.i.) in the diet at measured concentrations of < 5.0 (control), 252, 524, and 1,023 mg a.i./kg diet. Therefore, a LOAEC and NOAEC for indaziflam was identified at > 1,023 mg a.i./kg diet and 1,023 mg a.i./kg diet, respectively (MRID 47443243, U.S. EPA/OPP 2010a).

The second reproductive toxicity study in mallard ducks (15 pairs/dose level) was conducted over 22 weeks with measured dietary concentrations of < 5.0, 44, 157, and 468 mg a.i./kg diet. The U.S. EPA reviewer established a LOAEC and NOAEC of 95 mg ai/kg diet and < 95 mg a.i./kg diet, respectively, based on female weight gain and adult food consumption. The LOAEC and NOAEC for male weight gain was determined by the U.S. EPA reviewer at 1,015 mg a.i./kg diet and 334 mg a.i./kg diet, respectively. The results differ from the study authors' results for mean food consumption (U.S. EPA/OPP 2010a) (page 169-170). "Although a statistically-significant reduction ($p<0.05$) in overall (Weeks 1-22) food consumption was observed in the primary study at the 100 mg as/kg diet level (102.4 g) compared to the control (121.1 g), this difference was not observed at the two higher test levels and was thus not considered to be related to treatment. It was also reported by the study authors that food consumption mean values were within the range of historical control values" (MRID 47443244; pages 13 -14 of the associated DER). Although this study was considered scientifically sound, it was classified as "supplemental" by U.S. EPA because a definitive NOAEC could not be determined.

In addition, a 19-week secondary study is available on mallard ducks (MRID 47443244), but was considered to be supplemental data because indaziflam was only administered in the diet for 6 weeks, instead of the guideline-recommended 18 or more weeks. The dietary concentrations of indaziflam were also lower than the primary study. Effects to adult male weight gain were observed in the modified secondary study at all three treatment levels (44, 157, and 468 mg a.i./kg) and effects to female weight gain were observed at the two highest treatment levels (157, and 468 mg a.i./kg). However, there is uncertainty in the effects observed to male weight gain because there was a net mean weight loss, rather than weight gain, for all treatment levels and control. Regardless, the results of the secondary study provide supporting evidence that indaziflam may have an effect on adult male and female weight gain. The results of mean weight gain for the control, 44, 157, 468 mg a.i./kg treatment groups were -15.9, -35.3 (-121%), -46.1(-189), and -57.1 (-259) grams, respectively. The number in parenthesis is the respective percent reduction in treatment level mean vs. control mean. Birds in the lowest treatment level lost twice as much weight as the control, while the birds in the middle treatment group lost 3 times as much weight as the control, and birds in the highest treatment group lost 4 times as much weight as the control. The reviewer determined the LOAEC

and NOAEC to be 44 and <44 mg a.i./kg, respectively. The secondary study is considered to be supplemental data and supports the NOAEC determination in the primary study of < 95 mg a.i./kg based on female weight gain and adult food consumption (MRID 47443244).

Based on these toxicity studies, U.S. EPA used the NOAEC of 95 mg a.i./kg diet from the primary mallard duck study (MRID 47443244) to assess chronic effects, but there is an area of uncertainty that U.S. EPA noted in their risk assessment. This includes the lack of adequate data to derive a definitive NOAEC.

6.1.2.3. Reptiles and Amphibians (Terrestrial-Phase)

Information is not available on the toxicity of indaziflam to reptiles or terrestrial-phase amphibians in either the open literature or in the available U.S. EPA/OPP ecological risk assessment (U.S. EPA/OPP 2010a). In the absence of available data, birds are used as surrogates for reptiles and terrestrial-phase amphibians. While this is standard practice at U.S. EPA, a concern with the use of birds as a surrogate for amphibians involves the permeability of amphibian skin to pesticides and other chemicals (SERA 2014a). One study on amphibians showed that the skin of the frog *Rana esculenta* is much more permeable to several pesticides than pig skin (ear) and that these differences in permeability are consistent with differences in the structure and function of amphibian skin relative to mammalian skin (Quaranta et al. 2009). However, due to the lack of data on indaziflam, this risk assessment uses birds as surrogates for reptiles and amphibians, which is consistent with U.S. EPA's approach.

6.1.2.4. Terrestrial Invertebrates

Toxicity studies on terrestrial invertebrates are available for honey bees *(Apis mellifera)* and earthworms (*Eisenia foetida*) (U.S. EPA/OPP 2010a). Results of available toxicity studies indicate that technical grade active ingredient (TGAI) is "practically non-toxic" to these terrestrial invertebrates on an acute contact exposure basis. However, subacute effects (e.g., weight reduction) were observed in the earthworm study. The terrestrial invertebrate studies are summarized in Table 6-2 and discussed in the following subsections. Additional information is provided in Appendix 4, Table A4-1.

Table 6-2: Acute Toxicity of Indaziflam to Terrestrial Invertebrates

Species	Study Type	Exposure Duration	Result	Reference
Honey bee (TGAI)	Acute (Contact)	48-hour	LD_{50} > 100 µg a.i./bee NOAEL: 100 µg a.i./bee LOAEL: > 100 µg a.i./bee	MRID 47443245 (Acceptable)
Honey bee (Esplanade 500 SC)	Acute (Contact)	48-hour	LD_{50}: > 100 µg a.i./bee NOAEL: 100 µg a.i./bee LOAEL: > 100 µg a.i./bee	MRID 47743307 (Supplemental)
Honey bee (TGAI)	Acute (Oral)	48-hour	LC_{50} > 120 µg a.i./bee NOAEC: 120 µg a.i./bee LOAEC: > 120 µg a.i./bee	MRID 47443245 (Supplemental)

Species	Study Type	Exposure Duration	Result	Reference
Honey bee (Esplanade 500 SC)	Acute (Oral)	48-hour	LC_{50}: > 119.7 µg a.i./bee NOAEL: 119.7 µg a.i./bee LOAEL: > 119.7 µg a.i./bee	MRID 47743307 (Supplemental)
Earthworm (TGAI)	Acute (Contact)	14-day	LC_{50} > 1,000 mg a.i./kg dw soil NOAEC: 316 mg a.i./kg dw soil LOAEC: 562 mg a.i./kg dw soil	MRID 47443269 (Supplemental)

6.1.2.4.1. Honey Bees

An acute contact study in honey bees using technical grade indaziflam was submitted by the registrant to U.S. EPA for review (MRID 47443245). In this study, honey bees were exposed to indaziflam (as TGAI) over a 48-hour period at a nominal concentration of 100 µg a.i./bee. No mortalities or sub-lethal effects were noted in the control or single treatment level yielding NOAEL and LD_{50} values of 100 and > 100 µg a.i./bee, respectively, indicating that indaziflam is "practically non-toxic" to honey bees on an acute contact exposure basis. This study also provided supplemental information on acute oral toxicity. The oral toxicity test was conducted for 48 hours at a nominal concentration of 120 µg ai/bee. No mortalities or sub-lethal effects were noted in the control or single treatment group during the 48-hour exposure in the oral test, yielding an LC_{50} value of > 120 µg ai/bee and NOAEC value of 120 µg ai/bee (U.S. EPA/OPP 2010a). This study provides the toxicity data for U.S. EPA's risk assessment.

A second acute contact study and supplemental acute oral toxicity study in honey bees was submitted to U.S. EPA (MRID 47743307). Honey bees were exposed to indaziflam (as Esplanade 500 SC) over a 48-hour period at nominal concentrations of 100 µg a.i./bee (contact) and 120 µg a.i./bee (oral). The actual intake of indaziflam during the oral study was 119.7 ug a.i./bee. For the contact test, mortality was 1.7% (one bee died) and study results include an LD_{50} value of > 100 µg a.i./bee. The LC_{50} value for the oral test was > 119.7 µg a.i./bee. No sublethal effects were noted in the oral or contact study. The LOAELs for the oral and contact tests were > 119.7 and > 100 µg a.i./bee, respectively. The NOAELs for the oral and contact tests were 119.7 and 100 µg a.i./bee, respectively (U.S. EPA/OPP 2010a).

As summarized in Table 6-2, the acute oral and contact LD_{50} and LC_{50} values are similar for technical grade indaziflam and indaziflam formulations. The similarities between the toxicity values suggest that other ingredients (i.e. inerts) in the indaziflam formulations do not contribute substantially to toxicity.

6.1.2.4.2. Earthworms

Earthworms (*Eisenia foetida*) were exposed to indaziflam TGAI (94.5%) (MRID 47443269) in soil at measured concentrations of 0, 100, 178, 316, 562 and 1,000 mg a.i./kg dry weight (dw) of soil for 14

days. A NOAEC and LOAEC of 316 and 562 mg a.i./kg dw of soil, respectively, were identified based on the percentage of body weight loss. Mortality did not exceed 3% in any of the treatment groups. Indaziflam was considered by U.S. EPA to be "non-toxic" to earthworms at concentrations of 316 mg a.i./kg dw of soil or less. This study was classified as supplemental by U.S. EPA given that it was not conducted according to any standard OPPTS Guidelines. However, it was found to be scientifically sound (U.S. EPA/OPP 2010a).

Five other toxicity studies were submitted for indaziflam formulations and environmental metabolites as summarized in Appendix 4 Table A4-2. These studies were all considered to be supplemental by U.S. EPA because of protocol deviations such as a 14-day testing period instead of 28 days, differences in light intensity, temperature differences, or differences in the amount of soil per replicate. Additionally, MRID 47743316 did not test up to the limit of 1,000 mg/kg dry weight of soil.

6.1.2.5. Terrestrial Plants (Macrophytes)

6.1.2.5.1. Standard Toxicity Studies

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 relative to a control.

For indaziflam, Tier II plant testing results were submitted by the registrant for the two formulations of indaziflam with the highest percentage of active ingredient, including Esplanade 500 SC (43.6 – 44.87% a.i.) and BCS-AA10717 20WSP (19.6 – 20.3%), compared to a control (U.S. EPA/OPP 2010a). The results of the Tier II testing of indaziflam formulations for the most sensitive species are summarized in Table 6-3 and Appendix 5 includes a list of the studies conducted for all species. Table A5-1 presents toxicity studies for seedling emergence and Table A5-2 for vegetative vigor toxicity studies.

Table 6-3: Toxicity of Indaziflam to Terrestrial Plants for the Most Sensitive Species

Exposure Scenario	Toxicity Study	Formulation	Species	Toxicity Reference Value (lb a.i./Acre)	Reference (Classification)
Monocot	Plants – Seedling Emergence	BCS- AA10717-20WSP (20.3% a.i.)	Ryegrass	EC_{25} (survival) = 0.00016 NOAEC = 0.000062	MRID 47443246 (Acceptable)
Dicot	Plants – Seedling Emergence	BCS- AA10717-20WSP (20.3% a.i.)	Oilseed rape	EC_{25} (emergence) = 0.00011 NOAEC = 0.000062	MRID 47443246 (Acceptable)
Monocot	Plants – Seedling Emergence	Indaziflam 500 SC (43.6% a.i.)	Onion	EC_{25} (shoot length) = 0.00017 NOAEC = 0.000146	MRID 47443247 (Acceptable)
Dicot	Plants – Seedling Emergence	Indaziflam 500 SC (43.6% a.i.)	Tomato	EC_{25} (shoot length) = 0.00024 NOAEC = 0.000146	MRID 47443247 (Acceptable)

Exposure Scenario	Toxicity Study	Formulation	Species	Toxicity Reference Value (lb a.i./Acre)	Reference (Classification)
Monocot	Plants – Vegetative Vigor	BCS- AA10717-20WSP (19.6% a.i.)	Ryegrass	EC_{25} (survival) = 0.0031 NOAEC = 0.002273	MRID 47443248 (Supplemental) [1]
Dicot	Plants – Vegetative Vigor	BCS- AA10717-20WSP (19.6% a.i.)	Turnip	EC_{25} (dry weight) = > 0.000906 NOAEC = < 0.000906	MRID 47443248 (Supplemental) [1]
Monocot	Plants – Vegetative Vigor	Indaziflam 500 SC (44.87% a.i.)	Ryegrass	EC_{25} (survival) = 0.0021 NOAEC = 0.000932	MRID 47443249 (Supplemental)[2]
Dicot	Plants – Vegetative Vigor	Indaziflam 500 SC (44.87% a.i.)	Soybean	EC_{25} (shoot length) = 0.0043 NOAEC = < 0.000375	MRID 47443249 (Supplemental)[2]

Table information taken from (U.S. EPA/OPP 2010a); Table C-17.
[1] Inhibition at 0.000906 lbs a.i./A was 18%; inhibition at 0.00227 lbs a.i./A was 31%. An adequate dose-response relationship could not be constructed to calculate an EC_{25} between these two concentrations.
[2] U.S. EPA reported that this study failed to define a NOAEC or EC_{25} corresponding to the lowest EC_{25} for dicots (i.e. soybean).

In standard assays for seedling emergence, four monocot plant species (corn, oat, barley, and ryegrass) and six dicot species (cucumber, sugarbeet, oilseed rape, soybean, sunflower, and buckwheat) were exposed to indaziflam as formulation BCS-AA10717 20WSP (TEP; 20.0% a.i.) (MRID 47443246) and the effects of seedling survival and emergence were measured for 21 days. The most sensitive monocot was ryegrass (*Lolium perenne*, var. Temprano) based on survival, with an EC_{25} of 0.00016 lbs a.i./A. The most sensitive dicot was oilseed rape (*Brassica napus*, var. Licapo) with an EC_{25} of 0.00011 lbs a.i./A.

Another seedling emergence test for the formulation Esplanade 500 SC (45.05% a.i.) evaluated the toxicity on five monocot plant species (barley, corn, oat, onion, and ryegrass) and seven dicot species (buckwheat, cucumber, oilseed rape, soybean, sugarbeet, sunflower, and tomato) (MRID 47443247). The most sensitive monocot was the onion (*Allium cepa,* var. Braunschweiger blutrot) based on shoot length, with an EC_{25} of 0.00017 lbs a.i./A. The most sensitive dicot was the tomato (*Lycopersicon esculentum*, var. Balkonstar) based on shoot length, with an EC_{25} of 0.00024 lbs a.i./A.

In standard assays for vegetative vigor, four monocot species (corn, onion, oat, and ryegrass) and six dicot species (cucumber, turnip, sugarbeet, sunflower, soybean, and buckwheat) were exposed to indaziflam as formulation BCS-AA10717 20WSP (TEP; 19.6% a.i.) and evaluated for 21-days (MRID 47443248). The most sensitive monocot, based on survival, was ryegrass with an EC_{25} of 0.0031 lbs a.i./A. The most sensitive dicot, based on dry weight, was turnip (*Brassica rapa*, var. Wilhelmburger gelbe). The EC_{25} was visually determined to lie between the lowest concentration and the next highest concentration (EC_{25} = > 0.000906).

Vegetative vigor test for the formulation Esplanade 500 SC (44.87% a.i.) was conducted on four monocot species (corn, onion, oat, and ryegrass) and seven dicot species (cucumber, oilseed rape, sugarbeet, sunflower, soybean, tomato, and buckwheat) for 21 days (MRID 47443249). The most sensitive monocot species, based on survival, was ryegrass (EC_{25} = 0.0021 lbs a.i./A). The most

sensitive dicot species based on shoot length was soybean (*Glycine max*, var. Erin), with an EC_{25} of 0.0043 lbs a.i./A.

Based on the results of the submitted toxicity tests, both monocots and dicots in general appear more sensitive to exposures in seedling emergence testing than those from vegetative vigor testing for both formulations. This is consistent with indaziflam's mode of action as a pre-emergent herbicide. Both formulations also exhibit similar levels of toxicity (i.e. of the same magnitude) for both monocots and dicots.

6.1.2.5.2. Other Toxicity Studies

Several field studies are available in the open literature on the effective use of indaziflam for the control of weed seedlings (Abit and Hanson 2013; Begitschke et al. 2018; Blanco et al. 2015; Brosnan et al. 2011; Brosnan and Breeden 2012; Brosnan et al. 2012; Brosnan et al. 2015; Edwards et al. 2015; Grey et al. 2018; Gonzalez-Delgado et al. 2017; Henry et al. 2012; Kaapro and Hall 2012; Malardo et al. 2017; McCullough et al. 2013; Ramirez et al. 2012; Saha et al. 2017; Sebastian et al. 2016; Sebastian, et al. 2017). As discussed in Sections 5.1.2 and 6.1.2.5.1, indaziflam is toxic to both monocots and dicots, while other CBI herbicides are more active on dicots (Sebastian et al. 2017).

FS risk assessments do not summarize efficacy studies in detail except to the extent that the studies contain relevant information regarding effects on non-target vegetation. For example, a study was conducted at tree nurseries in California to evaluate crop safety of several herbicides on commonly grown peach, plum, and peach/plum hybrid rootstocks budded to almond scions (Abit and Hanson 2013). This involved pre-emergence and post-emergence applications of indaziflam at an application rate of 0.046 to 0.17 lb a.i./acre. Indaziflam provided good weed control and was determined to be relatively safe in this experiment. However, because significant injury to emerging peach seedlings (Nemaguard) was observed, the authors noted that additional work is needed on herbicide rates, timing, and method of application before the herbicides evaluated can be safely applied to newly planted rootstock on a broader scale. This effect level is higher than the NOAEC for the most sensitive dicot in the standard registrant seedling emergence assay for indaziflam (i.e. an NOAEC of 0.000062 lb a.i./acre from MRID 47443248 as summarized in Table 6-3 and Appendix 5).

Another study evaluated the effects of indaziflam on newly established olive trees over three years in the southeastern U.S. (loamy sand soils) (Grey et al. 2016). Multiple spring and autumn applications of indaziflam at different rates were applied to the same newly planted or 1-year old olive trees in different experiments in consecutive years. Visual injury, height, and caliper diameter measures were taken monthly during the growing season up to six times. Regression analysis of treatments over time indicated no differences in olive tree growth for plots with indaziflam at 38, 75 or 150 g a.i./hectare (i.e. 0.034, 0.067, or 0.13 lb a.i./acre) up to five times in three years, compared with nontreated controls.

In a similar experiment, the effects of indaziflam on young pecan trees were evaluated over four years in sandy loam soils (Grey et al. 2018). After winter pecan tree planting, multiple spring or autumn herbicide applications were applied to the same pecan trees in different experiments in consecutive years. Visual injury, height, and caliper diameter measurements were taken up to six times during the growing season. Regression analysis of treatments indicated no differences in pecan tree growth with indaziflam at 73 or 146 g a.i./hectare applied up to six times in three years or

at 37, 73, or 146 g a.i./hectare (i.e., 0.033, 0.65, or 0.13 lb a.i./acre) applied up to five times in 3 years, as compared with nontreated controls.

Studies are also available on the effect of indaziflam in forestry plantations (Kaapro and Hall 2012). Over 20 forestry trials were conducted in the major forestry growing areas on mainland Australia between 2008 and 2009. The rates used varied from 75 to 300 g a.i./hectare (i.e. 0.067 to 0.27 lb a.i./acre). These trials covered both pre and post planting on *Pinus* and *Eucalyptus* species and results showed weed control to be dose-related and stronger with monocot species rather than dicots. Specifically, indaziflam was found to be safe on *Pinus* species when applied pre and post-planting. However, it was only considered safe on *Eucalyptus* species when applied pre-planting.

Field research trials were also conducted to evaluate the tolerance of western conifer species to indaziflam (Quicke 2016). Esplanade F or equivalent suspension concentrate formulations of indaziflam containing 1.67 lbs a.i./gallon were evaluated at rates ranging from 51 to 307 g a.i./ha (i.e. 0.045 to 0.27 lb a.i./acre). Trials were conducted both prior to planting (site preparation) and after planting (herbaceous weed control), which included the following: ponderosa pine, sugar pine, coast redwood, Douglas-fir and western larch (site preparation); ponderosa pine, sugar pine, coast redwood and Douglas-fir (herbaceous weed control). Treatment applications (5 oz or 7 oz) varied from one day before planting, one year after planting or two years after planting. Other variables included incorporation of other supplements (e.g., Accord XRT II, Milestone, Velpar, Chopper or Oust). The study concluded that Douglas fir, coast redwood, ponderosa pine, and western larch are tolerant to Esplanade due to the lack of increase in brownout, needle damage, or bud damage. Results for sugar pine could not be located in the report (Quicke 2016).

6.1.2.6. Terrestrial Microorganisms

Studies on terrestrial microorganisms are not required by U.S. EPA for pesticide registration. Therefore, U.S. EPA's ecological risk assessment on indaziflam do not address effects on terrestrial microorganisms. Studies regarding the toxicity of indaziflam on microorganisms were not identified in the open literature.

6.1.3. Aquatic Organisms

6.1.3.1. Fish

Acute and chronic toxicity studies that describe the hazard potential of indaziflam to freshwater and marine fish are summarized in Table 6-4 and discussed in the following subsections. Appendix 6 presents the information in greater detail (Table A6-1 for acute studies and A6-2 for chronic studies).

Table 6-4: Acute and Chronic Toxicity of Indaziflam to Fish

Exposure Duration	Species/ Chemical	Fish Type	Endpoint	Toxicity Measurement	Reference (Classification)
Acute	Bluegill sunfish AE 1170437 (94.5% a.i.)	Freshwater	Mortality	96-hr LC_{50} = 0.32 mg total a.i./L[1] 96-hr NOAEC = 0.21 mg total a.i./L	MRID 47443233 (Supplemental)

Exposure Duration	Species/ Chemical	Fish Type	Endpoint	Toxicity Measurement	Reference (Classification)
Acute	Bluegill sunfish AE 1170437 (94.5% a.i.)	Freshwater	Sublethal effects	96-hr NOAEC = 0.21 mg total a.i./L 96-hr LOAEC = 0.39 mg total a.i./L	MRID 47443233 (Supplemental)
Acute	Rainbow trout AE 1170437 (94.5% a.i.)	Freshwater	Mortality	96-hour LC_{50} = 0.57 mg total a.i./L 96-hour NOAEC = 0.42 mg total a.i./L	MRID 47443234 (Supplemental)
Acute	Rainbow trout AE 1170437 (94.5% a.i.)	Freshwater	Sublethal effects	96-hr NOAEC = 0.42 mg total a.i./L 96-hr LOAEC = 0.78 mg total a.i./L	MRID 47443234 (Supplemental)
Acute	Fathead Minnow FDAT (99.3% a.i.)	Freshwater	Mortality	96-hr LC_{50}: > 101 mg a.i./L 96-hour NOAEC = 101 mg a.i./L	MRID 47443230 (Acceptable)
Acute	Fathead Minnow FDAT (99.3% a.i.)	Freshwater	Sublethal effects	96-hour NOAEC = 101 mg a.i./L 96-hour LOAEC > 101 mg a.i./L	MRID 47443230 (Acceptable)
Acute	Fathead Minnow Carboxylic Acid (96.6% a.i.)	Freshwater	Mortality	96-hour LC_{50} > 103 mg a.i./L 96-hour NOAEC = 103 mg a.i./L	MRID 47443231 (Acceptable)
Acute	Fathead Minnow Carboxylic Acid (96.6% a.i.)	Freshwater	Sublethal effects	96-hour NOAEC = 103 mg a.i./L 96-hour LOAEC: > 103 mg a.i./L	MRID 47443231 (Acceptable)
Acute	Bluegill sunfish AE 1170437 SC 500 g/L	Freshwater	Mortality and sublethal effects	96-hour LC_{50} = 0.372 mg total a.i./L 96-hour NOAEC = 0.251 mg total a.i./L (LOAEC not listed)	MRID 47743305 (Supplemental)
Chronic	Fathead Minnow BCS-AA10717 (94.5% a.i.)	Freshwater	Reproduction & Growth[2]	35-day NOAEC = 0.464 mg total a.i./L[1] 35-day LOAEC = 1.02 mg total a.i./L[1]	MRID 47443236 (Supplemental)
Acute	Sheepshead minnow BCS-AA10717 (94.5% a.i.)	Estuarine/ Marine	Mortality	96-hr LC_{50} = 0.96 mg total a.i./L[1] 96-hr NOAEC: 0.43 mg a.i./L	MRID 47443232 (Supplemental)

Exposure Duration	Species/ Chemical	Fish Type	Endpoint	Toxicity Measurement	Reference (Classification)
Acute	Sheepshead minnow BCS-AA10717 (94.5% a.i.)	Estuarine/ Marine	Sublethal effects	96-hr NOAEC: 0.43 mg a.i./L 96-hr LOAEC: 0.77 mg a.i./L	MRID 47443232 (Supplemental)
Chronic		Estuarine/ Marine	No studies available		

[1] Total dissolved and undissolved
[2] Chronic effects to reproduction and growth based on fry survival, and total fry length and weight.

6.1.3.1.1. Acute Toxicity

Studies on the acute toxicity of technical grade indaziflam in fish were submitted to U.S. EPA in support of the registration of indaziflam and are summarized below and in Appendix 6. Acute toxicity studies were conducted in three species of freshwater fish (bluegill sunfish, fathead minnow, and rainbow trout) and in one saltwater species (sheepshead minnow) (U.S. EPA/OPP 2010a). U.S. EPA typically uses 96-hour LC_{50} values in fish to assess the potential for acute risks in fish. Several of the studies are considered supplemental because centrifugation was not used to measure dissolved test concentrations (MRID 47443233, MRID 47443234, MRID 47743305, and MRID 47443232).

The acute toxicity of technical grade indaziflam in freshwater fish was evaluated in three studies. In bluegill sunfish (*Lepomis macrochirus*), a 96-hour LC_{50} of 0.32 mg total a.i./L and a NOAEC of 0.21 mg total a.i./L was identified based on lethal and sublethal effects (MRID 47443233). The sublethal effects observed included loss of equilibrium, loss of vertical orientation, labored respiration, and lying on the bottom. A 96-hour LD_{50} of 0.57 mg total a.i./L was identified in rainbow trout (*Oncorhynchus mykiss*; MRID 47443234). The NOAEC was based on mortality, at a value of 0.42 mg total a.i./L. Loss of equilibrium was observed at the highest treatment concentration at 4 hours with complete mortality observed at 24 hours. This precluded the ability to observe sublethal effects thereafter. In fathead minnow (*Pimephales promelas*), a 96-hour LC_{50} of 0.77 mg total a.i./L and a NOAEC of 0.27 mg total a.i./L was identified for sublethal effects (MRID 47443229). The sublethal effects observed were dose-dependent and included loss of equilibrium and erratic behavior.

A study was also submitted on the toxicity of Esplanade 500 SC to bluegill sunfish (MRID 47743305). In this study, a 96-hour LC_{50} of 0.372 mg total a.i./L and a NOAEC of 0.251 mg total a.i./L was identified based on lethal and sublethal effects. Sublethal effects were dose-dependent and included fish on the bottom of the aquarium, dark coloration, hyperactivity, inactivity, labored respiration, loss of equilibrium with lateral deviation, and/or lying on their sides or backs.

An acute toxicity study was also conducted to evaluate the effects of indaziflam on estuarine/marine fish. In this study, sheepshead minnow (*Cyprinodon variegatus*) were exposed to technical grade indaziflam (MRID 47743232). The 96-hour LC_{50} was reported at 0.960 mg total a.i./L and a NOAEC of 0.430 mg total a.i./L. The NOAEC is based on observed dose-dependent effects, including loss of equilibrium, loss of vertical orientation, lying on the bottom, and mortality. The measured concentrations are thus considered to be total concentrations of indaziflam.

Based on these results, both technical grade indaziflam and Esplanade 500 SC are categorized as "highly toxic" to freshwater fish on an acute exposure basis. Indaziflam is also considered "highly toxic" to estuarine/marine fish on an acute exposure basis. The LC_{50} based on bluegill sunfish (0.32 mg total a.i./L) was used by U.S. EPA to assess risk of indaziflam use to freshwater fish (U.S. EPA/OPP 2010a).

Furthermore, two acute studies evaluated the toxicity of the environmental metabolites FDAT (MRID 47443230) and indaziflam- carboxylic acid (MRID 47443231) in freshwater fish using fathead minnow. The environmental metabolites of indaziflam in the aquatic environment are further discussed in Section 4.2. The results of both studies demonstrate that toxicity is three times lower compared to that associated with technical grade indaziflam and indaziflam formulation Esplanade 500 SC. Mortality and sublethal effects were not observed in the at the concentrations of metabolites tested. Based on these results, FDAT and indaziflam-carboxylic acid were categorized as "practically nontoxic" to freshwater fish on an acute exposure basis (U.S. EPA/OPP 2010a).

No acute toxicity studies are available on indaziflam's formulations or metabolites in estuarine/marine fish.

6.1.3.1.2. Chronic Toxicity

A study on the chronic toxicity of technical grade indaziflam is summarized Appendix 6. In this study, fathead minnows were exposed in early life stages (eggs/embryo) to indaziflam for 35 days (MRID 47443236). A NOAEC and LOAEC of 0.464 and 1.02 mg total a.i./L, respectively, were identified based on fry survival, total length, and dry weight. Mortality was usually preceded by loss of equilibrium, lying on the bottom, and/or labored respiration. This study was classified by U.S. EPA as "supplemental" as a statistically significant difference (13%, $p < 0.01$) was found between negative and solvent controls for mean dry weight. Furthermore, centrifugation was not used for the analysis of the dissolved test exposure concentrations. Therefore, all reported measured concentration values are total concentrations of dissolved and undissolved test substance (U.S. EPA/OPP 2010a). As a result, toxicity values will underestimate risk (undissolved test material will not contribute to toxicity; therefore, toxicity values based on dissolved substance only would be lower).

No chronic toxicity studies are available on indaziflam's formulations or metabolites in freshwater fish. Also, no chronic toxicity studies are available in estuarine/marine fish.

6.1.3.2. Amphibians (Aquatic-Phase)

Information was not submitted by the registrant on the toxicity of indaziflam to amphibians. Amphibian toxicity studies with indaziflam were also not identified in the open literature. Per U.S. EPA standard practice, fish are used as surrogates for aquatic-phase amphibians in the absence of data on amphibians (U.S. EPA/OPP 2010a).

6.1.3.3. Aquatic Invertebrates

Both acute and chronic toxicity studies are available on freshwater and estuarine/marine invertebrates. These studies are summarized in Table 6-5 and discussed in the following subsections. Appendix 7 presents the information in greater detail (Table A7-1 for acute studies and A7-2 for chronic studies).

Table 6-5: Acute and Chronic Toxicity of Indaziflam to Aquatic Invertebrates

Exposure Duration	Species/ Chemical	Type of Invertebrate	Endpoint	Toxicity Measurement	Reference (Classification)
Acute	Water flea AE 1170437 (94.5%)	Freshwater	Immobility	48 hr EC_{50} = > 9.88 mg total a.i./L[1] 48 hr NOAEC = 4.86 mg a.i./L	MRID 47443226 (Supplemental)
Acute	Water flea AE 1170437 SC 500 g/L	Freshwater	Immobility	48 hr EC_{50} = > 38 mg total ai/L 48 hr NOAEC = < 2.3 mg total ai/L	MRID 47743303 (Supplemental)
Acute	Water flea BCS-AA10717 SC 200 g/L	Freshwater	Immobility	48 hr EC_{50} = 37.5 mg total ai/L 48 hr NOAEC = 8.26 mg total a.i./L	MRID 47743304 (Supplemental)
Subacute	Midge BCS-AA10717 (94.5%) AE 1170437 (90.3% principle a.i.)	Freshwater	Mortality	*Pore Water Exposure* 10-day LC_{50} = > 2.2 mg a.i./L 10-day NOAEC = 2.2 mg a.i./L	MRID 47443238 (Supplemental)
Chronic	Water flea BCS-AA10717 (94.5%) AE 1170437 90.3% (principle a.i.)	Freshwater	Reproduction & Growth[2]	21-day NOAEC = 340 µg total a.i./L[1] 21-day LOAEC = 800 µg total a.i./L[1]	MRID 47443235 (Supplemental)
Acute	Eastern oyster BCS-AA10717 (94.5%) AE 1170437 (90.32 %)	Estuarine/ Marine	Shell Deposition	96-hr EC_{50} = 0.92 mg total a.i./L 96-hr NOAEC = 0.47 mg total a.i./L	MRID 47443228 (Supplemental)
Acute	Saltwater mysid AE 1170437 (94.5%)	Estuarine/ Marine	Mortality	96-hr LC_{50} = 1.5 mg a.i./L 96-hr NOAEC = 1.06 mg a.i./L	MRID 47443227 (Acceptable)

Exposure Duration	Species/ Chemical	Type of Invertebrate	Endpoint	Toxicity Measurement	Reference (Classification)
Subacute	Amphipod BCS-AA10717 (94.5%) AE 1170437 90.3% (principle a.i.)	Estuarine/ Marine	Mortality	*Pore Water Exposure* 10-day LC_{50} = > 3,800 µg a.i./L	MRID 47443239 (Supplemental)
Chronic		Estuarine/ Marine	No studies available		

[1] Total dissolved and undissolved
[2] Based upon treatment-related effects on decreased growth (body length and dry weight) and reduced number of neonates per reproductive day.

6.1.3.3.1. Acute Toxicity

Similar with fish, acute and chronic studies are required by U.S. EPA to assess the effects of indaziflam on aquatic invertebrates. These studies are summarized in detail in Appendix 7. One study evaluated the acute toxicity of technical grade indaziflam in the water flea (Daphnia magna) (MRID 47443226). This study yielded a 48-hour EC_{50} of > 9.88 mg total a.i./L and a NOAEC of 4.86 mg total a.i./L for sublethal behavioral effects (quiescence). Based on these results, U.S. EPA classified indaziflam as "moderately toxic" to the water flea under acute conditions (U.S. EPA/OPP 2010a). While this study was considered scientifically sound by U.S. EPA, it was classified as "supplemental" because centrifugation was not used to identify dissolved test concentrations as specified in the Standard Test Guideline. Thus, the measured concentrations are considered to be total concentrations of indaziflam (as opposed to a dissolved concentration).

Two acute studies were also submitted on the toxicity of indaziflam formulations Esplanade 200 SC and Esplanade 500 SC in the water flea. In the study using Esplanade 200 SC (MRID 47743304), an EC_{50} value of 37.5 mg total a.i./L and a NOAEC (based on immobility) of 8.26 mg total a.i./L was reported. Besides treatment-related immobility, no other sublethal effects were observed. The other study used Esplanade 500 SC (MRID 47743303) and reported a 48-hour EC_{50} of > 38 mg total a.i./L and a NOAEC of < 2.3 mg total a.i./L based on sublethal effects, including lying on the bottom, quiescence, and paleness. Both of these studies were classified as "supplemental" because the test media was not centrifuged at test termination to determine the dissolved concentrations of test substances. Therefore, reported measured concentration values are total concentrations of test substances in the test media. Based on these two studies, the formulated products do not show greater toxicities than the technical grade indaziflam to freshwater invertebrates.

In addition, a subacute freshwater whole sediment toxicity test is available and provides toxicity data on sediment-dwelling freshwater invertebrates. In this study, the midge (*Chironomus tentans*) was exposed to sediment spiked with indaziflam in an intermittent flow through system for 10 days (MRID 47443238). The results of the testing identified a 10-day LC_{50} of > 2.2 mg a.i./L based on pore water concentrations and a 10-day LC_{50} of > 100 mg a.i./kg sediment dw based on mean-measured sediment concentrations. The 10-day EC_{50} (dry weights) based on mean-measured overlying water concentrations was > 0.18 mg total a.i./L. This study was considered by U.S. EPA as "supplemental" because centrifugation of test media was not conducted for the overlying water.

Acute toxicity in estuarine/marine invertebrates were also evaluated using technical grade indaziflam on the Eastern oyster (*Crassostrea virginica*), the mysid shrimp (*Americamysis bahia*), and the marine amphipod (*Leptocheirus plumulosus*). In the Eastern oyster study (MRID 47743228), a 96-hour EC_{50} of 0.920 mg total a.i./L was identified based on an 88% decrease in shell deposition compared to control. The corresponding NOAEC was identified as 0.470 mg total a.i./L. Mortality was not observed in either the control or any of the treatment groups. Based on these results, indaziflam (TGAI) is categorized by U.S. EPA/OPP as "highly toxic" to estuarine/marine mollusks on an acute exposure basis (U.S. EPA/OPP 2010a).

The acute toxicity on mysid shrimp reported a 96-hour EC_{50} of 1.5 mg a.i./L (MRID 47443227), indicating that indaziflam is "moderately toxic" to estuarine/marine invertebrates on an acute exposure basis. The corresponding NOAEC was identified as 1.1 mg a.i./L based on sublethal effects (i.e. surfacing, lethargy, and erratic swimming) and mortality. In addition, a subacute whole sediment toxicity test was submitted to provide toxicity data on marine benthic invertebrates (MRID 47743239). Results showed that indaziflam is "moderately toxic" to the saltwater mysid (*Americamysis bahia*) on a subacute exposure basis. This was based on mean measured sediment pore water concentrations, which yielded an LC_{50} of > 3.8 mg a.i./L. Based on mean measured sediment concentrations, an LC_{50} of > 180 mg a.i./kg dw was identified with a corresponding NOAEC for lethality of 180 mg a.i./kg sediment dw and an LC_{50} of > 1.4 mg a.i./L was identified based on mean measured overlying water concentrations.

In summary, indaziflam is classified as slightly toxic (EC_{50} = 10 - 100 mg a.i./L) to moderately toxic (EC_{50} = 1 -10 mg a.i./L) to freshwater invertebrates and moderately toxic (EC_{50} = 1 -10 mg a.i./L) to highly toxic (EC_{50} = 0.1 – 1 mg a.i./L) to estuarine invertebrates on an acute exposure basis.

6.1.3.3.2. Chronic Toxicity

Chronic toxicity studies with indaziflam exposure to freshwater aquatic invertebrates is limited to one test study with the water flea (MRID 47443235)**.** In this study, first-generation (F_0) survival (parental immobilization), reproduction (time to first brood release and neonates per reproductive day), growth (total length and dry weight), and sublethal signs of toxicity were assessed. A 21-day NOAEC for indaziflam was identified at 0.340 mg total a.i./L based on effects on decreased growth and the reduced number of neonates per reproductive day. This study was considered scientifically sound by U.S. EPA/OPP. However, it was classified as "supplemental" because effects to offspring (F_1 generation) were not reported. Also, centrifugation was not used to identify dissolved test concentrations as specified in the Standard Test Guideline. The measured concentrations are thus considered to be total concentrations of indaziflam (U.S. EPA/OPP 2010a).

Chronic studies of freshwater aquatic invertebrates exposed to indaziflam formulations or metabolites are not available from the studies submitted by the registrant nor in the open literature. Also, no chronic toxicity studies are available in estuarine/marine invertebrates.

6.1.3.4. Aquatic Plants

6.1.3.4.1. Algae

Acute studies are available on the toxicity of technical grade indaziflam, indaziflam formulations, and four different metabolites to green algae (*Pseudokirchneriella subcapitata*), cyanobacteria

(*Anabaena flos-aquae*), and two diatom species (*Navicula pelliculosa* and *Skeletonemia costatum).* The results of these tests are summarized in Table 6-6 and Appendix 8. Appendix 8 presents the information in greater detail (Table A8-1 for algae toxicity studies).

Based on the results presented in Table 6-6, the most sensitive species of algae identified by U.S. EPA was the marine diatom (*S. costatum*) with a reported 96-hour EC_{50} of 0.027 mg a.i./L and NOAEC of 0.0051 mg a.i./L for reduced biomass. The least sensitive species was green algae (*P. subcapitata*), with a 72-hour EC_{50} of 11 mg a.i./L and NOAEC of < 5.37 mg a.i./L for cell density. Comparison of the toxicity of green algae at 72 hours between technical grade indaziflam and the metabolites indicates that the toxicity of indaziflam-olefin is of the same order of magnitude as the parent compound while the toxicity of indaziflam-hydroxyethyl is one order of magnitude less than the parent compound. Carboxylic acid and diaminotrizaine show toxicity to green algae at two to three orders of magnitude less than that of the parent.

Table 6-6: Acute Toxicity of Indaziflam to Algae

Chemical	Species	Result[1] (mg a.i./L)	Affected Endpoint	Reference (Classification)
Indaziflam (TGAI)	Freshwater Green Algae (*Pseudokirchneriella subcapitata)*	96-hr EC_{50} = 0.077 NOAEC = 0.038	Biomass	MRID 47743309 (Acceptable)
Indaziflam (TGAI)	Freshwater Green Algae (*Pseudokirchneriella subcapitata)*	96-hr EC_{50} = 0.074 NOAEC = 0.0242	Biomass	MRID 47443261 (Acceptable)
Indaziflam (TGAI)	Freshwater Green Algae (*Pseudokirchneriella subcapitata)*	72-hr EC_{50} = 0.064	Cell Density	MRID 47443261 (Acceptable)
Indaziflam (Esplanade 500 SC)	Freshwater Green Algae (*Pseudokirchneriella subcapitata)*	72-hr EC_{50} = 0.051 NOAEC = < 0.034	Cell Density	MRID 47743310 (Supplemental)
Indaziflam (Esplanade 200 SC)	Freshwater Green Algae (*Pseudokirchneriella subcapitata)*	72-hr EC_{50} = 0.053 NOAEC = 0.0168	Cell Density	MRID 47743311 (Supplemental)
Indaziflam-Diaminotrizaine **Fluoroethyldiamino triazine (FDAT)**	Freshwater Green Algae (*Pseudokirchneriella subcapitata)*	72-hr EC_{50} = 11 NOAEC = < 5.37	Cell Density	MRID 47443262 (Supplemental)
Indaziflam-Carboxylic Acid	Freshwater Green Algae (*Pseudokirchneriella subcapitata)*	72-hr EC_{50} = > 9.4 NOAEC = 4.6	Not Determined	MRID 47443263 (Supplemental)
Indaziflam-Hydroxyethyl	Freshwater Green Algae (*Pseudokirchneriella subcapitata)*	72-hr EC_{50} = 0.55 NOAEC = 0.33	Cell Density	MRID 47443264 (Supplemental)
Indaziflam-Olefin	Freshwater Green Algae (*Pseudokirchneriella subcapitata)*	72-hr EC_{50} = 0.054 NOAEC = 0.0102	Biomass	MRID 47443265 (Supplemental)

Chemical	Species	Result[1] (mg a.i./L)	Affected Endpoint	Reference (Classification)
Indaziflam (TGAI)	Freshwater Diatom *(Navicula pelliculosa)*	96-hr EC_{50} = 0.087 total NOAEC = 0.0177 total	Biomass	MRID 47443266 (Supplemental)
Indaziflam (TGAI)	Marine Diatom (*Skeletonemia costatum*)	96-hr EC_{50} = 0.027 NOAEC = 0.0051	Biomass	MRID 47443267 (Acceptable)
Indaziflam (TGAI)	Freshwater Cyanobacteria *(Anabaena flos-aquae)*	96-hr EC_{50} = 0.750 total NOAEC = 0.115 total	Cell Density	MRID 47443268 (Supplemental)

[1] Based on information from U.S. EPA's ecological risk assessment (U.S. EPA/OPP 2010a; Table C-7) and the individual MRIDs.

6.1.3.4.2. Aquatic Macrophytes

The toxicity studies submitted by the registrant for freshwater vascular plant duckweed (*L. gibba*) are summarized in Table 6-7. Appendix 8 presents the information in greater detail (Table A8-2 for aquatic vascular plant toxicity studies using Duckweed).Two studies were submitted using TGAI indaziflam and one with the indaziflam formulation Esplanade 500 SC. Five toxicity studies were submitted for exposure to five different indaziflam environmental metabolites, including triazine-indanone, FDAT, indaziflam-carboxylic acid, indaziflam-hydroxyethyl, and indaziflam-olefine. All the duckweed toxicity studies are classified as "acceptable" with the exception to the FDAT study.

Based on the results presented in Table 6-6, the highest toxicity in duckweed was observed using Esplanade 500 SC, with reported EC_{50} and NOAEC values of 0.000061 mg a.i./L and 0.0000194 mg a.i./L, respectively, for frond number. Technical grade had a similar toxicity (EC_{50} = 0.000067 mg a.i./L) in duckweed compared to Esplanade 500 SC (EC_{50} = 0.000061 mg a.i./L). For the indaziflam metabolites, results showed that the toxicity of the indaziflam metabolites to duckweed is one to seven orders of magnitude less than that of technical grade indaziflam or Esplanade 500 SC; results indicate that indaziflam is more toxic to duckweed than the indaziflam metabolites.

As discussed in the previous section (6.1.3.4.1), the reported EC_{50} values for algae are in the range of 0.027 mg a.i./L (marine diatom) and 11 mg a.i./L (green algae). Based on this comparison, aquatic plants are less tolerant (i.e. more sensitive) to indaziflam than algae.

Table 6-7: Most Sensitive Toxicity Values for Aquatic Vascular Plants Using Duckweed

Chemical	Result[1] (mg a.i./L)	Affected Endpoint	Reference (Classification)
Indaziflam (TGAI)	7-day EC_{50} = 0.000067 NOAEC = 0.000031	Frond Area	MRID 47443250 (Acceptable)
Indaziflam (TGAI)	7-day EC_{50} = 0.00035 NOAEC = 0.000167	Frond Number	MRID 47443256 (Supplemental)

Chemical	Result[1] (mg a.i./L)	Affected Endpoint	Reference (Classification)
Indaziflam (Esplanade 500 SC)	7-day EC_{50} = 0.000061 NOAEC = 0.0000194	Frond Number	MRID 47443308 (Acceptable)
Indaziflam-Olefin	7-day EC_{50} = 0.00034 NOAEC =0.00009	Frond Area	MRID 47443255 (Acceptable)
Indaziflam-Hydroxyethyl	7-day EC_{50} = 0.00051 NOAEC = 0.00025	Frond Area	MRID 47443254 (Acceptable)
Triazine-indanone	7-day EC_{50} = 0.012 NOAEC = 0.00609	Frond Area	MRID 47443251 (Acceptable)
FDAT	7-day EC_{50} = 0.051 NOAEC = < 0.0111	Frond Number	MRID 47443252 (Supplemental)
FDAT	7-day EC_{50} = > 0.0352 NOAEC = < 0.0111	Frond Area	MRID 47443252 (Supplemental)
FDAT	7-day EC_{50} = > 0.0352 NOAEC = < 0.0111	Frond Area (based on growth rate)	MRID 47443252 (Supplemental)
Indaziflam-Carboxylic Acid	7-day EC_{50} = 4.0 NOAEC =1.13	Frond Number	MRID 47443253 (Acceptable)

[1] Based on information from U.S. EPA's ecological risk assessment (U.S. EPA/OPP 2010a; Table C-8) and the individual MRIDs.

6.2. Exposure Assessment

6.2.1. Overview

A standard nationwide set of exposure assessments for terrestrial and aquatic organisms is provided in the Excel workbook for indaziflam (Attachment 1). The workbook contains a set of worksheets that detail each exposure scenario. In FS risk assessments, the methodology and results of calculations are provided in the worksheets with the intention of keeping the text simpler in the main report. 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 6.4. All exposure assessments are based on an application rate of 0.091 lb a.i./acre of indaziflam. The FS may modify the assumptions and inputs to better represent a specific site in future risk assessment.

For terrestrial organisms, exposures are assessed for mammals, birds, invertebrates, plants, and microorganisms. Because toxicity data are not available on terrestrial-phase amphibians and reptiles (Section 6.1.2.3), exposure assessments for these terrestrial vertebrates were not developed. For mammals and birds, the highest exposures are associated with the consumption of contaminated vegetation. This is a common pattern for pesticides that are applied to or intended to treat vegetation.

Exposure assessments for terrestrial invertebrates include direct spray and drift, ingestion of contaminated vegetation or prey, and contact with contaminated soil. The highest exposures for terrestrial invertebrates are associated with direct spray and spray drift.

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 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 may favor runoff, particularly sites with predominantly clay soils. Potential exposures involving the use of contaminated water for irrigation are also significant. While exposures associated with the movement of indaziflam on soil particles by wind do not appear to be a substantial source of exposure, the product labels for indaziflam provide cautionary language on this exposure route.

Exposures of aquatic organisms and plants to indaziflam are based on the same information used to assess the exposure to terrestrial species from 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 contaminated vegetation or prey, ingestion of contaminated water, and consumption of contaminated fish. For these exposure scenarios, five non-target mammals and four non-target birds of varying sizes are considered and summarized in Table 6-8.

Table 6-8: Terrestrial Non-Target Mammals and Birds Used in the Ecological Risk Assessment

Animal	Representative Species	Species Type	Body Weight (grams)	Food Consumption[3]	Water Consumption
Small omnivore	Mice	Mammals[1]	20	2.514 $W^{0.507}$ [Eq 3-48]	0.099 $W^{0.9}$ [Eq 3-17]
Larger omnivore	Squirrels	Mammals[1]	400	2.514 $W^{0.507}$ [Eq 3-48]	0.099 $W^{0.9}$ [Eq 3-17]
Canid	Fox	Mammals[1]	5,000	0.6167 $W^{0.862}$ [Eq 3-47]	0.099 $W^{0.9}$ [Eq 3-17]
Large Herbivore	Deer	Mammals[1]	70,000	1.518 $W^{0.73}$ [Eq 3-46]	0.099 $W^{0.9}$ [Eq 3-17]
Large Carnivore	Bear	Mammals[1]	70,000	0.6167 $W^{0.862}$ [Eq 3-47]	0.099 $W^{0.9}$ [Eq 3-17]
Small bird	Passerines	Birds[2]	10	2.123 $W^{0.749}$ [Eq 3-36]	0.059 $W^{0.67}$ [Eq 3-15]
Predatory (carnivorous) bird	Owls	Birds[2]	640	1.146 $W^{0.749}$ [Eq 3-37]	0.059 $W^{0.67}$ [Eq 3-15]

Animal	Representative Species	Species Type	Body Weight (grams)	Food Consumption[3]	Water Consumption
Piscivorous (fish-eating) bird	Herons	Birds[2]	2,400	1.916 $W^{0.704}$ [Eq 3-38]	0.059 $W^{0.67}$ [Eq 3-15]
Large herbivorous bird	Geese	Birds[2]	4,000	1.146 $W^{0.749}$ [Eq 3-37]	0.059 $W^{0.67}$ [Eq 3-15]

[1] Mammal Sources: Reid 2006; U.S. EPA/ORD 1993.
[2] Bird Sources: Sibley 2000; Dunning 1993; U.S. EPA/ORD 1993
[3] 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).

Because of the relationship of body weight to surface area as well as 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 (i.e. consumption of food items), not all the mammal and avian receptors are considered in each exposure scenario (SERA 2014a).

Indaziflam 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 of Attachment 1. 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 may 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 indaziflam application by broadcast spray (Attachment 1 Worksheet F01a). The absorbed dose over the first day is estimated using the assumption of first-order dermal absorption, which is based on the QSAR method as discussed in Section 5.1.3.2.1. 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 indaziflam 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). These estimates of absorbed doses of indaziflam for this exposure scenario are intended to be the conservative upper limit of exposures and account for uncertainties in the estimation of indaziflam doses associated with direct spray.

Direct spray exposure scenarios are not evaluated for large mammals. Allometric relationships demonstrate that large mammals are exposed to lower amounts of indaziflam (relative to body weight) of indaziflam compared to smaller mammals. Also, the direct spray exposure scenario estimates of indaziflam for small mammals are below a level of concern (Section 5.6). As a result, calculation of direct spray exposure scenarios for large mammals would have no impact on the characterization of risk.

6.2.2.1.2. Dermal Contact with Contaminated Vegetation

When estimating the potential significance of dermal contact with 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 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 contaminated vegetation adds relatively little uncertainty to this risk assessment because the consumption of contaminated vegetation is the greatest source of exposure (Section 6.2.2.1.3).

6.2.2.1.3. Ingestion of Contaminated Vegetation or Prey

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

The initial concentrations of indaziflam on contaminated food items are based on the residues rates from Fletcher et al. (1994) as summarized in Table 5-22. Residue rates are provided for four different classes of plant material, including short grass, tall grass, broadleaf vegetation, and fruits. As summarized in Table 5-22, 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 Attachment 1. The methods of estimating the peak and time-weighted average concentrations of indaziflam 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 may move in and out of the treated areas over a prolonged period of time. While estimates of the proportion of the 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 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). The consumption of contaminated insects by a small mammal, a larger (400 g) mammal, and a small bird are also considered (Worksheets F09a-c).

6.2.2.1.4. Ingestion of Contaminated Water

Mammals may be exposed to indaziflam by direct ingestion of contaminated surface water. The methods for estimating indaziflam 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 Attachment 1.

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 in the open literature. Therefore, this variability is not considered in the exposure assessment. Regardless, the upper and lower bound estimates of indaziflam concentrations in surface water vary substantially, as summarized in Table 5-21. Given this variability in the estimated concentrations of indaziflam 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 (Attachment 1 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 (Reid 2006). As summarized in Table 6-8, 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 indaziflam concentration in water and the BCF for indaziflam in fish (SERA 2014a). The concentrations of indaziflam in water are summarized in Section 5.2.2.4.5. A BCF of 46 for whole fish is reported by U.S. EPA and discussed in Section 5.2.2.5. 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 may be exposed to indaziflam through direct contact or consumption of contaminated vegetation or prey. This section summarizes the exposure associated with the direct spray and drift, ingestion of contaminated vegetation or prey, and contact with contaminated soil. Table 6-9 includes a list of the non-target invertebrates used to assess exposure levels.

Table 6-9: Terrestrial Non-Target Invertebrates Used in the Ecological Risk Assessment

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

[1] Sources: Humphrey and Dykes 2008; Reichle et al. 1973; Winston 1987
[2] For honey bees, food consumption based on activity and caloric requirements. For herbivorous insects, consumption estimates are based on fractions of body weight (g food consumed/g bw).
[3] 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.
[4] 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 much higher dose of indaziflam 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 Attachment 1. 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 are based on Tier 1 estimates from AgDRIFT (Teske et al. 2003) 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 may 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.

6.2.2.2.2. Ingestion of Contaminated Vegetation or Prey

Terrestrial invertebrates may be exposed to indaziflam through the consumption of contaminated vegetation or contaminated prey. For broadcast foliar applications, estimates of residues on contaminated vegetation or prey are based on estimated residue rates (i.e. mg/kg residues per lb applied) from Fletcher et al. (1994), which are summarized in Table 5-22.

An estimate of food consumption is necessary to calculate a dose level for a foraging herbivorous insect. As described in SERA (2014a), insect food consumption varies depending on the caloric requirements in a given life stage or activity of the insect and the caloric value of the food to be consumed. While the derivation of consumption values is beyond the scope of the current analysis, general food consumption values are readily available and are based on estimated food consumption per unit body weight. One study evaluated the food consumption patterns of insect herbivores in a forest canopy and estimated that insect herbivores may consume vegetation at a rate of about 0.6 of their body weight per day (Reichle et al. 1973). Higher values in the range of 1.28 to 2.22 (fresh weight) are reported in another study on the consumption of various types of vegetation by the tobacco hornworm (Waldbauer 1968). Consistent with previous FS risk assessments, this assessment uses food consumption factors of 1.3 (0.6 to 2.2) kg food/kg bw. The lower bound of 0.6 is taken from Reichle et al. (1973), and the central estimate and upper bound are taken from the range of values provided by Waldbauer (1968).

The estimated exposures in terrestrial herbivorous insects are summarized in Table 6-10 and Attachment 1 Worksheet G08. The details of the calculations for these scenarios are provided in Worksheets G07a to G07d of Attachment 1.

Table 6-10: Summary of Exposure Assessments for the Herbivorous or Predatory Insects

Food Item	Exposure	Receptor	Central	Lower[1]	Upper[1]	Detail Worksheet
Fruit/Large Insects	Acute	Insect	8.28E-01	1.75E-01	3.00E+00	G07a
Broadleaf/Small Insects	Acute	Insect	5.32E+00	8.19E-01	2.70E+01	G07b
Short Grass	Acute	Insect	1.01E+01	1.64E+00	4.80E+01	G07c
Long Grass	Acute	Insect	4.26E+00	6.55E-01	2.20E+01	G07d

[1] The lower and upper dose represent the 95% confidence interval.
Note: Dose measured in mg a.i./kg/day or mg a.i./kg/event.

6.2.2.2.3. Contact with Contaminated Soil

FS risk assessments do not typically include estimates of soil exposures because toxicity values for soil invertebrates are not always available. However, in the case of indaziflam, toxicity studies are available in earthworms and these studies indicate no effects at concentrations of 316 mg a.i./kg dw. Based on the results summarized in Appendix 9 from the GLEAMS-Driver modeling, the estimated peak concentrations of indaziflam in the top 12 inches of soil are lower = 0.197, central = 0.220, and upper = 0.331 mg a.i./kg dw soil at a unit application rate of 1 lb a.i./acre (i.e. the applicate rate used

in the GLEAMS-Driver modeling). At maximum labeled application rate of 0.091 lb a.i./acre, the estimated peak concentrations of indaziflam would be lower = 0.018, central = 0.020, and upper = 0.030 mg a.i./kg dw soil. These levels of exposure are far below the NOAEC of 316 mg a.i./kg dw.

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 Attachment 1 Worksheet G05a. 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 (Teske et al. 2003). These estimates are summarized in Worksheets G05a and G05b of Attachment 1. The worksheets were customized to include estimates of drift at 0, 25, 50, 100, 300, 500 and 900 feet downwind for aerial, ground broadcast, and backpack 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 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 or BLM 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 Esplanade 200 SC mentions that coarse or greater droplet sizes should be used in ground applications to reduce spray drift. For Esplanade F, the product label specifies that medium to large droplets should be used for both aerial and ground applications. 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) are 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 may impact non-target plants. In contrast, percolation represents the amount of the herbicide that is transported below the root zone, which may 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 Attachment 1. 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 of 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 9 (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., 0.0481 (0.00000684 - 0.372) 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 indaziflam 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 9, 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 indaziflam 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.

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.

6.2.2.3.5. Wind Erosion

Wind erosion may lead to pesticides being transported off-site. The amount of indaziflam 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 Attachment 1. For this risk assessment, it is assumed that indaziflam is incorporated into the top 1 cm of soil, which is identical to the depth of incorporation used in GLEAMS modeling (Table 5-18). 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 (Allen and Fryrear 1977; SERA 2014a).

As summarized in Worksheet G06b, off-site losses from wind erosion are estimated to reach as much as 0.014% of the application rate. 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 to 10 metric tons/ha/year) (Patric 1976). Thus, losses due to wind erosions following pesticide applications under forest canopies or heavily vegetated areas may 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) may 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 indaziflam, but the product labels for Esplanade 200 SC and Esplanade F provide a discussion on spray drift management and specifically direct the applicator to not apply when wind speeds are greater than 10 mph, gusty, or below 2 mph (due to inversion potential). The applicator should also not apply the formulated products when there is a potential for drift to areas where sensitive crops and plants are growing.

As discussed further in Section 6.4.2.5.4, the current risk assessment does not raise substantial 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 indaziflam due to the wind erosion. Regardless, the product labels must be considered carefully prior to applying indaziflam.

6.2.3. Aquatic Organisms

The concentrations of indaziflam 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 and summarized in Table 5-21.

6.3. Dose-Response Assessment

6.3.1. Overview

The toxicity values used in the ecological risk assessment are summarized in Table 6-11. 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 algae
8. Aquatic macrophytes

Based on the lack of toxicity data for reptiles or for 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 6-11 are expressed as active ingredient. Appendix 2 and 3 contains additional information about the toxicity studies to mammals and birds, respectively.

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 or most conservative NOAEC values are selected for the FS risk assessment.

1 **Table 6-11: Toxicity Values Used in the Ecological Risk Assessment**

Group/Organism	Type	Exposure	Endpoint	Toxicity Value	Reference
Terrestrial Animal: Mammals	N/A	Acute (gavage)	Neurotoxicity NOAEL, rats	50 mg a.i./kg bw/day	Section 6.3.2.1
Terrestrial Animal: Birds	N/A	Acute (capsule/ gavage)	Acute dose NOAEL, bobwhite quail and zebra finch	2,000 mg a.i./kg bw	Section 6.3.2.2
Terrestrial Animal: Honey Bee (contact)	N/A	Acute	Acute contact assay	862 mg a.i./kg bw	Section 6.3.2.4.1
Terrestrial Animal: Honey Bee (oral)	N/A	Acute	Acute oral assay	1,034 mg a.i./kg bw	Section 6.3.2.4.2
Terrestrial Animal: Mammals	N/A	Chronic (dietary)	Neurotoxicity NOAEL, dogs	2.0 mg a.i./kg bw/day	Section 6.3.2.1
Terrestrial Animal: Birds	N/A	Chronic (dietary)	Chronic NOAEL, mallard duck	95 mg a.i./kg diet	Section 6.3.2.2
Terrestrial Plants[6]: Soil	Sensitive	Chronic	Oilseed rape, dicot, NOAEC	0.000062 lb a.i./acre	Section 6.3.2.5 6.3.2.4.3
Terrestrial Plants[6]: Soil	Tolerant	Chronic	Tomato, dicot, NOAEC	0.000146 lb a.i./acre	Section 6.3.2.5 6.3.2.4.3
Terrestrial Plants[6]: Foliar	Sensitive	Chronic	Soybean, dicot, NOAEC	0.000375 lb a.i./acre	Section 6.3.2.5
Terrestrial Plants[6]: Foliar	Tolerant	Chronic	Ryegrass, monocot, NOAEC	0.002273 lb a.i./acre	Section 6.3.2.5
Aquatic Animals: Fish	Sensitive	Acute	Bluegill sunfish, chronic NOAEC	0.464 mg a.i./L	Section 6.3.3.1
Aquatic Animals: Fish	Tolerant	Acute	Fathead minnow, chronic NOAEC	1.02 mg a.i./L	Section 6.3.3.1
Aquatic Animals: Invertebrates	Sensitive	Acute	Eastern oyster, NOAEC	0.47 mg a.i./L	Section 6.3.3.3
Aquatic Animals: Invertebrates	Tolerant	Acute	*Daphnia magna,* NOAEC	4.86 mg a.i./L	Section 6.3.3.3
Aquatic Animals: Fish	Sensitive	Chronic	Bluegill sunfish, NOAEC	0.464 mg a.i./L	Section 6.3.3.1

[6] Because the NOAEC for soybean (< 0.000375 lb a.i./acre) for vegetative vigor is lower than the NOAEC value reported for turnip, the NOAECs for oilseed rape and soybean are used for the risk characterization of sensitive species.

Group/Organism	Type	Exposure	Endpoint	Toxicity Value	Reference
Aquatic Animals: Fish	Tolerant	Chronic	Fathead minnow, NOAEC	1.02 mg a.i./L	Section 6.3.3.1
Aquatic Animals: Invertebrates	Sensitive	Chronic	Acute-to-chronic ratio method based on *Daphnia magna* chronic	0.032 mg a.i./L	Section 6.3.3.3
Aquatic Animals: Invertebrates	Tolerant	Chronic	*Daphnia magna,* NOAEC	0.340 mg a.i./L	Section 6.3.3.3
Aquatic Plants: Algae	Sensitive	Chronic	Marine diatom (*S. costatum*), NOAEC	0.0051 mg a.i./L	Section 6.3.3.4.1
Aquatic Plants: Algae	Tolerant	Chronic	Green algae (*P. subcapitata*), NOAEC	5.37 mg a.i./L	Section 6.3.3.4.1
Aquatic Plants: Macrophytes	Sensitive	Chronic	Not determined	Not determined	Section 6.3.3.4.2
Aquatic Plants: Macrophytes	Tolerant	Chronic	Duckweed (*L. gibba)*, NOAEC	0.0000194 mg a.i./L	Section 6.3.3.4.2

6.3.2. Terrestrial Organisms

6.3.2.1. Mammals

As discussed in Section 5.3.2, U.S. EPA/OPP derived an acute RfD for indaziflam of 0.50 mg a.i/kg bw/day for all populations. This acute RfD is based on the NOAEL of 50 mg a.i./kg bw/day from the acute neurotoxicity study in rats and an uncertainty factor of 100 [50 mg a.i./kg bw/day ÷ 100]. Acute toxicity values are only available in rats. Therefore, potential differences across species could not be determined.

For repeated dose studies, U.S. EPA selected a developmental study in rats to assess chronic effects in mammals. In this study, NOAELs of 69 and 85 mg a.i./kg bw/day were observed in males and females, respectively. However, based on subchronic LOAELs, dogs appear to be more sensitive than rats by a factor of about 38 (572 mg/kg bw/day ÷ 15 mg/kg bw/day ≈ 38.13). For chronic LOAELs, dogs are more sensitive than rats by a factor of about 50 (329.5 mg/kg bw/day ÷ 6.5 mg/kg bw/day ≈ 50.69). Because the most sensitive endpoint for indaziflam involves neurotoxic effects in dogs, as described in Section 5.1.5, the chronic neurotoxicity study in dogs serves as the basis for the dose-response in both the human health and ecological risk assessments described in this report

6.3.2.2. Birds

For the acute dose-response assessment in birds, the NOAEL of 2,000 mg a.i./kg bw was used to assess potential risks of acute exposures in birds (MRID 47443240). As discussed in Section 6.1.2.2 and summarized in Table 6-1, no adverse effects were noted at the highest doses tested (i.e. 2,000 mg a.i./kg bw for the oral study in quail and 5,215 mg a.i./kg bw in mallard ducks).

For chronic exposures, U.S. EPA/OPP used a dietary NOAEC of 95 mg a.i./kg diet to assess chronic risks. As summarized in Table 6-1, a non-definitive[7] NOAEC of < 95 mg a.i./kg diet was observed in a reproduction study on mallard ducks (MRID 47443244). A secondary reproduction study in mallard ducks was submitted and reported a NOAEC of < 44 mg ai/kg diet. However, the results from this secondary study are not directly comparable to the results from the primary study since birds in the secondary study were only dosed for 6 weeks vs 22 weeks. Thus, U.S. EPA used the NOAEC of 95 mg a.i./kg diet from the primary study to assess chronic effects. As discussed in Section 6.1.2.2.3, there is area of uncertainty given that the current data in mallard ducks is not adequate to derive a definitive NOAEC.

Dietary concentrations (mg/kg diet) are converted to mg/kg bw/day doses using a food consumption factor of 0.07 kg food/kg bw, which is based on reproduction studies in quail and mallards (SERA 2007a). Using this food consumption factor, the dietary NOAEC of 95 mg a.i./kg diet corresponds to 6.7 mg a.i./kg bw/day.

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 cannot be derived for this group of organisms.

6.3.2.4. Terrestrial Invertebrates

6.3.2.4.1. Contact Toxicity Value (Honey Bees)

Contact toxicity studies are typically used to assess the effects of direct spray or spray drift to terrestrial insects. As summarized in Section 6.1.2.4.1 and Table 6-2, two contact toxicity studies are available in honey bees. Both studies reported a NOAEL value of 100 µg a.i./bee. Taking the average body weight of 116 mg for a bee, this NOAEL is equivalent to a dose of about 862 mg a.i./kg bw [0.1 mg ÷ 0.000116 kg ≈ 862.07 mg a.i./kg bw].

6.3.2.4.2. Oral Toxicity Value (Honey Bees)

FS risk assessments attempt to characterize risks to terrestrial invertebrates from the consumption of contaminated vegetation following broadcast applications. The results of oral toxicity studies in honey bees are typically used to assess risks associated with this scenario. Based on the available oral toxicity studies discussed in Section 6.1.2.4.1, a NOAEL of 119.7 µg a.i./bee was used in the dose-response assessment. This NOAEL is equivalent to a dose of about 1,034 mg a.i./kg bw [0.120 mg ÷ 0.000116 kg ≈ 1,034 mg a.i./kg bw].

6.3.2.4.3. Soil Toxicity Values (Earthworms)

As discussed in Section 6.1.2.4.2, indaziflam was considered by U.S. EPA to be “non-toxic" to earthworms at concentrations of 316 mg a.i./kg dw of soil or less based on an available toxicity study. In this study, a NOAEC and LOAEC of 316 and 562 mg a.i./kg dw of soil, respectively, were identified based on the percentage of body weight loss (MRID 47443269). FS risk assessments do not

[7] A non-definitive NOAEC = free-standing NOAEL, with no associated LOAEL, therefore, no adverse effects observed at the highest dose tested

typically derive HQs for earthworms, and there is no reason to alter this practice in the current risk assessment. Based on the NOAEC of 316 mg a.i./kg dw soil, a qualitative characterization of risk is discussed briefly in Section 6.4.2.4.3.

6.3.2.5. Terrestrial Plants (Macrophytes)

As summarized in Section 6.1.2.5 and Table 6-3, adequate data are available for developing toxicity values for both sensitive and tolerant plant species involving soil exposures (i.e. herbicide runoff to an untreated field) and foliar exposures (i.e. direct spray, wind erosion, or drift).

For sensitive species, the U.S. EPA's ecological risk assessment uses the EC_{25} of 0.00011 lb a.i./acre for seedling emergence (oilseed rape [dicot]) and the EC_{25} of > 0.000906 lb a.i./acre for vegetative vigor (turnip [dicot]). FS risk assessments typically use the same studies and species used by U.S. EPA in the dose-response assessment, but use the NOAECs rather than the EC_{25} values. As summarized in Table 6-3, the NOAEC values associated with the EC_{25} values used by U.S. EPA are 0.000062 lb a.i./acre (seedling emergence in oilseed rape) and > 0.000906 lb a.i./acre (vegetative vigor in turnip). However, because the NOAEC for soybean (< 0.000375 lb a.i./acre) for vegetative vigor is lower than the NOAEC value reported for turnip, the NOAECs for oilseed rape and soybean are used for the risk characterization of sensitive species.

For tolerant species, tomato and soybean appear to be more tolerant of indaziflam for seedling emergence and vegetative vigor than other test species (e.g., cucumber, turnip), respectively, based on the EC_{25} values. The EC_{25} for tomato (dicot) is 0.00024 lb a.i./acre and the EC_{25} for soybean (dicot) is 0.0043 lb a.i./acre. As summarized in Table 6-3, the NOAEC values associated with the EC_{25} values used by U.S. EPA are 0.000146 lb a.i./acre (seedling emergence in tomato) and 0.000375 lb a.i./acre (vegetative vigor in soybean). However, because the NOAEC for ryegrass (0.002273 lb a.i./acre) for vegetative vigor testing is higher than the NOAEC value reported for soybean, the NOAECs for tomato and ryegrass are used for the risk characterization of tolerant species.

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

6.3.3.1. Fish

For characterizing risks to fish, U.S. EPA used an acute NOAEC of 0.210 mg total a.i./L and a chronic NOAEC of 0.464 mg a.i./L (U.S. EPA/OPP 2010a). As discussed in Section 6.1.3.1, the lowest 96-hr LC_{50} value is 0.320 mg total a.i./L in bluegill sunfish, with an associated NOAEC for mortality of 0.210 mg total a.i./L (MRID 47443233). In the chronic study in fathead minnow, a NOAEC and LOAEC values of 0.464 and 1.02 mg total a.i./L, respectively for decreased fry survival, length, and weight (MRID 47443236).

Typically, FS risk assessments use the studies selected by U.S. EPA in risk characterization of sensitive species of fish. However, this approach is not adopted for indaziflam because the estimated acute NOAEC (0.210 mg total a.i./L) is less than the chronic NOAEC (of 0.464 mg a.i./L). Consistent with FS risk assessment practice, the acute NOAEC should be greater than or equal to the chronic NOAEC.

Therefore, the chronic NOAEC is adopted and used for the acute dose-response assessment (SERA 2014a).

The U.S. EPA does not typically derive separate risk estimates for potentially tolerant species of fish, which is a routine practice in FS risk assessments. For acute and chronic exposures, the dose-response assessment is based on the chronic 35-day NOAEC of 1.02 mg a.i./L in fathead minnow (MRID 47443236). Similar to the sensitive species of fish, the acute 96-hour NOAEC of 0.27 mg a.i./L based on sublethal effects in fathead minnow (MRID 47443229) is not used because the acute NOAEC is less than the chronic NOAEC of 1.02 mg a.i./L.

6.3.3.2. Amphibians (Aquatic-Phase)

Because of the lack of toxicity data on aquatic phase amphibians, no dose-response assessment for this group of organisms was developed. As noted in Section 6.1.3.2, U.S. EPA uses fish as surrogates for aquatic phase amphibians and this approach is discussed further in the risk characterization (Section 6.4.3.2).

6.3.3.3. Aquatic Invertebrates

6.3.3.3.1. Acute Toxicity Values

For acute exposures to freshwater invertebrates, U.S. EPA noted an acute EC_{50} of > 9.88 mg total a.i./L and NOAEC value of 4.86 mg total a.i./L in the water flea (*Daphnia magna)* (MRID 47443226). However, due to the lack of a definitive EC_{50} value, U.S. EPA did not characterize risk associated with acute exposures in freshwater invertebrates. Note that for small aquatic invertebrates, EC_{50} values are typically used as functional LC_{50} values. For acute exposures to estuarine and marine invertebrates, a definitive acute EC_{50} of 0.92 mg total a.i./L in eastern oyster (MRID 47443228) is used by U.S. EPA for characterizing risks to estuarine/marine invertebrates (U.S. EPA/OPP 2010a). The corresponding acute NOAEC was 0.47 mg total a.i./L.

Given the few species of aquatic invertebrates on which data are available relative to the large number of species of aquatic invertebrates, FS risk assessments generally identify and use data on the most sensitive and most tolerant species of aquatic invertebrates to characterize risks. Although a definitive EC_{50} is not available in *Daphnia magna,* the toxicity data is used to represent the most tolerant species of aquatic invertebrates. Easter oyster is used to represent the most sensitive species.

6.3.3.3.2. Chronic Toxicity Values

As discussed in Section 6.1.3.3.2, only one chronic study is available on freshwater aquatic invertebrates exposed to indaziflam (MRID 47443235) and no studies are available for estuarine/marine invertebrates. For chronic exposures to freshwater invertebrates, the U.S. EPA uses a NOAEC of 0.340 mg total a.i./L based on effects on growth and the number of neonates per reproductive day in *Daphnia magna*.

In the absence of a chronic study in estuarine invertebrates, the ratio of the acute LC_{50} to the chronic NOAEC in *Daphnia magna* is used to estimate a chronic NOAEC in estuarine invertebrates. This use of acute to chronic ratios is included in the National Academy of Sciences recent recommendations on the assessment of risks to threatened and endangered species (NRC 2013). For *Daphnia magna*,

the ratio of the acute LC_{50} to the chronic NOAEC is about 29 [9.88 mg total a.i./L ÷ 0.340 mg total a.i./L ≈ 29.0588]. Using this ratio and the acute LC_{50} of 0.920 mg total a.i./L in eastern oyster, the chronic NOAEC for eastern oyster is estimated as 0.032 mg total a.i./L [0.920 mg total a.i./L ÷ $29_{acute \div chronic}$ ≈ 0.03172 mg total a.i./L]. Based on this, the chronic NOAEC of 0.032 mg total a.i./L is used for the risk characterization of sensitive species of aquatic invertebrate in this RA for sensitive species. Note that the U.S. EPA value of 0.340 mg total a.i./L was used for tolerant species in this RA.

6.3.3.4. Aquatic Plants

6.3.3.4.1. Algae

Based on the results presented in Table 6-6 and summarized in Section 6.1.3.4.1, the most sensitive species of algae identified by U.S. EPA was the marine diatom (*S. costatum*) with a reported 96-hour EC_{50} of 0.027 mg a.i./L and NOAEC of 0.0051 mg a.i./L (MRID 47443267). The least sensitive species was green algae (*P. subcapitata*), with a 72-hour EC_{50} of 11 mg a.i./L and NOAEC of < 5.37 mg a.i./L. Consequently, the NOAEC values of 0.0051 mg a.i./L and 5.37 mg a.i./L were used in the dose-response assessment to characterize risks associated with sensitive and tolerant species of algae, respectively.

6.3.3.4.2. Aquatic Macrophytes

For the characterization of vascular aquatic plants, U.S. EPA used the standard toxicity studies submitted by the registrant for freshwater vascular plant duckweed (*L. gibba*). As discussed in Section 6.1.3.4.2 and summarized in Table 6-6, two studies were submitted using TGAI indaziflam and one with the indaziflam formulation Esplanade 500 SC. Five toxicity studies were also submitted to assess exposures to five different indaziflam metabolites.

The lowest toxicity values in duckweed observed using Esplanade 500 SC, were reported EC_{50} and NOAEC values of 0.000061 mg a.i./L and 0.0000194 mg a.i./L, respectively. Consequently, the NOAEC of 0.0000194 mg a.i./L is used in this risk assessment. In the absence of data on the sensitivity of other species of aquatic macrophytes to indaziflam, the NOAEC of 0.0000194 mg a.i./L is applied to tolerant species. The NOAEC for indaziflam in sensitive species of aquatic macrophytes is treated as a data gap.

6.4. Risk Characterization

6.4.1. Overview

Terrestrial Organisms. Application of indaziflam could adversely affect mammals and birds by the consumption of contaminated vegetation. Damage can also occur to non-target terrestrial plants either by unintended direct application, off-site drift, off-site losses associated with runoff, or the misuse of contaminated surface water for irrigation. Off-site losses associated with the transport of contaminated soil by wind were also evaluated and found not to be a risk to non-target terrestrial vegetation.

In the case of terrestrial invertebrates, there is no basis for asserting that application of indaziflam will lead to significant or even detectable signs of toxicity to honey bees or herbivorous insects. No

data are available on the toxicity of indaziflam to reptiles or amphibians (terrestrial or aquatic phase). Thus, no risk characterization for these groups of organisms is developed.

Aquatic Organisms. The most substantial non-target impact of indaziflam applications made near surface water will involve effects on aquatic macrophytes. Direct effects on fish, aquatic invertebrates, and algae are also likely, but the impact would be less severe than the damage to aquatic macrophytes. Based on estimated peak concentrations in surface water, adverse effects in macrophytes may be anticipated at the central and upper bound estimates of acute exposure for sensitive species. Over prolonged periods after indaziflam applications at a rate of 0.091 lb a.i./acre, adverse effects could be apparent at the upper bounds of exposure for tolerant species of macrophytes. It is important to note that the risk characterization is based on estimates that are not applicable to site-specific applications made in FS or BLM programs. Thus, site-specific information could reduce the estimates of risks to non-target aquatic macrophytes and other classes of organisms.

Secondary Effects. While the risk characterization for indaziflam focuses on the potential for direct toxic effects, there is potential for secondary effects. Terrestrial applications of any effective herbicide, including indaziflam, 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 may 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 indaziflam or herbicide applications.

6.4.2. Terrestrial Organisms

6.4.2.1. Mammals

The quantitative risk characterization for mammals exposed to indaziflam is summarized in Worksheet G02a of Attachment 1. As with the human health risk assessment (Section 5.4.3), the predominant route of exposure involves the consumption of contaminated vegetation. The subsections below summarize the risk characterization for accidental and non-accidental exposures.

6.4.2.1.1. Accidental Exposures

All HQ values for accidental exposures are below the level of concern (maximum HQ = 0.4). This is not unusual given that most accidental exposure scenarios of concern in FS risk assessments involve an accidental spill into surface water. For many pesticides applied to vegetation, the exposures of mammals to the pesticide in contaminated vegetation exceed the exposures associated with a spill into water.

6.4.2.1.2. Non-Accidental Exposures

The HQ values associated with the consumption of contaminated vegetation following applications of indaziflam are the only HQs that exceed the level of concern (HQ = 1). As summarized in Attachment 1 Worksheet G02a, exceedances in the level of concern occur at the upper bounds of the HQs for the acute consumption of contaminated short grass (HQ = 1.3) and the chronic consumption of fruit (HQ = 1.2) by small mammals. The central and upper bound HQs for the chronic consumption of broadleaf foliage (HQ = 1.6 and HQ = 8, respectively), tall grass (HQ = 1.3 and HQ = 7,

respectively), and short grass (HQ = 3 and HQ = 15, respectively) by small mammals exceed the level of concern. The upper bound HQs for the chronic consumption of broadleaf foliage exceed the level of concern for a medium mammal (HQ = 1.9) and a larger mammal (HQ = 1.1). Other exceedances include the upper bound HQs for the chronic consumption of short grass, which exceed the level of concern for a medium mammal (HQ = 3) and a large mammal (HQ = 1.9). In addition, chronic consumption of contaminated tall grass by a medium mammal (HQ = 1.5) exceeds the level of concern.

As discussed in Section 5.3.5 (Dose-Severity Relationships), HQs of 2 for acute exposures and 3 for chronic exposures does not raise substantial concern based on the ratio of the LOAEL to NOAEL for chronic exposures. Nonetheless, the upper bound HQs for the consumption of broadleaf foliage (HQ = 8), tall grass (HQ = 7), and short grass (HQ = 15) exceed an HQ of 3 for small mammals in chronic scenarios. Consequently, the possibility of adverse effects cannot be ruled out. However, it should be noted that there are substantial differences in the toxicity of indaziflam to different groups of mammals. As discussed in Section 5.3.3 and summarized in Table 5-23, the dose-response assessment for mammals is based on a NOAEL for nerve fiber degeneration in the brain, spinal cord, and sciatic nerve in dogs, specifically the NOAEL of 2 mg a.i./kg bw/day and a LOAEL of 6 mg a.i./kg bw/day in males. However, in rats, no developmental effects were noted at doses up to 69 mg a.i./kg bw/day. If the sensitivity of rats is typical of other species of rodents, no adverse effects would be anticipated in rodents at HQs of up to 34.5, which is the NOAEL in rats divided by the NOAEL for dogs [69 mg a.i./kg bw/day ÷ 2 mg a.i./kg bw/day].

In addition, the HQs for mammals are based on the assumption that 100% of the diet is contaminated (SERA 2014a). This assumption may be unrealistic for some acute exposures and may be rare in terms of chronic exposures, at least for larger mammals because larger animals may move in and out of the treated areas. While the potential for a limited consumption of contaminated vegetation is not considered quantitatively in the current risk assessment, this consideration could be justified at least for some species in site-specific applications of indaziflam. Also, all HQs are based on the conservative assumption that the maximum application rate of 0.091 lb a.i./acre will be used. Thus, exposure levels will be reduced if a lower application rate is considered in a site-specific assessment.

6.4.2.2. Birds

The quantitative risk characterization for birds exposed to indaziflam is summarized in Worksheet G02b of Attachment 1. The subsections below summarize the risk characterization for accidental and non-accidental exposures.

6.4.2.2.1. Accidental Exposures

As with mammals, all HQ values for accidental exposures are below the level of concern. The highest HQ is for the consumption of contaminated fish by a piscivorous bird (HQ = 0.01).

6.4.2.2.2. Non-Accidental Exposures

As summarized in Attachment 1 Worksheet G02b, none of the HQs associated with acute non-accidental exposures exceed level of concern. The highest HQ is for the consumption of contaminated short grass by a small bird (HQ = 0.08). This is consistent with U.S. EPA's assessment

that indaziflam is "practically non-toxic" to birds on an acute and oral and subacute dietary exposure basis.

For chronic exposures, the upper HQs associated with the consumption of contaminated broadleaf foliage (HQ = 6), tall grass (HQ = 5), and short grass (HQ = 11) by small birds exceed the level of concern. The upper bound HQ for the chronic consumption of short grass (HQ = 1.2) by a large bird also exceeds the level of concern. In addition, the central HQs for the chronic consumption of broadleaf foliage (HQ = 1.2) and short grass (HQ = 2) by small birds exceed the level of concern.

Considerations with the risk characterization for birds are similar to the factors noted for mammals. These factors include the assumption that 100% of the diet is contaminated and uncertainties in the availability of data to derive a definite NOAEC.

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, U.S. EPA typically uses birds as surrogates for reptiles and terrestrial-phase amphibians.

6.4.2.4. Terrestrial Invertebrates

As discussed in Section 6.2.2.2, three sets of exposure scenarios are developed for terrestrial invertebrates following terrestrial foliar applications of indaziflam: direct spray and spray drift (Section 6.2.2.2.1), the consumption of contaminated vegetation or prey (Section 6.2.2.2.2), and exposure to contaminated soil (Section 6.2.2.2.3). As detailed in the following subsections, none of these exposure scenarios lead to HQs that reach a level of concern (HQ = 1).

6.4.2.4.1. Direct Spray and Spray Drift

Risks associated with direct spray and spray drift are summarized in Worksheet G09 of Attachment 1. Based on risk characterization, the direct spray of a honey bee with indaziflam leads to HQ values far below the level of concern. The highest HQ value is 0.007, which is below of level of concern by a factor of 143 [1 ÷ 0.007 ≈ 142.8]. Given these very low HQs, there is no basis for asserting that terrestrial insects would be at risk due to the deposition of indaziflam.

6.4.2.4.2. Contaminated Vegetation or Prey

HQs for herbivorous insects based on the consumption of contaminated vegetation are summarized in Worksheet G08b of Attachment 1. As discussed in Section 6.3.2.4.2, the toxicity value used for the dose-response assessment is an oral NOAEL in honey bees of 1,034 mg a.i./kg bw. As summarized in Worksheet G08b, the upper bounds of the HQs range from 0.003 (the consumption of fruit or large insects) to 0.05 (the consumption of short grass), which are below the level of concern. Based on these results, there is no basis for suggesting that herbivorous insects are likely to be at risk from the consumption of contaminated vegetation. This risk characterization is limited by the nature of toxicity data on terrestrial invertebrates (i.e. data limited to honey bees). This limitation is common for many herbicides, particularly new herbicides for which the open literature is limited and only standard U.S. EPA-required studies are available.

6.4.2.4.3. Contaminated Soil

HQs for contact with or the consumption of contaminated soil are not typically derived in either U.S. EPA or FS risk assessments. However, in the case of indaziflam, a soil toxicity study in earthworms is available, and the NOAEC for a 14-day duration is 316 mg a.i./kg dw soil. As discussed in Section 6.2.2.2.3, the GLEAMS modeling for the current risk assessment estimates concentrations of indaziflam in the top 12 inches of soil of 0.018 (lower estimate), 0.020 (central estimate), and 0.030 (upper estimate) mg a.i./kg dw soil for a unit application rate of 0.091 lb a.i./acre. Taking the soil concentrations as the numerator and the earthworm NOAEL as the denominator, the corresponding upper bound HQ for the earthworm would be 0.00009, which is below the level of concern (HQ = 1).

6.4.2.5. Terrestrial Plants

6.4.2.5.1. Direct Spray and Spray Drift

The HQs for sensitive and tolerant species of terrestrial plants are summarized in Worksheet G05a (fine droplet sizes) and Worksheet G05b (course droplet sizes) of Attachment 1. The worksheets are customized to reflect four sets of values for drift: aerial application, ground high-boom broadcast application, ground low-boom broadcast application, and backpack application. As detailed in Section 6.3.2.5, all HQs are based on NOAECs from studies on vegetative vigor (foliar applications) (i.e. NOAEC of < 0.000375 lb a.i./acre for a sensitive species of dicot (soybean) and a NOAEC of 0.002273 lb a.i./acre for a tolerant species of monocot (ryegrass)).

Although indaziflam is intended to be applied as a pre-emergent herbicide, if inadvertent direct foliar spray of sensitive species of dicots (e.g., soybean) occurs at the application rate of 0.091 lb a.i./acre, the impact will be severe (HQ = 243), and damage to the vegetation will be apparent. Similarly, damage to tolerant species may be apparent following direct spray (HQ = 40).

Based on estimates of drift using AgDRIFT, risks to sensitive species remain above the level of concern downwind from the application site for distances of at least 900 feet for fine droplets and about 500 feet for course droplets downwind following aerial application. For other application methods, HQs are at or below the level of concern at distances of 300 feet downwind of the application site. Thus, the risks will be greatest with aerial applications and least with other application methods such as backpack applications. However, these HQs should be viewed as only rough estimates (Tier 1). As discussed in Section 6.2.2.3.2, AgDRIFT is a relatively sophisticated model, and numerous site- and application-specific parameters can be used to refine the estimates of potential risk. In the assessment of any planned application of indaziflam, it would be prudent to use AgDRIFT with site- and application-specific parameters to refine the HQs presented in Worksheet G05a (fine droplet sizes) and Worksheet G05b (course droplet sizes) in Attachment 1.

6.4.2.5.2. Soil Exposures by Runoff

Risks to non-target vegetation associated with runoff and sediment losses to a field adjacent to the treated site are estimated in Attachment 1 Worksheet G04. For soil exposures, the toxicity values are based on seedling emergence assays. As summarized in Table 6-3 and discussed in Section 6.3.2.5, HQs are calculated using an NOAEC of 0.000062 lb a.i./acre for a sensitive species of dicot (oilseed rape) and an NOAEC of 0.000146 lb a.i./acre for a tolerant species of dicot (tomato). The

exposure estimates are based on runoff and sediment losses from GLEAMS-Driver, as discussed in Section 5.2.2.4.3.

For tolerant species of plants, the central estimate HQ is 31 (lower=0.0003 to upper=249). For sensitive species of plants, the central HQ is 73 (lower=0.01 to upper=587). As with the estimates of drift, the estimates of off-site transport in runoff and sediment should be regarded as only rough estimates. Also, the extreme range of the HQs reflects the nature of the generic (non-site-specific) GLEAMS-Driver modeling on which the exposure assessment is based. Given this information, the HQs may represent estimates of exposure levels that are not applicable to site-specific applications made in FS or BLM programs. Thus, site-specific information could reduce the estimates of risks to non-target vegetation.

6.4.2.5.3. Contaminated Irrigation Water

The HQs for non-target plants associated with using indaziflam contaminated surface water for irrigation are summarized in Worksheet G06a of the Attachment 1. The key variables in this exposure scenario are the expected concentrations in ambient water (Section 6.2.2.3.4) and the amount of irrigation water applied, which is assumed to be 1 inch as a central estimate with a range of 0.25 inch to 2 inches. The HQs for tolerant species exceed the level of concern only at the upper bounds of exposure (HQ = 3). For sensitive species, the HQs exceed the level of concern at the central (HQ = 1.2) and upper (HQ = 15) bounds of exposure. Based on the HQs for tolerant species, risks could occur to plants at the upper bounds of exposure. For sensitive species, risks are substantial at the upper bounds of exposure and moderate at the central estimate.

Also, as with the estimates of risks from runoff, the exposure components of the HQs are based on the GLEAMS-Driver simulations. Consequently, the upper bound risks will be most commonly associated with site conditions, including high rates of rainfall and soils conducive to runoff and/or percolation losses.

6.4.2.5.4. Wind Erosion

Risks to non-target vegetation associated with wind erosion of contaminated soils are summarized in Worksheet G06b of Attachment 1. Based on the assumptions typically used in FS risk assessments (Section 6.2.2.3.5), risks associated with this exposure scenario are far below the level of concern for both tolerant species (upper HQ = 0.005) and sensitive species (upper HQ = 0.03). Based on the upper bound HQ, the risks to sensitive species are below the level of concern by a factor of 33. Therefore, the current risk assessment does not raise substantial concerns for wind erosion relative to other routes of exposure.

6.4.2.6. Terrestrial Microorganisms

The toxicity of indaziflam 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

The risk characterization for fish is summarized in Attachment 1 Worksheet G03. None of the HQs for non-accidental acute and chronic exposures exceed the level of concern (HQ = 1).

For accidental exposures, the upper bound HQ for tolerant species (HQ = 1.6) exceeds the level of concern. The upper bound HQ for sensitive species (HQ = 4) also exceeds the level of concern. These HQ values are associated with a peak concentration in water of about 1.7 mg a.i./L. For tolerant species of fish, this value is only slightly above the NOAEC of 1.02 mg a.i./L. However, the value is higher in sensitive species by a factor of 4. Thus, there may be a modest potential for adverse effects in fish following spills of indaziflam.

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

The risk characterization for aquatic invertebrates is summarized in Attachment 1 Worksheet G03. As with fish, none of the HQs for non-accidental acute and chronic exposures exceed the level of concern (HQ = 1).

For accidental exposures, the upper bound HQ for sensitive species (HQ = 4) exceeds the level of concern. For tolerant species, the HQs are below the level of concern (upper HQ = 0.3). Qualitatively, the HQs suggest that it is unlikely that tolerant species of invertebrates would be adversely affected. However, for sensitive species, potential adverse effects may occur depending on site conditions. In areas with a low potential for water contamination, no adverse effects on even sensitive species of aquatic invertebrates are anticipated. In areas with a higher potential for water contamination, adverse effects in sensitive species of invertebrates cannot be ruled out.

6.4.3.4. Aquatic Plants

6.4.3.4.1. Algae

The risk characterization for algae is summarized in Attachment 1 Worksheet G03. For non-accidental acute exposures, the central HQs are 0.4 (lower = 0.0005 to upper = 2) for sensitive algal species and 0.0004 (lower = 0.0000004 to upper = 0.002) for tolerant species. Thus, HQs are below the level of concern (HQ = 1), with exception to the upper bound HQ for sensitive algal species, which is slightly above the NOAEC by a factor of 2. For longer-term exposures, the HQs are all below the level of concern.

For accidental exposures, the central HQs are 37 (lower = 1.6 to upper = 327) for sensitive species and 0.04 (lower = 0.002 to upper = 0.3) for tolerant species. In the event of a substantial accidental spill, adverse effects on sensitive algae are likely to occur. However, these results are conservative and may be better refined using site-specific conditions. This is important to consider given that the estimated concentration in water will vary substantially with site-specific factors such as soil type

and rainfall. For example, at sites or in regions where water contamination might be minimal due to weather, the location of surface water with respect to the application site, or other factors, risks to algae could be minimal.

In the absence of a site-specific assessment, the current national risk assessment justifies extreme caution when applying indaziflam near surface water. This cautionary language is consistent with language on product labels for the representative formulations of indaziflam considered explicitly in this risk assessment. Specifically, the product labels for Esplanade 200 SC and Esplanade F use the following language:

> *This product is toxic to fish, aquatic invertebrates, and plants. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean watermark.*

6.4.3.4.2. Macrophytes

The risk characterization for aquatic macrophytes is summarized in Attachment 1 Worksheet G03. As discussed in Section 6.3.3.4.2, toxicity data on aquatic macrophytes are limited to studies on duckweed, and the highest toxicity in duckweed was observed using Esplanade 500 SC, with a NOAEC value of 0.0000194 mg a.i./L. Based on this NOAEC, aquatic plants are more sensitive to indaziflam than algae. Due to the absence of data on the sensitivity of other species of aquatic macrophytes to indaziflam, the NOAEC of 0.0000194 mg a.i./L is applied to tolerant species.

For non-accidental acute exposures, the central HQ is 103 (lower = 0.1 to upper = 657) for tolerant species. For longer-term exposures, the central HQ is 1.9 (lower = 0.002 to upper = 12). Based on these HQ values, adverse effects on even tolerant species could be evident during acute and chronic exposures. As with the risk characterization for algae, the levels of exposure will depend on site-specific considerations. Consequently, refinements in the exposure assessment for aquatic macrophytes would be justified in applications of indaziflam that are near surface water.

For accidental exposures, the central HQ is 9,755 (lower = 429 to upper = 85,845) for tolerant species. This HQ value is far above the level of concern and indicates that severe adverse effects are likely to occur during an event of a substantial accidental spill. Thus, extreme caution should be taken when applying indaziflam to ensure that surface water is not contaminated during application.

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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.
Language	Literature published in a language other than English.
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 U.S. EPA's OPPTS harmonized guidelines but do not upon review.
Unrelated	Literature that is not related to the herbicide/pesticide or the HHERA.

Appendix 2: Toxicity to Mammals

Unless otherwise indicated, the study summaries and MRID numbers are taken from U.S. EPA/OPP (2010a, 2010b, 2010c) and supplemented with information from DERs submitted by the registrant. These are the subset of studies that U.S. EPA/OPP selected for use in their risk assessment.

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Table A2-1: Acute Oral Toxicity Studies

Species	Exposure	Response	Reference
Rat (Wistar HsdCpb:Wu rats) 2 groups of 3 female rats (age 10-12 weeks, body weight ranged from 169 g to 194 g). Fasted for 16-24 hours prior to administration of dose. No control group.	Indaziflam (AE 1170437; 94.5% a.i.) Doses: Single oral dose of 2,000 mg a.i./kg bw by gavage after being fasted for approximately 16-24 hours. Two-week oral acute study.	LD_{50} >2,000 mg a.i/kg bw Test animals were monitored for mortality and clinical signs for 2 weeks. On day 15, surviving animals were sacrificed, necropsied and examined for gross pathological changes. Because no deaths and no clinical signs occurred in the first group, the same procedure was repeated with the same limit dose level. All animals survived and gained weight during the study. No clinical signs or gross pathological findings were observed. U.S. EPA classifies as "practically non-toxic."	MRID 47443280 Acceptable Pp. 170-171 (U.S. EPA/OPP 2010a)
Rat (Wistar rats) 2 groups of 3 adult female rats (age 9-13 weeks; body weight: ranged from 168 to188 g). No control group.	Indaziflam (AE 1170437; 95.7% a.i.) Doses: Single oral dose of 2,000 mg a.i./kg bw by gavage. Two-week oral acute study	LD_{50} >2,000 mg a.i/kg bw Test animals were monitored for mortality and clinical signs for 2 weeks. All test animals were necropsied at the end of the study or as soon as possible after death. 5/6 test animals dosed at 2,000 mg/kg survived, gained weight and appeared healthy	MRID 47443281 Acceptable Page 171 (U.S. EPA/OPP 2010a)

Species	Exposure	Response	Reference
		throughout the study period. The single test animal that died (study day 4) appeared healthy up to time of death. At necropsy, autolysis was noted in the test animal that died during the study period. No cause of death was reported. No gross internal findings were observed at necropsy for the test animals that survived the study. U.S. EPA classifies as "practically non-toxic."	

Table A2-2: Subchronic and Chronic Oral Toxicity Studies

Species	Study Type	Exposure	Response	Reference
Rat (Wistar rats) 10 rats/sex/dose Rats were 6 weeks of age and body weights ranged from 191-217 g for males and 151-177 g for females	Subchronic	Indaziflam (AE 1170437; 98.7% a.i.) Doses: 0, 200, 5000 or 10,000 ppm in diet for 13 weeks. Equivalent to 0, 14, 338 or 689 mg/kg/day for males and 0, 16, 410 or 806 mg/kg/day for females. 10 rats were similarly treated for 13 weeks at 0 and 10,000 ppm and subsequently allowed 4 weeks of control diet (recovery period). 90-day oral toxicity study	Males: NOAEL 14 mg/kg/day; LOAEL 338 mg/kg/day Females: NOAEL 410 mg/mg/day; LOAEL 806 mg/kg/day No adverse treatment related effects were noted on clinical signs, motor activity, sensory reactivity, grip strength, ophthalmoscopic examination, hematology, urinalysis, or gross or histological pathology. At the 5,000 ppm and 10,000 ppm dose levels, statistically increases in thyroid stimulating hormone (TSH) were observed in males at week 3, but not week 13. At 10,000 ppm, one female in the recovery group was sacrificed moribund on Day 20. Microscopic examination did not reveal any clear cause of moribundity. Body weights were decreased compared to controls in the main group in males and females. The LOAEL is 5000 ppm in males (equivalent to 338 mg/kg/day) based on thyroid effects. The LOAEL is 10,000 ppm in females (equivalent to 806 mg/kg/day) based on increased mortality, decreased body weights and body weight gains (also in males) and decreased	MRID 47443287 Acceptable Page 45 (U.S. EPA/OPP 2010b)

Species	Study Type	Exposure	Response	Reference
			food consumption in females. Body weight gains during the treatment interval (days 1 to 90) were decreased by 10-13% in both sexes. Decreased food consumption was noted in the females on days 8-50 (5-20%). The NOAEL is 200 ppm in males (equivalent to 14 mg/kg/day) and 5,000 ppm (410 mg/kg/day) in females.	
Mouse (C57BL/6J) 10 mice/sex/dose Mice were approximately 6 weeks of age and body weights ranged from 16. 1 to 20.5 g for males and 14.3 to 17.1 g for females	Subchronic	Indaziflam (AE 1170437; 96.5% a.i.) Doses: 0, 100, 500 or 1,200 ppm in diet for 13 weeks Equivalent to 0, 19, 91 or 218 mg/kg/day for males and 0, 23, 118 or 256 mg/kg/day for females. 90-day oral toxicity study	Males: NOAEL = 91 mg/kg/day; LOAEL 218 mg/kg day Females: NOAEL = 118 mg/kd/day; LOAEL = 256 mg/kg/day No adverse treatment-related effects were observed on clinical chemistry, organ weights or gross or microscopic pathology. At 1,200 ppm, one female was moribund sacrificed on Day 10. No clear cause of death could be determined, but this death was presumed to be due to treatment. The female exhibited hunched posture and wasted appearance, and one male also exhibited hunched posture. Body weights were decreased in both sexes throughout treatment. At 1,200 ppm, decreased body weights were observed throughout treatment in males (reduced 9-16%) and females (decreased 11-19%). Overall body weight gain was only slight	MRID 47443288 Acceptable Page 45 (U.S. EPA/OPP 2010b)

Species	Study Type	Exposure	Response	Reference
			decreased at 500 ppm (8-11% and not statistically significant). At 1,200 ppm, decreased food consumption was observed throughout treatment in males (3-17%) and females (14-29%). The LOAEL was 1,200 ppm (218 mg/kg/day in males and 256 mg/kg/day in females) based on increased mortality and wasted appearance in females, increased hunched posture in both sexes, decreased body weights, body weight gains and food consumption in both sexes. The NOAEL was 500 ppm (91 mg/kg/day in males and 118 mg/kg/day in females).	
Dog (Beagle) 4 dogs/sex/dose. Dog were 6-7 months of age and body weights ranged from 6.6-8.6 kg for males and 5.4-7.2 kg for females	Subchronic	Indaziflam (AE 1170437; 94.5-99.4% a.i.) Doses: 0, 7.5, 15 or 30 mg/kg/day by gavage 90-day oral toxicity	Males and Females: NOAEL = 7.5 mg/kg/day Males and Females: LOAEL = 15 mg/kg/day At 30 mg/kg/day, three dogs presented with seizures on days 15, 22 and 35, respectively, and were killed on the day of the seizures were observed. Treatment-related clinical findings observed in these dogs included: seizures in the male, aggressive, tremors, ataxia, labored breathing, pupil no reaction to light or sluggish, decreased activity, circling, and sores due to seizures in the females. Due to the seizures, dosing of the 30 mg/kg/day group was halted on day 35 and the	MRID 47443289 Acceptable Page 45 (U.S. EPA/OPP 2010b)

Species	Study Type	Exposure	Response	Reference
			surviving dogs of this group were euthanized on day 36. At this dose, male dogs displayed decreased body weight gain for days 0-35 compared to all other groups, while females lost weight during this period compared to the other groups. Treatment-related histopathologic findings were observed in the nervous system (brain, spinal cord and sciatic nerve). In the males, slight multifocal axonal degeneration of the sciatic nerve was observed in 1/4 dogs and minimal to moderate multifocal axonal degeneration of the spine was noted in 4/4 dogs, compared to 0 controls. In the females, minimal to slight multifocal axonal degeneration was observed int eh brain in 2/4 dogs, minimal to slight focal/multifocal axonal degeneration was observed in the sciatic nerve in 2/4 dogs, and minimal to moderate multifocal axonal degeneration of the spinal cord was noted in 4/4 dogs, all compared to 0 controls. The LOAEL is 15 mg/kg/day, based on axonal degeneration in the nervous system of both sexes. The NOAEL is 7.5 mg/kg/day.	

Species	Study Type	Exposure	Response	Reference
Rat (Wistar rats; Rj: WI (IOPS HAN) 70 rats/sex/dose. Rats were 6 weeks of age with body weights ranging from 224 to 226 g for males and 167 to169 g for females	Chronic	Indaziflam (AE 1170437; 93.1% a.i.) Doses: 0, 300, 3,000 or 10,000 ppm in the diet (6,000 in females after Day 280 due to toxicity) Equivalent to 0, 14, 136 or 474 mg/kg/day for males and 0, 19, 185 or 589 mg/kg/day for females 2-year oral toxicity	Males: NOAEL = 136 mg/kg/day and LOAEL = 474 mg/kg/day Females: NOAEL = 19 mg/kg/day and LOAEL = 185 mg/kg/day In the 10,000/6,000 ppm females, a treatment-related affect was observed on mortality. During the first 3 weeks of treatment, four 10,000 ppm females were killed moribund, due to severe clinical signs and body weight loss and no moribund sacrifices were made in the control group. There were numerous clinical signs of an effect on the nervous system in the 6,000 ppm females (days 281-378), including dilated pupils, limited use of limbs, tremors, hindlimbs splayed, low alertness, noisy respiration, soiled nose and soiled anogenital region. At 3,000 ppm, clinical signs of neurotoxicity were also seen in females, with lower incidence and effects observed at later times in the study than at the high dose. Effects observed included dilated pupils (10%), limited use of limbs (7.1%), tremors, splayed hindlimbs, low alertness and noisy respiration (all 2.9%), soiling of nose or anogenital region (1.4 to 4.3%) and labored or noisy respiration (1.4 or 2.9%). Mydriasis was observed in one female. Overall body	MRID 47443296 Acceptable Page 46 (U.S. EPA/OPP 2010b)

Species	Study Type	Exposure	Response	Reference
			weight gains (days 1-372) were slightly decreased in both sexes (9-11%). Decreased food consumption was noted during week period 1-2 in males (18%) and females (29%) and week period 1-13 in females (10%). Increases in thyroid stimulating hormone were observed in the 300 (11%), 3,000 (15%) and 10,000 (49%) ppm males at week 3, but no changes were observed at week 14. Other thyroid hormones were not affected by treatment and no changes were seen in females. Female LOAEL is based on clinical signs of toxicity and mydriasis. Male LOAEL is based on decreased body weight, food consumption and thyroid effects (transiently increased in TSH).	
Dog (Beagle) 4 dogs/sex/dose. Dogs were 7-9 months with body weights ranging from6.9 to10.1 kg for males and 6.0 to7.8 kg for females	Chronic	Indaziflam (AE 1170437; 94.5% a.i.) Doses: 0, 60, 225 or 450 ppm in the diet Equivalent to 0, 2, 6 or 12 mg/kg/day for males and 0, 2, 7 or 11 mg/kg/day for females 12-month oral toxicity	Males: NOAEL = 2 mg/kg/day and LOAEL = 6 mg/kg/day Females: NOAEL = 2 mg/kg/day and LOAEL = 7 mg/kg/day In addition to evaluation of standard chronic toxicity study parameters, a neurological examination was performed monthly from months 7 through 11 and just prior to termination. One high dose male was sacrificed on day 190 due to seizures that	MRID 47443294 (Main Study) MRID 47443295 (Dietary Stability) Acceptable Pp. 46-47 (U.S. EPA/OPP 2010b)

Species	Study Type	Exposure	Response	Reference
			were not considered treatment related: this animal had dilatation of the lateral ventricles and no seizures were observed in the subchronic dog study with bolus dosing at 15 mg/kg/day. Overall (day 0-364) body weight gains were decreased by 12% in males and by 21% in the females. Treatment-related microscopic findings were primarily observed within the dorsal funiculi of the spinal cord at 225 and 450 ppm. The lesion was characterized by axonal degeneration of individual nerve fibers, consisting of fragmented and lysed axonal fibers, sometimes associated with phagocytic macrophages forming a digestion chamber. Endpoints for both sexes based on microscopic lesions of the nervous system.	

Table A2-3: Acute, Subchronic, and Developmental Neurotoxicity Studies

Species	Study	Exposure	Response	Reference
Rat (Wistar Han Crl: WI(Han)) 12 rats/sex/dose. For the initial study body weights of males ranged from 247.9 to 319.4 g and females ranged from 162.2 to 216.2 g For the follow-up study, 12 female rats were given a single oral dose and observed for 1-2 days. Body weights of females ranged from 168.0 to 203.8 g.	Acute Neurotoxicity Screening Battery	Indaziflam (AE 1170437; 93.14% a.i.) Initial study dosing was 0, 50, 100 or 2000 mg/kg by gavage in corn oil. In follow-up study, doses were 0, 25 and 50 mg/kg.	NOAEL = 50 mg/kg LOAEL = 100 mg/kg Non-fasted rats were given a single oral (gavage) dose and observed for 14-15 days. In the initial study, 3/6 females receiving 2,000 mg/kg were found dead on the day following treatment. 500 mg/kg was considered the high dose in the females. At 100 mg/kg, treatment-related effects were limited to non-statistically significant decreases observed in total session motor (-14%) and locomotor (-21%) activities in the females on Day 0. The effects are considered treatment-related based on the observed dose-response and reduction in locomotor activity > 20%, but are a threshold effect level. No treatment-related effects were observed at 25 or 50 mg/kg. No compound-related effects on body weight, body weight gain, brain weight, or gross pathology were observed at any dose in either sex. The neurotoxicity LOAEL is 100 mg/kg and is based on decreased motor and locomotor activity in females.	MRID 47443310 Acceptable Page 49 (U.S. EPA/OPP 2010b)
Rat (Wistar Han Crl: WI(Han)) 12 rats/sex/dose. Rats were approximately 8 weeks old, body weights ranged from 232 to 302.4 for males	Subchronic Neurotoxicity Screening Battery	Indaziflam (BCS-AA10717; 93.14% a.i.) Dose levels included: 0, 200, 4000 or 8000/10,000 ppm. Equivalent to: 0,	Males: NOAEL = 243.6 mg/kg/day and LOAEL = 585.7 mg/kg/day Females: NOAEL = 306.9 mg/kg/day and LOAEL = 580.9 mg/kg/day Neurobehavioral assessment (functional observational battery (FOB) and motor activity testing) was performed using all rats at	MRID 474433309 Acceptable Page 49 (U.S. EPA/OPP 2010b)

Species	Study	Exposure	Response	Reference
and 146.9 to 195.4 g for females.		12.2, 243.6 or 585.7 mg/kg/day for males and 0, 15.1, 306.9 or 580.9 mg/kg/day for females. 13-week oral study	pre-dosing and weeks 2,4,8, and 13. At study termination, 6 rats/sex/group were anesthetized and perfused *in situ* for neuropathological examination. At 10,000 ppm for males and 8,000 ppm for females, clinical signs to toxicity included tremors (1M, 5F), repetitive chewing movements (1M), perianal stain (9M, 1F), red lacrimal stain (2M), red nasal stain (3M vs 1 control), and urine stain (1F). In the females, body weight was decreased by 9-12% throughout the study and overall body weight gain was decreased by 30%. During the FOB sessions, body weights were decreased by 10-13% in the females throughout treatment. Terminal body weights were decreased by 9%. In the males, food consumption was decreased by 12-18% on days 0-7, 21-28 and 28-35. In the females, food consumption was decreased by 13-19% beginning on days 21-28 and continuing for all remaining weeks measured. Compound-related FOB effects included tremors, repetitive chewing, brown perianal stain and red lacrimal stain. In the females, total session motor activity was decreased by 34% at week 2 and by 27% at week 4 and total session locomotor activity was decreased by 42-43% at weeks 2 and 4. LOAELs based on decreased total session motor and locomotor activity in females, clinical signs/FOB effects in males and females (tremors, repetitive	

Species	Study	Exposure	Response	Reference
			chewing motion and perianal and lacrimal staining), decreased body weights in females and cumulative body weight gain in males and females.	
Pregnant Rat (Wistar Han Crl: WI(Han)) from gestation day (GD) 6 through lactation day (LD) 21 30 rats/dose Rats were 11 weeks of age at cohabitation; with body weights ranging from 187 to240 g for females. Body weights of males not reported (only used for mating)	Developmental Neurotoxicity	Indaziflam (AE 1170437; 93.14% a.i.) Doses were 0, 150, 1,000 or 7,000 ppm in the diet (high dose reduced to 4,000 ppm on LD4). Equivalent to 0, 13, 83.8 or 432 mg/kg/day for adult females. Pups were not directly dosed.	Maternal NOAEL = 83.8 mg/kg/day LOAEL = 432 mg/kg/day, Maternal: No treatment-related mortality occurred. Toxicity was only observed in the 7,000/4,000 ppm group. Treatment-related clinical signs were evident beginning on GD 6 as coarse tremor, dilated pupils, nasal stain and repetitive chewing movements in one animal. In the FOB, treatment-related effects were first evident on GD 6, and included dilated pupils, unresponsive to sunlight, tremor and repetitive chewing movements. Effects on body weight, body weight gain and food consumption were only observed in the 7,000/4,000 ppm group. Body weights were decreased on GD 13 and 20 (-7 to 13%), resulting in a decreased cumulative body weight gain (GD 0-20) of 42%. Effect on food consumption is unclear due to excessive feed spillage at the high dose during the first week of treatment followed by a change in feeders. Food consumption was similar to controls during GD 13-20. The maternal LOAEL of 432 mg/kg/day is based on clinical signs, decreased body weights and body weight gains. The NOAEL is 83.8 mg/kg/day.	MRID 47443311 Acceptable Page 49 (U.S. EPA/OPP 2010b)

Species	Study	Exposure	Response	Reference
			Offspring (males and females) NOAEL = 83.8 mg/kg/day LOAEL = 432 mg/kg/day Decreased body weights were noted in both sexes up to postnatal day (PND) 4, post-culling (-14 to 17%) and up to PND 21 in both sexes (- 5 to 10%). Males postweaning had slightly decreased body weights. Decreased motor activity (-29%) on PND 21 in males was considered treatment-related, but was not seen at other measurement times nor in females. The offspring LOAEL is 432 mg/kg/day based on decreased body weights and decreased motor activity in male pups at PND 21. The NOAEL is 83.8 mg/kg/day.	

Table A2-4: Subchronic Immunotoxicity Toxicity Studies

Species	Exposure	Response	Reference
Rat (Wistar; Hsd Cpb: WU) 8 rats/sex/dose. Rats were approximately 6 weeks old. Body weights ranged from 126 to161 g for males and 124 to159 g for females.	Indaziflam (AE 1170437; 93.12% a.i.) Doses: 0, 300, 3000 or 6000 (females) or 10,000/6000 (males) ppm in the diet. Equivalent to 0, 27.7, 258 or 528 mg/kg/day for males and 0, 31, 334.2 or 737.9 mg/kg/day for females. 30-day oral immunotoxicity study	**Systemic** Males: NOAEL = 258.8 mg/kg/day and LOAEL = 528.0 mg/kg/day Females: NOAEL = 334.2 mg/kg/day and LOAEL = 737.9 mg/kg/day Males receiving 10,000 ppm displayed severe body weight loss compared to controls; therefore, the dose for this group was reduced to 6,000 ppm on day 16. One male rate in the 10,000/6,000 ppm group was observed with piloerection, pallor, sunken flanks, poor general condition, reduced motility, hunched back and tremor. At necropsy, this animal was emaciated and had diminished spleen and thymus. At 10,000/6,000 ppm, tremor, hunched back and high-stepping gait were observed in both sexes; piloerection and pallor were noted in the males; and uncoordinated gait was observed in females. Overall (days 1-29) body weight gains were decreased by 75%. Absolute (g/rat/day) and relative (g/kg by/day) food consumption were decreased in the males by 50% and 22%, respectively. LOAEL endpoint based on mortality (one male sacrificed *in extremis*), clinical signs of toxicity in males and females (including tremor, abnormal gait, pallor, hunched back), decreased food and water consumption in males and decreased body weight/weight gain in males and females. **Immunotoxicity** NOAEL: Males =528.0 mg/kg/day	MRID 47443313 Acceptable Page 51 (U.S. EPA/OPP 2010b)

		Females = 737.9 mg/kg/day LOAEL: not established Immunotoxicity was investigated by performing a plaque-forming cell assay following immunization with sheep erythrocytes. Spleen cell counts were significantly decreased in the 10,000/6,000 ppm males compared to the control; however, the decrease was within the range of historical controls. The decreased cell counts may be due to decreases of body weight and spleen weights in the high dose males. The antibody forming cell assay did not show significant difference among treated and control groups in both sexes. The number of antibody forming cells per 10^6 spleen cells was increased in all treated groups in both sexes compared to controls. The increase could be stress-induced, as indicated by the slightly reduced body weights of the treated animals. Since the T-cell dependent antibody response assay is negative and evaluation of observational endpoints provide no evidence of immunotoxicity. The LOAEL for immunotoxicity was not observed and the NOAEL was the highest dose (10,000/6,000 ppm).	

Table A2-5: Reproductive and Developmental Toxicity Studies

Species	Stage	Exposure	Response	Reference
Rat (Sprague Dawley Crl; DC(SD)) 23 naturally-mated presumed pregnant rats/dose from gestation day (GD) 6-20. Body weights ranged from 239 to 299 g	Prenatal Development	Indaziflam (AE 1170437; 94.5% a.i.) Doses: 0, 10, 25 or 200 mg/kg/day by gavage	**Maternal** NOAEL = 25 mg/kg/day LOAEL = 200 mg/kg/day At 200 mg/kg/day, mean maternal body weight gain was reduced by 67% between GD6-8, compared to controls. Thereafter, body weight gains were decreased by 10-14%, resulting in a decrease of 14% for the overall (GD6-21) treatment period. At 200 mg/kg/day, maternal food consumption was decreased by 4-10% at each of the intervals throughout treatment, compared to controls. Body weight gains, corrected body weight gains, and food consumption at 10 and 25 mg/kg/day were compared to controls. The maternal LOAEL was 200 mg/kg/day based on decreased body weight gain and food consumption. **Developmental** NOAEL = 25 mg/kg/day LOAEL = 200 mg/kg/day Fetal body weights were significantly decreased by 7-9% at 200 mg/kg/day compared to controls. These decreases may correspond to the decreases noted in maternal food consumption, body weight gains, and corrected body weight gain. The decreased fetal body weights at 10 mg/kg/day were considered incidental	MRID 47443291 Acceptable Page 45 (U.S. EPA/OPP 2010b)

Species	Stage	Exposure	Response	Reference
			because they were minor and because similar decreases were not observed at 25 mg/kg/day. There were no treatment-related effects on development or ossification of the skeleton. No evidence of teratogenicity was observed. The developmental LOAEL was 200 mg/kg/day is based on decreased fetal body weights.	
Rabbit (New Zealand White Crl: KBL (NZW)) 23 naturally-mated presumed pregnant rabbits/dose group from GD 6-28. Female rabbits were approx. 18 weeks old with body weights ranging from 3.15-3.85 kg	Prenatal Development	Indaziflam (BCS - AA10717 93.14% a.i.) Doses: 0, 10, 25 or 60 mg/kg/day by gavage	**Maternal** NOAEL = 25 mg/kg/day LOAEL = 60 mg/kg/day At 60 mg/kg/day, one female was killed for humane reasons on GD 27 after having aborted. This animal had decreased food consumption and lost 0.17 kg between GD 24-26. Clinical signs consisted of few feces on GD 26 and 27. Pale liver was noted at necropsy. The abortion was not considered treatment-related. At 60 mg/kg/day, 3/23 females had mucoid feces on two or more occasions from GD 16 onwards, compared to 0 controls. Additionally, at this dose, 12/23 females had few feces on one or more occasions compared to 2/23 controls. Mean maternal body weight gain at 60 mg/kg/day was significantly decreased by 32% for the overall (GD6-29) treatment period, compared to	MRID 47443292 Acceptable Page 46 (U.S. EPA/OPP 2010b)

Species	Stage	Exposure	Response	Reference
			controls. Corrected body weight gain was significantly decreased by 200%. Corresponding to the decreased body weight gains at this dose, food consumption was decreased by 10-30% at each of the intervals throughout treatment, compared to controls. Although liver weights in the treated groups were compared to controls, pale liver was noted in 3/23 females, and white foci on the liver were found in 2/23 females at 60 mg/kg/day, compared to controls. There were no effects at the 10 or 25 mg/kg/day dose levels. The maternal LOAEL is 60 mg/kg/day based on decreased body weight gain and food consumption and macroscopic changes in the liver of one female. **Developmental** NOAEL = 60 mg/kg/day LOAEL = not established (>60 mg/kg/day). There were no premature delivers or complete litter resorptions. There were no effects of treatment on the numbers of litters, live foetuses, dead foetuses, early resorption, or late resorptions. Additionally, sex ratio and post-implantation losses in the treated groups were comparable to controls. There were no treatment-related effects on	

Species	Stage	Exposure	Response	Reference
			fetal growth or development as evidenced by fetal body weights in the treated groups that were comparable to controls and the absence of any effects on ossification of the skeleton. There were no treatment-related external, visceral or skeletal malformations or variations. The developmental LOAEL was not observed.	
Rat (Wistar Hanover Crl:WI (G1x/BRL/Han)IGS BR) 30 rats/sex/dose group for two consecutive generations P generation rats were approx. 8 weeks old and 9 weeks for F1 offspring Body weights for males ranged from 257.8 to 268.0 g and females ranged from 167.4 to 168.8 g for P generation. Body weights ranged from 234.7 to 302.2 for males and 164.7 to 191.2 g for females for F1 generation.	Reproduction and Fertility	Indaziflam (93.14-94.5% a.i.) Doses: 0, 150, 1000 or 8000 ppm in the diet; F1 high dose reduced to 4000 ppm at 5-17 days' postweaning Average P/F1 consumption (note: high dose not averaged due to F1 dose reduction) Male doses: 0, 10.4, 69.3 or 560.1 mg/kg/day (P males) and 317.6 mg/kg/day (F1 males, due to reduction in dietary dose) Female doses: 0, 12.9, 85.2 or 656.2 mg/kg/day (P females) and 355.2 mg/kg/day (F1 females, due	**Parental (P)** Males: NOAEL = 69.3 mg/kg/day and LOAEL = 560.1 mg/kg/day Females: NOAEL = 85.2 mg/kg/day and LOAEL = 656.2 mg/kg/day The P generation animals were fed dietary levels of 0, 150, 1000 or 8000 ppm beginning 10 weeks prior to mating to produce F1 litters. At 8,000 ppm, coarse tremors were observed in P females at various times during premating, gestation and lactation. Body weights were decreased in the P dams throughout pre-mating, resulting in a decrease of 27% in body weight gain for the pre-mating period (weeks 0-10). Absolute food consumption was decreased generally throughout pre-mating. Increased liver hypertrophy and increased liver weights were observed in the 1,000 ppm P males and in both sexes from both generations	MRID 47443293 Acceptable Page 46 (U.S. EPA/OPP 2010b)

Species	Stage	Exposure	Response	Reference
		to reduction in dietary dose)	at 8,000/4,000 ppm; however, effects were considered adaptive and not adverse. In the 8,000 ppm males, absolute and relative kidney weights were increased in the P generation. Hyaline degeneration in the kidneys was found in the P (15/30) and (6/30) F1 males both compared to 0 controls. Tubular regeneration in the kidneys was observed in the P males (13 treated vs. 3 control. The LOAEL for parental toxicity is 8,000 ppm based on coarse tremors in females from Weeks 6-17 and in gestation and lactation, decreased body weight/weight gain and food consumption and renal toxicity (tubular degeneration/ regeneration and increased weight) in males. **Offspring (F1)** Males: NOAEL = 69.3 mg/kg/day and LOAEL = 317.6 mg/kg/day Females: NOAEL = 85.2 mg/kg/day and LOAEL = 355.2 mg/kg/day F1 offspring (30/sex/dose group) selected to be parents of the next generation were initially fed the same test diet concentrations as their parents. However, due to severe toxicity in the F1 offspring after weaning, but	

Species	Stage	Exposure	Response	Reference
			before mating (age 26-38 days old) the high dose of 8,000 ppm was reduced to 4,000 ppm. F1 parents were fed the test diets for six weeks prior to mating and the F2 pups were maintained after weaning for evaluation of sexual maturation. In the F1 generation, body weights were decreased throughout pre-mating in both sexes. However, these decreases lessened overtime and were due to their decreased weights as pups. Relative and absolute food consumption in the F1 males was decreased for the overall pre-mating period. Body weights were decreased throughout gestation in both generations (30% and 19% in the P and F1 generations, respectively) and throughout lactation in both generations. In the F1 pups, the following clinical signs of toxicity were observed in the 8,000/4,000 ppm group: pups cold to touch, perianal stain, urine stain, weak, labored breathing, nasal stain, tremors, increased reactivity, distended abdomen, increased activity, myoclonus, diarrhea and soft stool. F1 pup body weights were decreased by 12-22% compared to controls throughout the post-natal period in both sexes. Body weight gains for	

Species	Stage	Exposure	Response	Reference
			the overall postnatal period at this dose were decreased by 22-24%. The LOAEL for offspring toxicity is 8000/4000 ppm based on clinical signs of toxicity (perianal, urine or nasal staining, diarrhea or soft stool, distended abdomen, weakness, tremors, myoclonus, increased activity and reactivity) and decreased pup body weights throughout postnatal period. **Reproductive** Males: NOAEL = 69.3 mg/kg/day (based on F1 intakes) and LOAEL = 317.6 mg/kg/day Females: NOAEL = 85.2 mg/kg/day (based on F1 intakes) and LOAEL = 355.2 mg/kg/day The only effect on reproductive parameters was delayed sexual maturation observed in male and female F1 and F2 pups at 8,000/4,000 ppm compared to controls. In F1 and F2 males, preputial separation showed delays of 9.3 and 3.3 days, respectively. In F1 and F2 females, vaginal patency showed delays of 6.8 and 2.4 days, respectively. There were no effects on treatment of estrous cycle duration or periodicity; follicle counts; the mating, fertility and gestation	

Species	Stage	Exposure	Response	Reference
			indices; pre-coital interval; gestation duration; or sperm motility, counts or morphology in either generation. The LOAEL for reproductive toxicity is 8,000/4,000 ppm based on delayed sexual maturation in males and females in F1 and F2 pups.	

Table A2-6: Carcinogenicity Toxicity Studies

Species	Study	Exposure	Response	Reference
Mouse (C57BL/6J) 50 mice/sex/dose. Approx. 6 weeks old; body weights ranged from 20.0 to 20.3 g for males and 17.2 to 17.3 g for females	Carcinogenicity	Indaziflam (AE 1170437; 93.14% a.i.) Doses: 0, 50, 250 or 1000 ppm in diet for up to 78 weeks Equivalent to 0, 6.8, 34 or 142 mg/kg/day for males and 0, 8.4, 42 or 168 mg/kg/day for females. Carcinogenicity	Males: NOAEL = 34 mg/kg/day and LOAEL = 142 mg/kg/day Females: NOAEL = 42 mg/kg/day and LOAEL = 168 mg/kg/day No adverse, treatment-related effects were observed on mortality or hematology. At 1,000 ppm, general systemic toxicity was indicated. An increased incidence of wasted appearance was noted, first observed after 2 weeks of treatment. Body weight gains were decreased by 43-46% in both sexes during days 1-92 and overall (days 1-540) body weight gain was decreased by 23% in males and 36% in females. Decreased food consumption was observed throughout the study in both sexes, and overall (weeks 1-77) food consumption was decreased by 9-12% in both sexes. In the 1,000 ppm males, decreased absolute and relative to body kidney weights were noted at the interim (decreased 15-27%) and terminal sacrifices (decreased 19-28%). In the 1,000 ppm females, increased incidences were observed of macroscopic black focus(i) in the stomach (5/50 vs 0/50 in controls) and red focus(i) in the stomach (4/50 vs 1/50 in controls). An increased	MRID 47743416 Acceptable Page 47 (U.S. EPA/OPP 2010b)

Species	Study	Exposure	Response	Reference
			incidence of minimal to moderate glandular erosion/necrosis in stomach (14/49 vs 1/50 in controls) was noted microscopically. At 1,000 ppm, increased incidences of the flowing lesions were observed grossly in the ovary: enlarged (6/50 vs 1/50 in controls) and black focus(i) (7/50 vs 0/50 in controls). An increased incidence of blood-gilled cyst(s)/follicle(s) (19/49 vs 11/50 in controls) was noted. Equivocal findings were noted in the liver (prominent lobulation in males and redistribution of vacuolation in both sexes) and spleen (weight in females). The LOAEL is based on increased incidence of wasted appearance in females; decreased body weight, body weight gains and food consumption in both males and females; and indications of renal toxicity and hepatotoxicity in males; and stomach and ovarian toxicity in females. At the doses tested, there was no treatment-related increase in tumor incidence when compared to controls. **No evidence of carcinogenicity**	
Rat (Wistar Rj: WI (IOPS HAN)) 60 rats/sex/ does. Approx. 6 weeks old; body	Combined Carcinogenicity/ Chronic Toxicity	Indaziflam (AE 1170437; 93.14% a.i.) 0, 300, 3000 or 10,000 ppm in the	Males: NOAEL = 12 mg/kg/day and LOAEL = 118 mg/kg/day Females: NOAEL = 17 mg/kg/day and LOAEL = 167	MRID 47743417 Acceptable Page 47 (U.S.

Species	Study	Exposure	Response	Reference
weights ranged from 224 to 226 g for males and 167 to 169 g for females		diet for up to 24 months Equivalent to 0, 12, 118 or 414 mg/kg/day for males and 0, 17, 167 or 452 mg/kg/day for females. The dietary level of 10,000 ppm was lowered to 6,000 ppm in females from day 281 of week 41 onwards. Combined carcinogenicity/chronic toxicity	mg/kg/day In the 3,000 ppm females during the second year, increased incidences in the following findings were observed: dilated pupil, limited use of limbs, tremors, hindlimbs splayed and low alertness. These findings were also observed during the first year. Although the increases in incidences were marginal, together these findings were indicative of an adverse neurotoxic effect. In the 3000 ppm females, body weights were decreased by 5-10% during weeks 78-102. Overall (days 1-708) body weight gain was decreased by 14%. The LOAEL was 3000 ppm and the NOAEL was 300 ppm. The LOAEL is based on decreased body weights and body weight gains, signs of neurotoxicity and renal toxicity in females, hepatotoxicity in both sexes, atrophic seminal vesicles and colloid alteration in the thyroid in males along with a transient increase in TSH in males. Thyroid alterations in males appeared to be secondary to liver effects. At 3,000 ppm and above, increased incidences were noted of white foci in liver in the males and enlarged liver in the females. Also, an increased incidence of dark kidney and during microscopic analysis, in increased incidence of	EPA/OPP 2010b)

Species	Study	Exposure	Response	Reference
			minimal to moderate bilateral basophilic renal tubules. Decreased survival was observed at 452 mg/kg/day in females and both males and females showed more pronounced clinical signs of toxicity. At the doses tested, there was no treatment-related increase in tumor incidence when compared to controls. **No evidence of carcinogenicity**	
Bacterial reverse gene mutation assay (*Salmonella. typhimurium*)	Gene mutation	Indaziflam (AE 1170437 90.32% a.i.) 0, 16, 50, 158, 500, 1581 or 5000 µg/plate in presence or absence of S9 activation. Trial 1 – plate incorporation method and Trial 2, pre-incubation method	**Negative** +/-S9 activation in *S. typhimurium* strains TA98, TA100, TA 102, TA1535, TA1537 for increased frequency of revertant colonies up to cytotoxic (500 µg/plate) and precipitating concentrations (5000 µg/plate). There was no evidence of induced mutant colonies over background.	MRID 47443297 Acceptable Page 47 (U.S. EPA/OPP 2010b)
Bacterial reverse gene mutation assay (*Salmonella. typhimurium*)	Gene mutation	Indaziflam (AE 1170437 95.7%) Trial 1: 0, 15, 50, 158, 500, 1502 or 5000 µg/plate in the presence or absence of S9 activation, plate-incorporation method Trial 2: 0, 100, 200, 400, 800, 1600 or 3200 µg/plate in the	**Negative** +/-S9 activation in *S. typhimurium* strains TA98, TA100, TA102, TA1535, TA1537 for increased frequency of revertant colonies up to cytotoxic (≥800 µg/plate) and precipitating (3200 µg/plate) concentrations. There was no evidence of induced mutant colonies over background.	MRID 47443301 Acceptable Page 48 (U.S. EPA/OPP 2010b)

Species	Study	Exposure	Response	Reference
		presence or absence of S9 activation, pre-incubation method		
Mammalian cell *in vitro* forward gene mutation (cultured V79 cells, HGPRT locus)	Gene mutation	Indaziflam (AE 1170437 90.32%) 0, 10, 100 or 1000 µg/mL in presence or absence of S9 activation	**Negative** for increased frequency of mutation in CHO cells (not cytotoxic). There was no evidence of induced mutant colonies over background in the presence or absence of S9-activation.	MRID 47443302 Acceptable Page 48 (U.S. EPA/OPP 2010b)
Mammalian in vitro cytogenetic assay (Chinese hamster V79 lung cells)	Cytogenetics	Indaziflam (AE 1170437 90.32%) 4 hr exposure, 14 hr recovery period: 0, 15, 30, 60, 90 or 120 µg/mL in the absence of S9 activation; 0, 50, 100, 160, 200 and 240 µg/mL in the presence of S9 activation. 4 hr exposure, 26 hr recovery period: 0, 60, 90 and 120 in the absence of S9 activation; 0, 160, 200 and 240 µg/mL 18 hr exposure, no recovery period in the absence of S9 activation: 0, 4, 8, 16, 20 and 24 µg/mL	**Negative** for induction of chromosomal aberrations above background in the presence or absence of S9 metabolic activation. Tested up to the limit of solubility (160 µg/mL, -S9). There was no evidence of chromosome aberrations induced over background in the presence or absence of S9-activation.	MRID 47443305 Acceptable Page 48 (U.S. EPA/OPP 2010b)
Mammalian *in vivo* micronucleus assay (young	Cytogenetics	Indaziflam (AE 1170437 90.32%) Two doses of 0,	**Negative** for induction of increased frequency of micronucleated polychromatic erythrocytes. There was no significant	MRID 47443308 Acceptable Page 48 (U.S.

Species	Study	Exposure	Response	Reference
male Hsd/Win mice)		10, 20 or40 mg/kg by IP injection in 0.5% aqueous Cremophor vehicle administered 24 hrs apart; harvested 24 hrs after second dose in bone marrow at any treatment time.	increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment times.	EPA/OPP 2010b)

Table A2-7: Acute Eye Irritation, Skin Irritation, and Skin Sensitization Toxicity Studies

Species	Irritation	Exposure	Response	Reference
Rabbit (Crl:KBL(NZW)BR) 3 female rabbits age not reported, body weights ranged from 3.0- to 3.3 kg	Acute eye	Indaziflam (AE 1170437 SC 500 g/l, total isomer purity of 94.5%) 0.1 g of pulverized AE 1170437 was instilled into the conjunctival sac of one eye in three female young adult rabbits. The untreated other eye served as a control. The test animals were scored for irritation at approximately 1, 24, 48, and 72 hours post-instillation.	No corneal opacity or iritis was observed during the study. No "positive" scores were observed during the study. Conjunctival redness (score of 1) was observed in one rabbit at 24 and 48 hours. All ocular irritation was resolved by 72 hours. In this study, the formulation is non-irritating to the eye. AE 1170437 SC 500 is classified as U.S. EPA Toxicity Category IV for primary eye irritation.	MRID 47743605 Acceptable
Rabbit (Crl:KBL(NZW)BR) 3 female young adult rabbits, body weights ranged from 2.3- 2.4 kg.	Acute dermal	Indaziflam (AE 1170437 SC 500 g/l, total isomer purity of 94.5%) 3 young adult female rabbits were dermally exposed to 0.5 g of pulverized of AE 1170437. The test substance was moistened with water and applied to the skin of the test animals under a gauze patch, held in place with non-irritating tape and held in place for 4 hours. Dermal irritation was scored based on the Draize system at 1, 24, 48, and 72 hours post-patch removal.	There were no signs of irritation at any time point for any animal. The Primary Dermal Irritation Index is 0.0 based on dermal irritation scores from 1 to 72 hours. AE 1170437 SC 500 is not an irritant to the skin and is classified as U.S. EPA Toxicity Category IV for primary dermal irritation. There were no relevant systemic intolerance reactions.	MRID 47743606 Acceptable

Species	Irritation	Exposure	Response	Reference
Guinea Pig (Crl:HA) 30 female guinea pigs (20 animals for the test group and 10 control animals) Guinea pigs were 5-6 weeks old and body weights ranged from 303 to 388 g Additional two animals were used for dose-finding for the challenge concentration.	Skin sensitization	Indaziflam (BCS-AA 10717 SC 500G g/l) The Buehler epicutaneous patch text was performed to determine whether the test material exhibits skin-sensitizing properties. The range finding doses tested (0, 25%, 50%, 100%) showed no skin effects as any concentration, therefore the following concentrations were chosen for the main study: 1st to 9th induction = 100%, Challenge = 100%. Animals were treated nine times over three weeks. The challenge was performed four weeks after the first dermal induction.	After the 1st and 8th induction, there were no skin effects in the test animals. After the 9th induction there were skin effects in two test animals (slight localized redness) and no skin effects in the control group. The challenge with the 100% test item concentration led to no skin effects in the test or control animals. Skin reactions were noted at 30 and 54 hours of exposure. Based on the results of this study, BCS-AA10717 SC 500G g/l is not considered to be a dermal sensitizer.	MRID 47743607 Acceptable

Table A2-8: Acute Dermal Exposure Toxicity Studies

Species	Exposure	Response	Reference
Rat (Wistar: HsdCpb:Wu) Five rats/sex. Age ranged from 9-13 weeks; body weight ranged from 250-258 g for males and 208 to 219 g for females	Indaziflam (AE 1170437 SC 500, total isomer purity 94%%) Dose: Single dermal application AE 1170437 SC 500 g/l	Dermal LD_{50} Males > 2000 mg/kg bw Dermal LD_{50} Females > 2000 mg/kg bw Dermal LD_{50} Combined > 2000 mg/kg bw All animals survived the study. All male animals and four female animals gained body weight during the study. One female animal did not gain weight between Day 8 and Day 15. No clinical signs or dermal irritation was observed. The necropsies performed at the end of the study revealed no particular findings. Based on the LD_{50}, AE 1170437 SC 500 g/l is classified as U.S. EPA Toxicity Category III.	MRID 47743603 Acceptable (direct source)
Rat (HsdCpb:Wu) 5 rats/sex approximately 9-13 weeks old with body weights ranging from 236 to 247 g for males and 210 to 229 g for females	Indaziflam (AE 1170437; total isomers 94.5%) Dose: Limit of 2000 mg/kg applied to a gauze patch which was placed on the back of each test animal, secured with tape and left in place for 24 hours.	All test animals survived, exceeded their initial body weights by the end of the study period and appeared healthy throughout. Slight body weight losses in 2 test animals (1/sex) were transient and not considered to be related to the test substance. No gross internal findings were observed at necropsy. Based on the observed LD_{50} being greater than 2000 mg/kg, AE 1170437 is classified as U.S. EPA Toxicity Category III for acute dermal toxicity.	MRID 47443282 Acceptable (direct source)

Table A2-9: Subchronic Dermal Exposure Toxicity Studies

Species	Exposure	Response	Reference
Rat (HsdCpb:Wu) 10 rats/sex/dose Approximately 9-12 weeks old; body weight ranged from 217-244 g for males, and 187 to 219 g for females	Indaziflam (AE 1170437; 90.32% a.i.) Doses: 0, 40, 200 or 1000 mg/kg/day applied to shaved intact skin for 6 hours/day for 5 days/week for 4 weeks (22/23 total applications in M/F) 28-day dermal toxicity	Systemic NOAEL = 1000 mg/kg/day LOAEL = not determined (>1000 mg/kg/day) Dermal NOAEL = 1000 mg/kg/day LOAEL = not determined (>1000 mg/kg/day). No adverse treatment-related effects on mortality, clinical signs of toxicity, body weight, food or water consumption, ophthalmoscopic exams, hematology, clinical chemistry, absolute or relative organ weights and gross or microscopic pathology were observed in either sex. The investigators concluded that dermal exposure up to 1000 mg/kg/day (limit dose) for a total of 22 of 23 applications during a 4-week period did not induce any adverse effects in rats. The NOAEL was 1000 mg/kg/day. Some indication of local dermal irritation was observed at all doses but the findings were transient and observed only in females, and therefore were not considered adverse.	MRID 47443290 Acceptable Page 45 (U.S. EPA/OPP 2010b)

Table A2-10: Acute Inhalation Toxicity Studies

Species	Exposure	Response	Reference
Rat (Wistar rats; Hsd Cpb:WU) 5 rats/sex. Approximate age 2-3 months; body weight ranged from 187 to 198 g for males and 171-196 g for females	AE 1170437 SC 500 g/l Test group was exposed to a mean maximum attainable aerosol concentration of 1.937 mg/L for 4 hours (nose only). Animals were observed for 14 days.	LC_{50} Males > 1.937 mg/L LC_{50} Females > 1.937 mg/L LC_{50} Combined > 1.937 mg/L Mortality did not occur at the maximum technically feasible concentration of 1.937 mg/L. Individual gross-pathological examinations of the rats indicate no observable necropsy findings at the rats tested. All rats in the control group tolerated the test without specific signs. The rats displayed the following transient clinical signs after exposure: Bradypnea, labored breathing patterns, breathing: irregular, piloerection, hair coat: ungroomed, motility reduced, motility increased, high-legged gait, gait: staggering, limp, convulsion, tremor, mydriasis. All rats were without signs at day 3. The average body temperature of the exposure groups was significantly decreased. In summary, the test item (liquid aerosol) proved to have low inhalation toxicity in rats. For both genders combined, the LC_{50} is greater than 1.937 mg/L. Based on the LC_{50} AE 1170437 SC 500 g/l is classified as U.S. EPA Toxicity Category III.	MRID 47743604 Acceptable
Rat (HsdCpb:Wu) 5 rats/sex Approximately 8-12 weeks old; body weight ranged from 204 to 210 g for males and 183-194 g for females	Indaziflam (AE 1170437; total isomers 94.5%) 5/sex young adult rats were exposed nose-only via the inhalation route to aerosolized AE 1170437 for 4 hours at a gravimetric concentration of 2300 mg/m^3 (2.3	LC_{50} Combined > 2.3 mg/L Males > 2.3 mg/L Females > 2.3 mg/L All test animals survived and exceeded their initial body weights by the end of the study. Transient clinical signs of toxicity included; pilo-erection, un-groomed appearance, mydriasis,	MRID 47443283 Acceptable

Species	Exposure	Response	Reference
	mg/L). Individual body weights were recorded prior to exposure and again on study days 1, 3, 7 and 14. The test animals were observed for mortality and clinical signs of toxicity several times on the day of exposure and at least once daily thereafter for the remainder of the 14 day study period. Rectal temperatures were taken shortly after exposure. All test animals were necropsied at the end of the study.	red tears, bradypnea, laboured breathing, reduced motility, limps, tremors, high-legged and staggering gait, salutatory spasm (clonic), chewing movements, and vomiting. Additionally, 2 female test animals revealed reduced cornea reflexes and 1 male test animal reacted "bizarre and violent" after the startle reflex. Test animals were asymptomatic by study day 5. Test animals appeared to show significant decreases in body temperature shortly after exposure, when compared to control temperatures. No gross internal findings were observed at necropsy. Based on the observed LC_{50} being greater than 2.3 mg/L, AE 1170437 is classified as U.S. EPA Toxicity Category IV for acute inhalation toxicity.	

Appendix 3: Toxicity to Birds

Unless otherwise indicated, the study summaries and MRID numbers are taken from U.S. EPA/OPP (2010a, 2010c) and supplemented with information from DERs submitted by the registrant. These are the subset of studies that U.S. EPA/OPP selected for use in their risk assessment.

Table A3-1: Acute Oral and Dietary Toxicity to Birds 162
Table A3-2: Chronic Dietary Toxicity to Birds 168

Table A3-1: Acute Oral and Dietary Toxicity to Birds

Species	Toxicity	Exposure	Response	Reference
Northern bobwhite quail (*Colinus virginianus*) 10 birds/dose. Approximately 16-weeks-old; body weights ranged from 191 to 202 g	Acute (Dose-based)	Indaziflam (AE 1170437; 90.3% a.i.) Single oral administration by capsule at nominal levels of 0 (control), 500, 1,000, and 2,000 mg a.i./kg bw. Observed for 14-days post exposure.	LD_{50} >2000 mg a.i/kg bw NOAEL = 2000 mg a.i./kg bw No treatment-related mortality occurred during the study, although two incidental deaths occurred due to injuries sustained while handling. No treatment-related clinical signs of toxicity, effects on body weight, or post-mortem gross lesions or unusual observations were observed at any treatment level. The only symptom observed was that of feather loss on one bird in the 2,000 mg a.i./kg bw level, which may or may not be attributed to intoxication. While there was a decrease in female food consumption at the 500 and 2,000 mg a.i./kg bw levels, there was no dose-response established, and thus the reductions were not considered to be related to treatment. U.S. EPA classifies as "practically non-toxic"	MRID 47443240 Acceptable Page 165 (U.S. EPA/OPP 2010a)

Species	Toxicity	Exposure	Response	Reference
Zebra Finch (*Poephila guttata)* 10 birds/dose Birds in adult plumage; no age provided. Body weights ranged from 10.7 to 14.1 g for males and 11.4 to 13.9 g for females	Acute (Dose-based)	Indaziflam (AE 1170437; 90.3% a.i.) Single oral administration by gavage at 0 (control) and 2,000 mg a.i./kg bw Observed for 14-days post exposure.	LD_{50} >2000 mg a.i./kg bw No mortalities occurred in the control group. A single mortality occurred in the treatment group. Gross necropsy was conducted on the one mortality from the 2,000 mg a.i./kg bw dosage group. The male was noted with a pasty vent and yellowish plaques on the left thoracic air sacs along with areas of consolidation in the lower left quarter of the left lung. The male also had a distended abdomen and large intestine, the latter of which was filled with fecal matter. The large intestine had areas of hyperemia. These findings were not considered treatment-related. The bird's death was determined to be due to intestinal and respiratory problems, not the treatment dose. All control birds were normal in appearance and behavior throughout the test. No apparent treatment related effects upon body weight occurred compared to the control. Clinical signs of toxicity were first observed 30 minutes after dosing (one male with slightly ruffled appearance). This male and all other birds were	MRID 47743306 Acceptable Pp. 165-166 (U.S. EPA/OPP 2010a)

Species	Toxicity	Exposure	Response	Reference
			normal in appearance and behavior approximately one hour after dosing. After 5 hours after dosing, 2 birds were noted with reduced reaction to external stimuli (sound and movement). On Day 1 of test, one male was noted with a ruffled appearance, and on Day 2 of test, four birds were noted with a slight ruffled appearance. All birds showed normal behavior and appearance on Days 3-7. On Day 8 of test, one male was again noted with slight ruffled appearance, and on day 9 of test this male was noted with a wind droop, ruffled appearance and lethargy. On Days 10 and 13 this male was noted with light ruffled appearance. This male was found dead on Day 14 with pasty excreta on his vent. A ruffled appearance was noted on Day 9, but was normal (appearance and behavior) for remainder of test. All other birds in the 2,000 mg a.i./kg bw treatment group were normal in appearance and behavior throughout the test. U.S. EPA classifies as "practically non-toxic"	

Species	Toxicity	Exposure	Response	Reference
Northern bobwhite quail (*Colinus virginianus*) 10 birds/dose Approximately 10-days old with body weights ranging from 22.5 to 29.1 g	Acute (Dietary-based)	Indaziflam (BCS-AA10717; 94.5% a.i. eight total isomers, AE 1170437 90.3% a.i. principle a.i.) Administered in the diet at concentrations of 0 (negative control), 313, 625, 1250, 2500, and 5000 mg a.i./kg diet. 8-day dietary study (5 days exposure and 3 days recovery). .	LC_{50}: >5007 mg a.i./kg diet NOAEC: 5007 mg a.i./kg diet No mortality occurred in any control or treatment level. The acute dietary LC_{50} was >5007 mg a.i./kg diet (mean measured). No treatment-related clinical signs of toxicity, effects on body weight or food consumption, or post-mortem gross lesions or unusual observations were observed at any treatment level. U.S. EPA classifies as "practically non-toxic"	MRID 47443241 Acceptable Page 167 (U.S. EPA/OPP 2010a)
Mallard duck (*Anas platyrhynchos*) 10 birds/dose approximately 8-days old with body weights ranging from 99.6 to 137.9 g	Acute (Dietary-based)	Indaziflam (BCS-AA10717; 94.5% a.i. eight total isomers, AE 1170437 90.3% a.i. principle a.i.) Administered in the diet at concentrations of 0 (negative control), 313, 625, 1250, 2500, and 5000 mg ai/kg diet. 8-day dietary study (5 days exposure and 3 days recovery).	LC_{50}: > 5,215 mg a.i./kg LOAEC: 5215 mg a.i./kg diet (based on treatment related effects on body weight and feed consumption) NOAEC: 2518 mg a.i./kg diet No mortality occurred in any control or treatment level. The acute dietary LC_{50} was > 5,215 mg a.i./kg diet (mean measured). No treatment-related clinical signs of toxicity or post-mortem gross lesions or unusual observations were observed at any treatment level. The mean body weights of birds from the 5215 mg a.i./kg diet level were	MRID 47443242 Acceptable Pp. 167-168 (U.S. EPA/OPP 2010a)

Species	Toxicity	Exposure	Response	Reference
			statistically-reduced (p<0.05) compared to the control on Days 5 and 8, and the difference in body weight was also statistically-reduced (p < 0.05) at this level during the exposure period. Although a statistically-significant reduction in body weight was observed on Day 8 in birds from the 1320 mg a.i./kg diet level, a similar reduction was not observed at the 2518 mg a.i./kg diet level, and thus this difference was not considered to be a result of treatment. The NOAEC for body weight data was 2518 mg a.i./kg diet. Based upon visual observation of the feed consumption data, an apparent treatment-related reduction was indicated during the first 3 days of exposure at the 5215 mg a.i./kg diet level. Feed consumption at this level was comparable to or exceeded control consumption during the final 2 days of exposure, as well as during the 3-day recovery period. The study authors reported that the effect on body weight and feed consumption at the 5215 mg a.i./kg diet level may be recoverable since body weight gain and	

Species	Toxicity	Exposure	Response	Reference
			food consumption were slightly higher (although not statistically significant) once the birds were offered untreated food in the recovery phase. U.S. EPA classifies as "practically non-toxic"	

Table A3-2: Chronic Dietary Toxicity to Birds

Species	Exposure	Response	Reference
Northern bobwhite quail (*Colinus virginianus*) 18 pairs/dose approximately 16 weeks old; body weights ranged from 169 to 215 g for males and 174 to 203 g for females	Indaziflam (BCS-AA10717; 94.5% a.i. eight total isomers, AE 1170437 90.3% a.i. principle a.i.) Administered to the birds in the diet at nominal concentrations of 0 (control), 250, 500, or 1000 mg as/kg diet. *ca.* 23-week Mean-measured concentrations (of AE 1170437) were < 5.00 (control), 252, 524, and 1023 mg a.i./kg diet, respectively One generation reproductive toxicity avian study.	LOAEC: > 1,023 mg a.i./kg diet NOAEC: 1,023 mg a.i./kg diet No treatment-related effects were observed on any adult or offspring parameter at any concentration level. No treatment-related mortality occurred during the study. The only mortality observed was a single control female that died between Weeks 9 and 23. No overt signs of intoxication were observed at any treatment level. The study authors reported that minor occurrences of feather loss and minor injuries were observed at all (including control) levels, and that these occurrences were associated with normal cage wear. No statistically significant differences were observed at any treatment level for feed consumption, body weight change or reproductive effects as compared to controls. All birds from the control and 500 mg as/kg diet levels, and five birds per sex from the 250 and 500 mg as/kg diet levels were necropsied at study termination. There were no indications of any treatment-related lesions or other findings. Several birds had feather loss that was associated with normal cage wear.	MRID 47443243 Acceptable Page 165 (U.S. EPA/OPP 2010a)
Mallard duck (*Anas platyrhynchos*) 15 pairs/dose. Birds approximately 16 weeks old; body weights ranged from	Indaziflam (BCS-AA10717; 94.5% a.i. eight total isomers, AE 1170437 90.3% a.i. principle a.i.) Administered to the birds	LOAEC: 95 mg a.i./kg diet NOAEC: < 95 mg a.i./kg diet (based on female weight gain and adult food consumption) No mortality occurred during the	MRID 47443244 (primary) Supplemental Pp. 169-170 (U.S. EPA/OPP

Species	Exposure	Response	Reference
930 to 1287 g for males and 881 to 1096 g for females.	in the diet at nominal concentrations of <5.00 (control), 95, 334, and 1015 mg a.i./kg diet. *ca.* 22-week avian reproduction study	primary study. No overt signs of intoxication were observed at any treatment level in either study. Minor occurrences of feather loss and minor injuries were observed at all (including control) levels, and were associated with normal cage wear. Although a statistically-significant reduction (p<0.05) in overall (Weeks 1-22) food consumption was observed in the primary study at the 100 mg as/kg diet level (102.4 g) compared to the control (121.1 g), this difference was not observed at the two higher test levels and was thus not considered to be related to treatment. For both studies, the study authors' analysis revealed no statistically significant differences at any treatment level compared to the control regarding adult male body weight change from study initiation to termination. The body weight change of adult females from the primary study, however, was statistically-reduced (p<0.05) compared to the control (253.1 g) at the 100 and 320 mg as/kg diet levels (161.1 and 180.1 g, respectively), but not at the 1000 mg as/kg diet level (202.9 g). For the primary study, all birds from the control and 1000 mg as/kg diet levels, and four birds per sex from the 100 and 3200 mg as/kg diet levels were necropsied at study termination. The study authors reported no statistically significant differences from the control for any reproductive endpoint at any treatment level for either study.	2010a)

Species	Exposure	Response	Reference
Mallard duck (*Anas platyrhynchos*) 15 pairs/dose Approximately 17 weeks old; with body weight ranging from 988 to 1316 g for males and 917 to 1144 g for females. 917-1316 g	Indaziflam (BCS-AA10717; 94.5% a.i.) Administered to the birds in the diet at nominal concentrations of <5.00 (control), 44, 157, and 468 mg as/kg diet. *ca.* 19-week avian reproduction study	LOAEC: 44 mg a.i./kg diet NOAEC: < 44 mg a.i./kg diet (based on male weight gain) One male bird from the 50 mg as/kg diet level of the supplemental study was found dead during Week 4 (prior to initiation of treatment). No overt signs of intoxication were observed at any treatment level in either study. No treatment-related effects on food consumption were indicated during exposure for either study. In the supplemental study, no statistically significant differences in female body weight change were observed at any level. For the secondary study, the reviewer's analysis determined that effects to male weight gain and female weight gain were biologically significant, although these effects were not detected to be statistically significant. For male weight gain, results show that all male birds, including the control lost weight. The results of mean weight gain for the control, 44, 157, 468 mg a.i./kg treatment groups were -15.9, -35.3 (-121%), -46.1(-189), and -57.1 (-259) grams, respectively. The reviewer determined the LOAEC and NOAEC to be 44 and < 44 mg a.i./kg, respectively. For the supplemental study, all birds from the control and 450 mg as/kg diet levels, six birds per sex (including the one decedent male and its pen-mate) from the 50 mg as/kg diet level, and five birds per sex from the 150 mg as/kg diet level were necropsied at the time	MRID 47443244 (secondary) Supplemental Pp. 169-170 (U.S. EPA/OPP 2010a)

Species	Exposure	Response	Reference
		of death. There were no indications of any treatment-related lesions or other findings. Several birds had feather loss and minor skin abrasions that were associated with normal cage wear. The study authors reported no statistically significant differences from the control for any reproductive endpoint at any treatment level for either study.	

Appendix 4: Toxicity to Terrestrial Invertebrates

Unless otherwise indicated, the study summaries and MRID numbers are taken from U.S. EPA/OPP (2010a, 2010c) and supplemented with information from DERs submitted by the registrant. These are the subset of studies that U.S. EPA/OPP selected for use in their risk assessment.

Table A4-1: Acute Toxicity to Honey Bees 172
Table A4-2: Acute Toxicity to Earthworms 174

Table A4-1: Acute Toxicity to Honey Bees

Species	Toxicity	Exposure	Response	Reference
Honey bee (*Apis mellifera*) 6 cages per dose, 10 bees per cage. Bees were 2-4 weeks old	Acute (Contact)	Indaziflam (BCS-AA10717; 94.5% a.i.) A 48 hour acute range finding study was performed and there were no significant compound-related effects. The doses used for the contact study included the control, 12.5, 25, 50, 100 and 200 µg a.i./bee. There was one dead bee at the 12.5 µg a.i./bee dose at 24 hours; and one dead bee at 100 µg a.i./bee after 48 hours. The nominal dose for the contact test was 100 µg a.i./bee. Observations at 4, 24 and 48 hours	LD_{50} >100 µg a.i./bee NOAEL: 100 µg a.i./bee LOAEL: > 100 µg a.i./bee No mortalities or sub-lethal effects were noted in the control or single treatment level yielding NOAEL and LD_{50} values of 100 and >100 µg a.i./bee, respectively. U.S. EPA classifies as "practically non-toxic"	MRID 47443245 Acceptable Page 174 (U.S. EPA/OPP 2010a)
Honey bee (*Apis mellifera*) 6 cages per dose, 10 bees per cage Between 2 and 4 weeks	Acute (Contact)	AE 1170437 SC 500 48 hours at nominal concentrations of 0 (negative control) and 100 µg a.i./bee.	LD_{50}: > 100 µg a.i./bee NOAEL: 100 µg a.i./bee LOAEL: > 100 µg a.i./bee By 48 hours in the contact test, mortality was 1.7% (one bee died). There were no sublethal effects in the controls or treated group.	MRID 47743307 Supplemental Pp. 174-175 (U.S. EPA/OPP 2010a)

Species	Toxicity	Exposure	Response	Reference
			U.S. EPA classifies as "practically non-toxic"	
Honey bee (*Apis mellifera*) 6 cages per dose, 10 bees per cage. Bees were 2-4 weeks old	Acute (Oral)	Indaziflam (BCS-AA10717; 94.5% a.i.) The doses used for the range finding oral study included the control, 12.5, 24.9, 49.9, 99.3 and 196.9 µg consumed a.i. /bee. There was one dead bee after 24 hours at the 99.3 µg/bee rate. The nominal dose for the oral test was 120 µg a.i./bee. After 1 hour, the treated feeding solution was removed and replaced with an untreated feeding solution. Observations at 4, 24 and 48 hours	LC_{50} > 120 µg a.i./bee NOAEC: 120 µg a.i./bee LOAEC: > 120 µg a.i./bee No mortalities or sub-lethal effects were noted in the control or single treatment group during the 48-hour exposure in the oral test. U.S. EPA classifies as "practically non-toxic"	MRID 47443245 Acceptable Page 174 (U.S. EPA/OPP 2010a)
Honey bee (*Apis mellifera*) 6 cages per dose, 10 bees per cage Between 2 and 4 weeks	Acute (Oral)	AE 1170437 SC 500 48 hours at nominal concentrations of 0 (negative control) and 120 µg a.i./bee. Actual intake concentration was 119.7 µg a.i./bee.	LC_{50}: >119.7 µg a.i./bee NOAEL: 119.7 µg a.i./bee LOAEL: >119.7 µg a.i./bee By 48 hours in the oral test, mortality was 0%. There were no sublethal effects in the control or treated groups. U.S. EPA classifies as "practically non-toxic"	MRID 47743307 Supplemental Pp. 174-175 (U.S. EPA/OPP 2010a)

Table A4-2: Acute Toxicity to Earthworms

Species	Exposure	Response	Reference
Earthworm (*Eisenia fetida* andrei)	Indaziflam (BCS-AA10717; 94.5% a.i. Total isomers AE1170437, 90.34% a.i.) 14 days at concentrations of 0 (control), 100, 178, 316, 562 and 1000 mg a.i./kg dw of soil. As a reference, worms were additionally exposed to Chloroacetamide A.R. at nominal concentrations of 5.6, 10, 18, 24 and 32 mg a.i./kg dw of soil.	LC_{50} > 1,000 mg a.i./kg dw soil NOAEC: 316 mg a.i./kg dw soil LOAEC: 562 mg a.i./kg dw soil Mean mortality did not exceed 3% in the control or any of the treatment groups. LOAEC based on sublethal effect of percent body weight change. Percent body weight loss averaged 5.9% in the negative control and ranged from 8.2 % (100 mg a.i./kg dw) to 15.6% (562 mg a.i./kg dw) in the treatment levels. The 1000 mg a.i./kg dw level showed a 15% decrease.	MRID 47443269 Supplemental Pp. 175-176 (U.S. EPA/OPP 2010a)
Earthworm (*Eisenia fetida*)	Indaziflam AE 1170437 SC 500 G (a.i. BCS-AA10717) 28 days at nominal concentrations of 0 (negative control), 10.0, 17.8, 31.6, 56.2, and 100.0 L form/ha. The converted concentrations in terms of mg ai/kg were 0 (negative control), 43.8, 78.0, 138.4, 246.2, and 438.0 mg form/kg dry weight of artificial soil, and are equivalent to 0 (negative control), 19.1, 34.0, 60.3, 107, and 191 mg a.i./kg dw soil. After 28 days, adult earthworms were removed and any offspring produced were exposed to the nominal concentrations for an additional 28 days.	The LC_{50} and EC_{50} values in the study were > 191 mg a.i./kg dw soil. The NOAEC, based on reproduction, was 34.0 mg a.i./kg dw soil. The LOAEC, based on reproduction was 60.3 mg a.i./kg dw soil. The active ingredient is considered to be toxic to earthworms at and above a concentration of 60.3 mg a.i./kg dw soil. There were no compound related toxic effects. No behavioral abnormalities or pathological symptoms were reported. This study is scientifically sound. This study follows guideline recommendations for an earthworm subchronic toxicity test (OPPTS 850.6200); however, this study failed to test concentrations up to the guideline recommended limit in an attempt to determine a definitive LC_{50}. This study is classified Supplemental.	MRID 47743316 Supplemental

Species	Exposure	Response	Reference
Earthworm (*Eisenia fetida*)	BCS-AA10717 SC 500 G (AI: Indaziflam) nominal concentrations of 0 (negative control), 100, 178, 316, 562, and 1000 mg a.i./kg dry weight of artificial substrate. 14-day acute toxicity study	The LC_{50} and EC_{50} values in the study were > 1000 mg a.i./kg dw soil. The NOAEC, based on body weight change, was 562 mg ai/kg dw soil. Mean % weight loss was 10% in the negative control, and was 10, 12, 9, 12, and 15% in the nominal 100, 178, 316, 562, and 1000 mg a.i./kg dw soil treatment groups, respectively. The LOAEC, based on body weight change was 1000 mg a.i./kg dw soil. The active ingredient is considered to be toxic to earthworms at and above a concentration of 1000 mg a.i./kg dw soil. There were no compound related toxic effects. No OPPTS guidance exists for a 14-day acute earthworm toxicity test, thereby making this a non-guideline test. This study is scientifically sound but was not conducted following any OPPTS guidelines.	MRID 47743315 Supplemental
Earthworm (*Eisenia fetida*)	AE 1170437-carboxylic acid 0 (negative control), 62.5, 125, 250, 500, and 1000 mg a.i./kg dry weight of artificial substrate 14-day acute toxicity study	The LC_{50} and EC_{50} values in the study were > 1000 mg a.i./kg dw soil. No mortality occurred during the 14-day study and no endpoints were affected. The overall NOAEC was 1000 mg a.i./kg dw soil. The LOAEC, based on body weight change was >1000 mg a.i./kg dw soil. The active ingredient is considered to be non-toxic to earthworms up to a concentration of 1000 mg a.i./kg dw soil. There were no compound related toxic effects.	MRID 47743314 Supplemental

Species	Exposure	Response	Reference
Earthworm (*Eisenia fetida*)	AE 1170437-triazine-indanone (a metabolite of Indaziflam) 0 (negative control), 10, 32, 100, 316, and 1000 mg a.i./kg dry weight of artificial substrate 14-day acute toxicity study	The LC_{50} and EC_{50} values in the study were > 1000 mg a.i./kg dw soil. No mortality occurred during the 14-day study. The NOAEC, based on body weight change, *i.e.* reduction, was 316 mg a.i./kg dw soil. The LOAEC, based on body weight change was 1000 mg a.i./kg dw soil. The active ingredient is considered to be toxic to earthworms at and above a concentration of 1000 mg a.i./kg dw soil. There were no compound related toxic effects. No OPPTS guidance exists for a 14-day acute earthworm toxicity test, thereby making this a non-guideline test. This study is scientifically sound but was not conducted following any OPPTS guidelines.	MRID 47743313 Supplemental
Earthworm (*Eisenia fetida*)	AE 1170437 diaminotriazine (a metabolite of Indaziflam, BCS-AA10717) at 0 (negative control), 62.5, 125, 250, 500, and 1000 mg a.i./kg dry weight of artificial substrate 14-day acute toxicity study	The LC_{50} and EC_{50} values in the study were > 1000 mg a.i./kg dw soil. The NOAEC, based on body weight change from day 0 to day 14 within each treatment level, was 500 mg a.i./kg dw soil. The LOAEC, based on body weight change was 1000 mg a.i./kg dw soil. The active ingredient is considered to be toxic to earthworms at and above a concentration of 1000 mg a.i./kg dw soil. There were no compound related toxic effects. No mortality occurred during the 14-day study No OPPTS guidance exists for a 14-day acute earthworm toxicity test, thereby making this a non-guideline test. This study is scientifically sound but was not	MRID 4743312 Supplemental

Species	Exposure	Response	Reference
		conducted following any OPPTS guidelines.	

Appendix 5: Toxicity to Terrestrial Plants

Unless otherwise indicated, the study summaries and MRID numbers are taken from U.S. EPA/OPP (2010a, 2010c) and supplemented with information from DERs submitted by the registrant. These are the subset of studies that U.S. EPA/OPP selected for use in their risk assessment.

Table A5-1: Seedling Emergence Toxicity Studies 178
Table A5-2: Vegetative Vigor Toxicity Studies 182

Table A5-1: Seedling Emergence Toxicity Studies

Species	Exposure	Response	Reference
Monocot: Barley (*Hordeum vulgare*) Corn (*Zea mays*) Oat (Avena sativa) Ryegrass (*Lolium perenne*)	BCS-AA10717-20WSP (20.3% a.i.)	<u>Barley (shoot length)</u> EC_{25} = 0.002273 lbs a.i./acre EC_{50}/IC_{50} = 0.002273 lbs a.i./acre NOAEC = 0.000906 lbs a.i./acre <u>Corn (shoot length)</u> EC_{25} = 0.0028 lbs a.i./acre EC_{50}/IC_{50} = 0.011 lbs a.i./acre NOAEC = 0.000364 lbs a.i./acre <u>Oat (survival)</u> EC_{25} = 0.0016 lbs a.i./acre EC_{50}/IC_{50} = 0.0026 lbs a.i./acre NOAEC = 0.000906 lbs a.i./acre <u>Ryegrass (survival)</u> EC_{25} = 0.00016 lbs a.i./acre EC_{50}/IC_{50} = 0.00031 lbs a.i./acre NOAEC = 0.000062 lbs a.i./acre Most sensitive monocot	MRID 47443246 Acceptable Pp. 184-185 (U.S. EPA/OPP 2010a)
Monocot: Barley (*Hordeum vulgare*) Corn (*Zea mays*) Oat (Avena sativa) Onion (*Allium cepa*) Ryegrass (*Lolium perenne*)	Indaziflam 500 SC (43.6% a.i. AE 1170437; 44.4% a.i. BCS-AA10717) 21-day seedling emergence study	<u>Barley (survival)</u> EC_{25} = 0.004 lbs a.i./acre EC_{50}/IC_{50} = 0.012 lbs a.i./acre NOAEC = 0.000932 lbs a.i./acre <u>Corn (shoot length)</u> EC_{25} = 0.0032 lbs a.i./acre EC_{50}/IC_{50} = 0.019 lbs a.i./acre NOAEC = 0.000374 lbs a.i./acre	MRID 47443247 Acceptable Pp. 182-184 (U.S. EPA/OPP 2010a)

Species	Exposure	Response	Reference
		Oat (survival) EC_{25} = 0.0013 lbs a.i./acre EC_{50}/IC_{50} = 0.002 lbs a.i./acre NOAEC = 0.000374 lbs a.i./acre Onion (shoot length) EC_{25} = 0.00017 lbs a.i./acre EC_{50}/IC_{50} = 0.00026 lbs a.i./acre NOAEC = 0.000146 lbs a.i./acre Most sensitive monocot Ryegrass (survival) EC_{25} = 0.00027 lbs a.i./acre EC_{50}/IC_{50} = 0.00047 lbs a.i./acre NOAEC = 0.000063 lbs a.i./acre	
Dicot: Buckwheat (*Fagopyrum esculentum*) Cucumber (*Cucumis sativa*) Oilseed rape (*Brassica napus*) Soybean (*Glycine max*) Sugarbeet (*Beta vulgaris*) Sunflower (*Helianthus annuus*)	BCS- AA10717-20WSP (20.3% a.i.) 21-day seedling emergence study	Buckwheat (survival) EC_{25} = 0.00062 lbs a.i./acre EC_{50}/IC_{50} = 0.0011 lbs a.i./acre NOAEC = 0.000364 lbs a.i./acre Cucumber (shoot length) EC_{25} = 0.00077 lbs a.i./acre EC_{50}/IC_{50} = >0.000906 lbs a.i./acre NOAEC = 0.000364 lbs a.i./acre Oilseed rape (emergence) EC_{25} = 0.00011 lbs a.i./acre EC_{50}/IC_{50} = 0.00027 lbs a.i./acre NOAEC = 0.000062 lbs a.i./acre Most sensitive dicot Soybean (emergence) EC_{25} = 0.000142 lbs a.i./acre EC_{50}/IC_{50} = 0.0038 lbs a.i./acre NOAEC = 0.000364 lbs a.i./acre	MRID 47443246 Acceptable Pp. 184-185 (U.S. EPA/OPP 2010a)

Species	Exposure	Response	Reference
		Sugarbeet (survival) EC_{25} = 0.00035 lbs a.i./acre EC_{50}/IC_{50} = 0.0005 lbs a.i./acre NOAEC = 0.000023 lbs a.i./acre Sunflower (shoot length) EC_{25} = 0.0033 lbs a.i./acre EC_{50}/IC_{50} = >0.01421 lbs a.i./acre NOAEC = 0.000906 lbs a.i./acre	
Dicot: Buckwheat (*Fagopyrum esculentum*) Cucumber (*Cucumis sativa*) Oilseed rape (*Brassica napus*) Soybean (*Glycine max*) Sugarbeet (*Beta vulgaris*) Sunflower (*Helianthus annuus*) Tomato (*Lycopersicon esculentum*)	Indaziflam 500 SC (43.6% a.i. AE 1170437; 44.4% a.i. BCS-AA10717) 21-day seedling emergence study	Buckwheat (shoot length) EC_{25} = <0.000932 lbs a.i./acre EC_{50}/IC_{50} = >0.00585 lbs a.i./acre NOAEC = 0.000374 lbs a.i./acre Cucumber (dry weight) EC_{25} = >0.000932 lbs a.i./acre EC_{50}/IC_{50} = >0.000932 lbs a.i./acre NOAEC = <0.000146 lbs a.i./acre Oilseed rape (survival) EC_{25} = 0.00076 lbs a.i./acre EC_{50}/IC_{50} = >0.000932 lbs a.i./acre NOAEC = 0.000146 lbs a.i./acre Tomato (shoot length) EC_{25} = 0.00024 lbs a.i./acre EC_{50}/IC_{50} = 0.00071 lbs a.i./acre NOAEC = 0.000146 lbs a.i./acre **Most sensitive dicot** Soybean (survival) EC_{25} = 0.00062 lbs a.i./acre EC_{50}/IC_{50} = 0.002 lbs a.i./acre NOAEC = 0.000146 lbs a.i./acre Sugarbeet (survival) EC_{25} = 0.00099 lbs a.i./acre EC_{50}/IC_{50} = 0.002 lbs a.i./acre NOAEC = 0.000374 lbs a.i./acre Sunflower (shoot length)	MRID 47443247 Acceptable Pp. 182-184 (U.S. EPA/OPP 2010a)

Species	Exposure	Response	Reference
		EC_{25} = 0.0083 lbs a.i./acre EC_{50}/IC_{50} = >0.01462 lbs a.i./acre NOAEC = 0.000932 lbs a.i./acre	

Table A5-2: Vegetative Vigor Toxicity Studies

Species	Exposure	Response	Reference
Monocots: Corn (*Zea mays*) Oat (Avena sativa) Onion (*Allium cepa*) Ryegrass (*Lolium perenne*)	BCS-AA10717-20WSP (19.6% a.i.) 21-day vegetative vigor study	<u>Corn (shoot length)</u> EC_{25} = 0.0056 lbs a.i./acre EC_{50}/IC_{50} = 0.027 lbs a.i./acre NOAEC = 0.002273 lbs a.i./acre <u>Oat (survival)</u> EC_{25} = 0.0078 lbs a.i./acre EC_{50}/IC_{50} = 0.012 lbs a.i./acre NOAEC = 0.005683 lbs a.i./acre <u>Onion (survival)</u> EC_{25} = 0.018 lbs a.i./acre EC_{50}/IC_{50} = 0.03 lbs a.i./acre NOAEC = 0.01421 lbs a.i./acre <u>Ryegrass (survival)</u> EC_{25} = 0.0031 lbs a.i./acre EC_{50}/IC_{50} = 0.0041 lbs a.i./acre NOAEC = 0.002273 lbs a.i./acre Most sensitive monocot	MRID 47443248 Supplemental Page 189 (U.S. EPA/OPP 2010a)
Monocots: Corn (*Zea mays*) Oat (Avena sativa) Onion (*Allium cepa*) Ryegrass (*Lolium perenne*)	Indaziflam 500 SC (44.87% a.i.) 21-day vegetative vigor study	<u>Corn (survival)</u> EC_{25} = 0.0083 lbs a.i./acre EC_{50}/IC_{50} = 0.02 lbs a.i./acre NOAEC = 0.002338 lbs a.i./acre <u>Oat (survival)</u> EC_{25} = 0.0048 lbs a.i./acre EC_{50}/IC_{50} = 0.0077 lbs a.i./acre NOAEC = 0.002338 lbs a.i./acre <u>Onion (survival)</u> EC_{25} = 0.05 lbs a.i./acre EC_{50}/IC_{50} = 0.065 lbs a.i./acre NOAEC = 0.005847 lbs a.i./acre	MRID 47443249 Supplemental Page 190 (U.S. EPA/OPP 2010a)

Species	Exposure	Response	Reference
		Ryegrass (survival) EC_{25} = 0.0021 lbs a.i./acre EC_{50}/IC_{50} = 0.0035 lbs a.i./acre NOAEC = 0.000932 lbs a.i./acre Most sensitive monocot	
Dicots: Buckwheat (*Fagopyrum esculentum*) Cucumber (*Cucumis sativa*) Soybean (*Glycine max*) Sugarbeet (*Beta vulgaris*) Sunflower (*Helianthus annuus*) Turnip (*Brassica rapa*)	BCS-AA10717-20WSP (19.6% a.i.) 21-day vegetative vigor study	Buckwheat (shoot length) EC_{25} = 0.012 a.i./acre EC_{05}/IC_{05}: 0.035 lbs a.i./acre NOAEC = 0.005683 lbs a.i./acre Cucumber (shoot length) EC_{25} = 0.0081 a.i./acre EC_{05}/IC_{05}: 0.033 lbs a.i./acre NOAEC = 0.002273 lbs a.i./acre Soybean (dry weight) EC_{25} = 0.002273 a.i./acre EC_{05}/IC_{05}: 0.015 lbs a.i./acre NOAEC = >0.0888 lbs a.i./acre Sugarbeet (shoot length) EC_{25} = 0.012 a.i./acre EC_{05}/IC_{05}: 0.038 lbs a.i./acre NOAEC = 0.005683 lbs a.i./acre Sunflower (shoot length) EC_{25} = 0.0095 a.i./acre EC_{05}/IC_{05}: 0.059 lbs a.i./acre NOAEC = 0.000906 lbs a.i./acre Turnip (dry weight) EC_{25} = >0.000906 a.i./acre EC_{05}/IC_{05}: <0.000906 lbs a.i./acre NOAEC = <0.000906 lbs a.i./acre Most sensitive dicot	MRID 47443248 Supplemental Page 189 (U.S. EPA/OPP 2010a)
Dicots: Buckwheat (*Fagopyrum esculentum*) Cucumber (*Cucumis sativa*) Oilseed rape	Indaziflam 500 SC (44.87% a.i.) 21-day vegetative vigor study	Buckwheat (survival) EC_{25} = 0.011 a.i./acre EC_{05}/IC_{05}: 0.0234 lbs a.i./acre NOAEC = 0.005847 lbs a.i./acre Cucumber (dry weight) EC_{25} = 0.024 a.i./acre	MRID 47443249 Supplemental Page 190 (U.S. EPA/OPP 2010a)

Species	Exposure	Response	Reference
(*Brassica napus*) Soybean (*Glycine max*) Sugarbeet (*Beta vulgaris*) Sunflower (*Helianthus annuus*) Tomato (*Lycopersicon esculentum*)		EC_{05}/IC_{05}: >0.0913 lbs a.i./acre NOAEC = 0.002338 lbs a.i./acre <u>Oilseed rape (survival)</u> EC_{25} = 0.016 a.i./acre EC_{05}/IC_{05}: 0.027 lbs a.i./acre NOAEC = 0.005847 lbs a.i./acre <u>Soybean (shoot length)</u> EC_{25} = 0.0043 a.i./acre EC_{05}/IC_{05}: 0.061 lbs a.i./acre NOAEC = <0.000374 lbs a.i./acre Most sensitive dicot <u>Sugarbeet (survival)</u> EC_{25} = 0.012 a.i./acre EC_{05}/IC_{05}: 0.022 lbs a.i./acre NOAEC = 0.002338 lbs a.i./acre <u>Sunflower (shoot length)</u> EC_{25} = 0.01 a.i./acre EC_{05}/IC_{05}: 0.063 lbs a.i./acre NOAEC = 0.002338 lbs a.i./acre <u>Tomato (dry weight)</u> EC_{25} = 0.02 a.i./acre EC_{05}/IC_{05}: >0.0366 lbs a.i./acre NOAEC = 0.005847 lbs a.i./acre	

Appendix 6: Toxicity to Fish

Unless otherwise indicated, the study summaries and MRID numbers are taken from U.S. EPA/OPP (2010a, 2010c) and supplemented with information from DERs submitted by the registrant. These are the subset of studies that U.S. EPA/OPP selected for use in their risk assessment.

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Table A6-2: Chronic Toxicity to Fish.....191

Table A6-1: Acute Toxicity to Fish

Species	Fish Type	Exposure	Response	Reference
Bluegill sunfish (*Lepomis macrochirus*) 10 fish/group	Freshwater	Indaziflam (94.5% a.i.) AE 1170437 Technical (AI: BCS-AA10717) Nominal concentrations of 0 (negative and solvent control), 0.09, 0.19, 0.38, 0.75, and 1.50 mg a.i./L. Mean measured concentrations: 0.10, 0.21, 0.39, 0.75 and 1.54 mg a.i./L Static conditions 96-hour acute study	Mortality LC_{50} = 0.32 mg total a.i./L NOAEC = 0.21 mg total a.i./L Sublethal effect NOAEC = 0.21 mg a.i./L LOAEC = 0.39 mg a.i./L Cumulative mortality after 96 hours was 0% in the negative and solvent control, as well as in the 0.10 and 0.21 mg a.i./L treatment groups. Mortality was 80%, 100% and 100% in the 0.39, 0.75, and 1.54 mg a.i./L treatment groups, respectively. There were no sublethal effects observed in the negative and solvent controls or the 0.10 and 0.21 mg a.i./L treatment groups. Toxicological symptoms, including loss of equilibrium, vertical orientation, labored respiration, and lying on the bottom were observed in 90% of fish from the 1.54 mg a.i./L treatment group after 4 hours; by 24 hours, all fish at this level and the one below it (0.75 mg a.i./L) had died. In the 0.39	MRID 47443233 Supplemental Pp. 128-129 (U.S. EPA/OPP 2010a)

Species	Fish Type	Exposure	Response	Reference
			mg a.i./L treatment level, the same suite of toxicological symptoms was apparent in 29% of surviving fish by 24 hours and in 25% of surviving fish by 48 hours; however, these effects subsided by 72 hours. All surviving fish in this group appeared normal at the 72 and 96-hour observation period. This study is scientifically sound; however, this study does not meet OPPTS 850.1075 guideline standards for a freshwater fish acute toxicity test because centrifugation was not conducted as part of the analysis for dissolved test substance. U.S. EPA classifies as "highly toxic"	
Rainbow trout (*Oncohynchus mykiss*) 10 fish/group	Freshwater	Indaziflam AE 1170437 Technical (AI: BCS-AA10717) (94.5% a.i.) Nominal concentrations of 0 (negative and solvent control), 0.09, 0.19, 0.38, 0.75, and 1.50 mg a.i./L. Mean measured concentrations: 0.10, 0.19, 0.42, 0.78, and 1.46 mg total a.i./L static conditions 96-hour acute study.	LC_{50}: 0.57 mg total a.i./L (95% C.I.:0.420-0.780 mg a.i./L) NOAEC: 0.42 mg a.i./L LOAEC: 0.78 mg a.i./L Based on mortality and sublethal effects. Cumulative mortality after 96 hours was 0% in the negative and solvent control, as well as in the 0.10-0.42 mg total a.i./L treatment groups. Mortality was 100% in the 0.78 and 1.46 mg total a.i./L treatment groups. There were no sublethal effects observed in the negative and solvent controls or the 0.10-0.78 mg total a.i./L treatment	MRID 47443234 Supplemental Pp. 129-130 (U.S. EPA/OPP 2010a)

Species	Fish Type	Exposure	Response	Reference
			groups. Loss of equilibrium was observed in the 1.46 mg total a.i./L treatment group at 4 hours in six fish. Complete mortality at 24 hours precluded the ability to observe sublethal effects thereafter. Centrifugation was not conducted to determine the dissolved test substance concentration in the test media. Uncertainty exists regarding the exposure of test substance to the test organism. U.S. EPA classifies as "highly toxic"	
Fathead Minnow *(Pimephales promelas)* 10 fish/group 3 replicates	Freshwater	AE 1170437 (metabolite of a.i.: BCS-AA10717) Diaminotriazine (99.3% a.i.) Common name: Fluoroethyldiaminotriazine (FDAT) Nominal concentrations of 0 (negative control) and 100 mg a.i./L. Mean measured concentration: < 1.01 and 101 mg a.i./L Static conditions 96-hour acute study.	LC_{50}: > 101 mg a.i./L EC_{50}: > 101 mg a.i./L NOAEC: 101 mg a.i./L LOAEC: > 101 mg a.i./L Based on mortality and sublethal effects. There were no effects on mortality or sublethal effects observed in the control or treatment level. The 96-h LC50 was > 101 mg a.i/L. There were no sublethal effects observed in the negative control or 101 mg a.i./L treatment group. U.S. EPA classifies as "practically non-toxic"	MRID 47443230 Acceptable Pp. 130-131 (U.S. EPA/OPP 2010a)
Fathead Minnow (*Pimephales promelas*) 10 fish/group	Freshwater	AE 1170437 Carboxylic Acid (96.6% a.i.) (metabolite of AI: BCS-AA10717) Nominal concentrations of 0 (negative control)	LC_{50}: > 103 mg a.i./L EC_{50}: > 103 mg a.i./L NOAEC: 103 mg a.i./L LOAEC: > 103 mg a.i./L Based on mortality and sublethal effects. There were no effects on	MRID 47443231 Acceptable Page 131 (U.S. EPA/OPP 2010a)

Species	Fish Type	Exposure	Response	Reference
3 replicates		and 100 mg a.i./L. Mean measured concentrations: 1.0 and 103 mg a.i./L Static conditions 96-hour acute study.	mortality, and no sublethal effects were observed in the control or treatment level. Cumulative mortality after 96 hours was 0% in the negative control and the 103 mg a.i./L treatment group. There were no sublethal effects observed in the negative control or 103 mg a.i./L treatment group U.S. EPA classifies as "practically non-toxic"	
Bluegill sunfish (*Lepomis macrochirus*) 10 fish/replicate 1 replicate/level	Freshwater	Indaziflam SC 500 (AE 1170437 SC 500 g/L (AI: BCS-AA10717) 45.08% a.i. two active isomers) Nominal concentrations of 0 (negative control), 0.250, 0.500, 1.00, 2.00, and 4.00 mg formulation/L equivalent to 0 (negative control), 0.113, 0.225, 0.451, 0.902, and 1.80 mg a.i./L. Mean measured a.i. (reviewer calculated): <0.000530 (<LOQ, control), 0.133, 0.251, 0.446, 0.913, and 1.77 mg a.i./L, respectively Static conditions 96-hour acute study.	LC_{50}: 0.372 mg total a.i./L (95% C.I.: 0.251 to 0.913 mg total a.i./L) NOAEC: 0.251 mg total ai/L Based on mortality and sublethal effects. After 24 hours, cumulative mortality was 0, 0, 0, 40, 100, and 100% for the control, 0.133, 0.251, 0.446, 0.913, and 1.77 mg total a.i./L levels, respectively (mean-measured concentrations); after 48, 72, and 96 hours, cumulative mortality was 0, 0, 0, 80, 100, and 100%, respectively. The 96-hour LC_{50} was 0.372 mg total a.i./L, which is equivalent to 0.825 mg total form/L. Clinical signs of toxicity were observed at the mean-measured 0.446 mg total a.i./L treatment levels, and included fish on the bottom of the aquarium, dark coloration, hyperactivity, inactivity, labored respiration, loss of equilibrium with lateral	MRID 47743305 Supplemental Page 132 (U.S. EPA/OPP 2010a)

Species	Fish Type	Exposure	Response	Reference
			deviation, and/or laying on their sides or backs. The NOAEC for mortality and clinical signs of toxicity was 0.251 mg total a.i./L, which is equivalent to 0.557 mg total form/L. The study was conducted up to the limit of solubility (1.80 mg a.i/L, nominal) of BCS-AA10717 and centrifugation was not conducted to determine the dissolved test substance concentrations in the test media. Uncertainty exists regarding the exposure of test substance to the test organism. Based on the results of this study, AE 1170437 SC 500 g/L (AI: BCS-AA10717) is highly toxic to bluegill sunfish.	
Sheepshead minnow (*Cyprinodon variegates*) juveniles 10 fish/group	Estuarine/ Marine	Indaziflam AE 1170437 Technical (AI: BCS-AA10717) (94.5%) Nominal concentrations of 0 (negative and solvent control), 0.09, 0.19, 0.38, 0.75, and 1.50 mg a.i./L. Mean-measured concentrations were <0.006 (<LOQ, negative and solvent control), 0.10, 0.21, 0.43, 0.77, and 1.56 mg total a.i./L static conditions 96-hour acute study.	LC_{50}: 0.96 mg a.i./L (95% C.I.: 0.43-1.56 mg total a.i./L) EC_{50}: 1.56 mg a.i./L NOAEC: 0.43 mg a.i./L LOAEC: 0.77 mg a.i./L Based on sub-lethal effects and mortality. Cumulative mortality after 96 hours was 0% in the negative and solvent control, as well as the 0.10, 0.21, and 0.43 mg a.i./L treatment groups. Mortality was 20% and 100% in the 0.77 and 1.56 mg a.i./L treatment groups, respectively. There were no sublethal effects observed in the negative and solvent	MRID 47443232 Supplemental Page 139 (U.S. EPA/OPP 2010a)

Species	Fish Type	Exposure	Response	Reference
			controls or the 0.10-0.43 mg a.i./L treatment groups. Toxicological symptoms such as loss of equilibrium, vertical orientation, and lying on the bottom were observed in the 0.77 mg a.i./L treatment group at 96 hours in one fish. At 4 hours, 3 fish in the 1.56 mg a.i./L treatment level had vertical orientation and showed loss of equilibrium, and by 24 hours, there was 100% mortality. This study is scientifically sound; however, this study does not meet OPPTS 850.1075 guideline standards for a freshwater fish acute toxicity test because centrifugation was not conducted as part of the analysis for dissolved test substance. U.S. EPA classifies as "highly toxic".	

[1] Total dissolved and undissolved

Table A6-2: Chronic Toxicity to Fish

Species	Exposure	Response	Reference
Freshwater Fish: Fathead Minnow (*Pimephales promelas*) 140 embryos/treatment level, divided into 35 embryos/cup, 1 cup/aquarium, and 4 replicate aquaria/treatment	Indaziflam BCS-AA10717 (94.5% eight total isomers) 90.3% AE 1170437 (principle a.i.) 2.82% AE 1170438 (active isomer of a.i.) Nominal concentrations of 0 (negative and solvent controls), 63, 125, 250, 500, and 1000 µg a.i./L (adjusted for purity). Mean measured concentrations: <5.95 (<LOQ, controls), 59.11, 142.1, 286.0, 465.3, and 1013 µg a.i./L Time-weighted average (TWA) concentrations (reviewer calculated) were <5.95 (<LOQ, controls), 58.21, 142.6, 286.6, 464.4, and 1020 µg total a.i./L. Flow-through test conditions 35-day chronic toxicity study.	NOAEC: 464.4 µg a.i./L LOAEC: 1020 µg total ai/L Based on fry survival, total length, and total weight. Fertilized eggs/embryos (140/level, <24 hours old) of fathead minnow were exposed to nominal concentrations of 0 (negative and solvent controls), 63, 125, 250, 500, and 1000 µg a.i./L (adjusted for purity). The 35-day LC/EC_{50} was values could not be determined due to a lack of an adequate dose-response relationship for any endpoint analyzed. However, based on fry survival, the LC_{50} value is likely to be between 464.4 and 1020 µg total a.i./L. Hatching occurred at all levels on Days 4 and 5, and hatching success averaged 92.1 to 98.6% for all levels, with no statistically significant differences observed. Similarly, survival of hatched alevins assessed on Day 5 ranged from 90.0 to 95.7%, with no treatment-related effects indicated. Post-hatch survival of fry, however, was adversely affected at the highest treatment level. Post-hatch survival (Day 35) ranged from 92.5 to 98.8% for the control through 465.3 µg total a.i./L levels, but was only 2.5% at the 1013 µg total a.i./L level ($p<0.05$). Death was generally preceded by loss of equilibrium, lying on the bottom, and/or labored respiration.	MRID 47443236 Supplemental Page 134 (U.S. EPA/OPP 2010a)

		Standard lengths ranged from 21.6 to 23.5 mm and dry weight ranged from 46.2 to 66.2 mg for all levels. A significant difference in mean dry weight was detected between the negative and solvent controls, with significantly lighter fish (13%) in the solvent control group. With the exception of the highest treatment, where growth was promoted 25% relative to the negative control (although mortality occurred in 3 out of the 4 replicates for this concentration), fish weights were significantly reduced relative to the negative control at all treated levels. The reviewer determined that the significant difference between the solvent and negative control casts sufficient uncertainty unto the data as to affect its acceptability. However, since no effects were detected relative to the solvent control at all treatment levels in which no mortality occurred, and effects to length showed similar results, there is confidence in determining a LOAEC and NOAEC regardless of whether the solvent control did indeed have a slight effect. This study is scientifically sound but does not fully meet OPPTS 850.1400 guideline standards for an early life stage toxicity study with freshwater fish. A significant statistical difference (13%, $p < 0.01$) was found between negative and solvent controls for mean dry weight of fish. Furthermore, centrifugation was not conducted as part of the	

		analysis for dissolved test substance.	
Estuarine/Marine Fish	No studies available		

Appendix 7: Toxicity to Aquatic Invertebrates

Unless otherwise indicated, the study summaries and MRID numbers are taken from U.S. EPA/OPP (2010a, 2010c) and supplemented with information from DERs submitted by the registrant. These are the subset of studies that U.S. EPA/OPP selected for use in their risk assessment.

Table A7-1: Acute Toxicity to Aquatic Invertebrates 194
Table A7-2: Chronic Toxicity to Aquatic Invertebrates 201

Table A7-1: Acute Toxicity to Aquatic Invertebrates

Species	Invertebrate	Exposure	Response	Reference
Water flea **(*Daphnia magna*)**	Freshwater	Indaziflam AE 1170437 (94.5%) Nominal concentrations of 0 (negative and solvent control), 0.63, 1.25, 2.5, 5.0, and 10 mg a.i./L. Mean-measured concentrations were <0.06 mg a.i./L (<LOQ, controls), 0.62, 1.23, 2.54, 4.86, and 9.88 mg a.i./L Static conditions 48-hour acute toxicity study.	EC_{50}: >9.88 mg a.i./L based on immobile daphnia NOAEC: 4.86 mg a.i./L based on sublethal behavioral effects (quiescence) Immobility and sublethal effects were observed at 24 and 48 hours. The 48-hour EC_{50} (based on immobile daphnia) was >9.88 mg a.i./L. The 48-hr NOAEC, based on sublethal behavioral effects, was 4.86 mg a.i./L. The observed sublethal effects included quiescence EPA classifies as "moderately to slightly toxic"	MRID 47443226 Supplemental Page 134 (U.S. EPA/OPP 2010a)
Water flea **(*Daphnia magna*)**	Freshwater	Indaziflam SC 500 (45.08%) Nominal concentrations of 0 (negative control), 5.7, 11, 23, 45, and 91 mg formulation/L, equivalent to 0 (control), 2.6, 5.1, 10, 21, and 41 mg ai/L, respectively.	EC_{50}: >38 mg total ai/L NOAEC: <2.3 mg total a.i./L based on sublethal effects Following 48 hours of exposure, immobility was 0% at the control through mean-measured 8.4 mg a.i./L levels, 10% at the 18 mg a.i./L level,	MRID 47743303 Supplemental Page 134 (U.S. EPA/OPP 2010a)

Species	Invertebrate	Exposure	Response	Reference
		Mean-measured concentrations were <0.26 (<LOQ, control), 2.3, 4.3, 8.4, 18, and 38 mg total a.i./L, respectively. Static conditions 48-hour acute toxicity study.	and 5% at the 38 mg a.i./L level. Sub-lethal signs of toxicity were observed at the 8.4, 18, and 38 mg a.i./L levels after 24 hours, and at all treatment levels by 48 hours. Effects included lying on the bottom, quiescence, and paleness. The 48-hour NOAEC (based on sublethal effects) and EC_{50} values were <2.3 and >38 mg ai/L, respectively, which are equivalent to <5.1 and >84 mg form/L, respectively. U.S. EPA classifies as "slightly toxic, at most".	
Water flea **(*Daphnia magna*)**	Freshwater	Indaziflam SC 200 (19.2%) Nominal concentrations of 0 (negative control), 20, 40, 80, 160, and 320 mg formulation/L, equivalent to 0 (control), 3.8, 7.7, 15, 31, and 61 mg a.i./L, respectively. Mean-measured concentrations were <0.00384 (<LOQ, control), 4.43, 8.26, 20.3, 32.2, and 87.4 mg total a.i./L, respectively. Static conditions 48-hour acute toxicity	EC_{50}: 37.5 mg total a.i./L NOAEC (mean-measured): 8.26 mg total a.i./L Cumulative immobility after 24 hours was 0, 0, 3, 3, 0, and 57% at the control, 4.43, 8.26, 20.3, 32.2, and 87.4 mg total a.i./L levels, respectively; cumulative immobility after 48 hours was 0, 0, 10, 23, 30, and 90% at the control, 4.43, 8.26, 20.3, 32.2, and 87.4 mg total a.i./L levels, respectively. Besides treatment-related immobility, no	MRID 47743304 Supplemental Page 135 (U.S. EPA/OPP 2010a)

<table>
<tr><th>Species</th><th>Invertebrate</th><th>Exposure</th><th>Response</th><th>Reference</th></tr>
<tr><td></td><td></td><td>study.</td><td>further effects on behavior were observed at any level. U.S. EPA classifies as “practically non-toxic” for formulated product</td><td></td></tr>
<tr><td>Midge (Chironomus tetans)

3rd instar, 10 to 11 days old

80 larvae per level, with 10 larvae per replicate vessel and 8 biological replicates per level</td><td>Freshwater</td><td>Indaziflam

BCS-AA10717 (94.5%)

AE 1170437 (90.3% principle a.i.)

Nominal concentrations of 0 (negative and solvent controls), 6.6, 14, 26, 52, and 100 mg a.i./kg sediment

<table>
<tr><th colspan="3">Mean Measured[a]</th></tr>
<tr><th>Sediment (mg TRR/kg)</th><th>Pore Water (mg TRR/L)</th><th>Overlying Water (mg TRR/L)</th></tr>
<tr><td><LOQ</td><td><LOQ</td><td><LOQ</td></tr>
<tr><td><LOQ</td><td><LOQ</td><td><LOQ</td></tr>
<tr><td>6.9</td><td>0.042</td><td>0.0070</td></tr>
<tr><td>15</td><td>0.10</td><td>0.015</td></tr>
<tr><td>27</td><td>0.38</td><td>0.030</td></tr>
<tr><td>50</td><td>0.72</td><td>0.070</td></tr>
<tr><td>100</td><td>2.2</td><td>0.18</td></tr>
</table>

[a] Results represent total radioactive residues (TRR) of BCS-AA10717, and were reviewer-calculated for pore and overlying water (individual results provided below). The LOQ was 0.053 to 0.075 mg/kg for sediment samples, 0.0090 and 0.0091 mg/L for pore water samples, and 0.0036 to 0.0039 mg/L for overlying water samples.

10-day test duration</td><td>Pore Water Concentrations:
LC_{50} mortality: >2.2 mg a.i./L
EC_{50} ash-free dry weights: >2.2 mg a.i./L
NOAEC (mortality): 2.2 mg a.i./L
NOAEC (dry weights): 2.2 mg a.i./L
Sediment Concentrations:
LC_{50} mortality: >100 mg a.i./kg dw
EC_{50} ash-free dry weights: >100 mg a.i./kg dw
NOAEC (mortality): 100 mg a.i./kg dw
NOAEC (dry weights): 100 mg a.i./kg dw
Overlying Water Concentrations:
LC_{50} mortality: >0.18 mg a.i./L
EC_{50} ash-free dry weights: >0.18 mg a.i./L
NOAEC (mortality): 0.18 mg a.i./L
NOAEC (dry weights): 0.18 mg a.i./L</td><td>MRID 47443238 Supplemental

Page 136 (U.S. EPA/OPP 2010a)</td></tr>
</table>

Species	Invertebrate	Exposure	Response	Reference
		intermittent flow-through system		
Eastern Oyster **(*Crassotrea virginica*)** **20 oysters per control and treatment level**	Estuarine/ Marine	Indaziflam BCS-AA10717 (94.5%) AE 1170437 (90.32 %) Nominal concentrations: 0 (negative and solvent control), 0.063, 0.13, 0.25, 1.0, and 2.0 mg a.i./L. time weighted average (TWA) concentrations: < 0.04 (control and solvent control), 0.061, 0.122, 0.24, 0.47, 0.89, 1.80 mg a.i./L. 96-h acute toxicity test.	EC_{50}: 0.92 mg total a.i./L (95% C.I.: 0.75-1.1 mg total a.i./L) NOAEC: 0.47 mg total a.i./L Endpoint is shell growth An initial shell deposition test was performed at 0.14, 0.27, 0.51, 1.1, 1.9, and 3.9 mg a.i./L (mean measured concentrations) in addition to a control and solvent control. There was 5% mortality noted at levels 1.1 and 3.9 mg a.i./L. The inhibition of shell growth as compared to the pooled control was significantly inhibited at test concentrations of 1.1 mg a.i./L and above. Shell growth was increased as compared to pooled controls at 0.14 and 0.51 mg a.i./L. Therefore, the test was repeated with the nominal concentrations reported in this DER. Centrifugation was not conducted to determine the dissolved test substance concentration in the	MRID 47443228 Supplemental Page 140 (U.S. EPA/OPP 2010a)

Species	Invertebrate	Exposure	Response	Reference
			test media; thus, there is uncertainty regarding the quantity of test substance dissolved in the test media and all reported measured concentration values are total concentrations of test substance in the test media. U.S. EPA classifies as "highly toxic**".**	
Saltwater mysid **(*Americamysis bahia*)** **Juveniles (<24 Hours)** **20 per treatment level and control, equally divided among two replicates**	Estuarine/ Marine	Indaziflam AE 1170437 (94.5%) Nominal concentrations: 0 (negative and solvent control), 0.31, 0.63, 1.3, 2.5, and 5.0 mg a.i./L; time-weighted average (TWA) concentrations were <0.100 (<LOQ; controls), 0.261, 0.521, 1.06, 1.88, and 4.00 mg a.i./L, respectively. 96-h acute toxicity test.	LC_{50}: 1.5 mg a.i./L (95% C.I.: 1.06-1.88 mg a.i./L) NOAEC: 1.06 mg a.i./L Based on mortality and sublethal effects No mortalities were observed in the controls or in the TWA 0.521 and 1.06 mg a.i./L treatment groups. Mortality was first noted in the 1.88 mg a.i./L treatment group after 24 hours of exposure, while mortality in the 4.0 mg a.i./L treatment group was first noted after only 4 hours of exposure. Complete mortality was observed at the highest treatment level after 24 hours. A single mortality was observed in the 0.261 mg a.i./L treatment group. No sub-lethal effects were observed in the	MRID 47443227 Acceptable Page 140 (U.S. EPA/OPP 2010a)

Species	Invertebrate	Exposure	Response	Reference
			controls or mean-measured 0.261-1.06 mg a.i./L treatment groups throughout the test, with all surviving mysids appearing normal and healthy. After 4 hours of exposure, surfacing was observed in the 1.88 mg a.i./L treatment group and lethargy and erratic swimming was observed in the 4.00 mg a.i./L treatment group. After 24 hours, effects in the 1.88 mg a.i./L treatment group included surfacing, lethargy and erratic swimming; from 48 hours until test termination, all surviving mysids at this level were swimming erratically. U.S. EPA classifies as "moderately toxic".	

<table>
<tr><th>Species</th><th>Invertebrate</th><th>Exposure</th><th>Response</th><th>Reference</th></tr>
<tr>
<td>Marine Amphipod

(Leptocheirus plumulosus)

Juvenile, 0.71 to 1.0 mm

100 amphipods per level, with 20 amphipods per replicate vessel and five biological replicates per level</td>
<td>Estuarine/ Marine</td>
<td>Indaziflam

BCS-AA10717 (94.5%)

AE 1170437 90.3% (principle a.i.)

Nominal concentrations of 0 (negative and solvent controls), 5.3, 11, 21, 42, and 170 mg a.i./kg dw sediment in a static system.

<table>
<tr><th colspan="3">Mean-Measured[a]</th></tr>
<tr><th>Sediment (mg TRR/kg)[b]</th><th>Pore Water (mg TRR/L)</th><th>Overlying Water (mg TRR/L)</th></tr>
<tr><td><LOQ</td><td><LOQ</td><td><LOQ</td></tr>
<tr><td><LOQ</td><td><LOQ</td><td><LOQ</td></tr>
<tr><td>5.7</td><td>0.10</td><td>0.039</td></tr>
<tr><td>12</td><td>0.24</td><td>0.082</td></tr>
<tr><td>26</td><td>0.46</td><td>0.17</td></tr>
<tr><td>40</td><td>1.0</td><td>0.36</td></tr>
<tr><td>110</td><td>2.0</td><td>0.68</td></tr>
<tr><td>180</td><td>3.8</td><td>1.4</td></tr>
</table>

[a] Results represent total radioactive residues (TRR) of BCS-AA10717, and were reviewer-calculated for pore and overlying water (individual results provided below). The LOQ was -0.026 to 0.028 mg/kg for sediment samples, 0.0040 and 0.0044 mg/L for pore water samples, and 0.0016 mg/L for overlying water samples.

10-day sediment exposure</td>
<td>Pore Water
LC_{50} mortality: >3.8 mg a.i./L
NOAEC (mortality): 3.8 mg a.i./L

Bulk Sediment
LC_{50} mortality: >180 mg a.i./kg dw
NOAEC (mortality): 180 mg a.i./kg dw

Overlying Water
LC_{50} mortality: >1.4 mg a.i./L
NOAEC (mortality): 1.4 mg a.i./L

This study is scientifically sound; however, the overlying water was not centrifuged to determine measured concentrations of the dissolved test substance in the test media.
classified as practically non-toxic.</td>
<td>MRID 47443239 Supplemental</td>
</tr>
</table>

Table A7-2: Chronic Toxicity to Aquatic Invertebrates

Species	Exposure	Response	Reference
Freshwater Invertebrate: Water flea **(*Daphnia magna*)**	Indaziflam BCS-AA10717 (94.5%) AE 1170437 90.3% (principle a.i.) Nominal concentrations of 0 (negative and solvent controls), 0.05, 0.13, 0.32, 0.80, and 2.0 mg a.i./L. Mean-measured concentrations were <0.003 (<LOQ, controls), 0.06, 0.14, 0.34, 0.80 and 2.0 mg total a.i./L, respectively. Static renewal conditions 21-day-chronic toxicity study.	LOAEC: 0.80 mg total a.i./L NOAEC: 0.34 mg total a.i./L Based upon treatment-related effects on growth (body length and dry weight) and neonates per reproductive day at the 0.80 and 2.0 mg total a.i./L levels at study termination. The 21-day EC_{50} for adult immobility was >2.0 mg total a.i./L, the highest concentration tested. The 21-day NOAEC was 0.34 mg total a.i./L, based upon treatment-related effects on growth (body length and dry weight) and neonates per reproductive day at the 0.80 and 2.0 mg total a.i./L levels at study termination; the EC_{50} values for neonates per reproductive day and dry weight were 1.6 and 1.7 mg total a.i./L, respectively. Centrifugation was not conducted to determine the dissolved test substance concentration in the test media; thus, all reported measured concentration values are total concentrations of test substance in the test media.	MRID 47443235 Supplemental Page 134 (U.S. EPA/OPP 2010a)
Estuarine/Marine Invertebrates	No studies available		

Appendix 8: Toxicity to Aquatic Plants

Unless otherwise indicated, the study summaries and MRID numbers are taken from U.S. EPA/OPP (2010a, 2010c) and supplemented with information from DERs submitted by the registrant. These are the subset of studies that U.S. EPA/OPP selected for use in their risk assessment.

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Table A8-2: Aquatic Vascular Plants Toxicity Studies Using Duckweed 206

Table A8-1: Algae Toxicity Studies

Species	Exposure	Response	Reference
Freshwater green algae (*Pseudokircheriella subcapitata*)	Indaziflam (94.5%) Nominal concentrations of 0 (negative and solvent controls), 25, 50, 100, 200, and 400 µg a.i./L under static conditions. 96-hour toxicity study.	96-hour EC_{50} = 74 µg a.i./L (Biomass) NOAEC = 24.2 µg a.i./L Most sensitive endpoint was biomass. 72-hour EC_{50}: 64 µg a.i./ L (cell density)	MRID 47443261 Acceptable Page 142 (U.S. EPA/OPP 2010a)
Freshwater green algae (*Pseudokircheriella subcapitata*)	Fluoroethyldiaminotriazine (99.3%) Nominal concentrations of 0 (negative control), 6.25, 12.5, 25, 50, and 100 mg a.i./L under static conditions. 72-hour toxicity study.	72-hour EC_{50} =11 mg a.i./L (Cell Density) NOAEC = < 5.37 mg a.i./L Most sensitive endpoint was cell density.	MRID 47443262 Supplemental Page 145 (U.S. EPA/OPP 2010a)
Freshwater green algae (*Pseudokircheriella subcapitata*)	Indaziflam – carboxylic acid (96.5%) Nominal concentrations of 0 (negative control), 0.63, 1.25, 2.5, 5.0, and 10 mg a.i./L under static conditions. Mean-measured concentrations were < 0.05 (<LOQ, control), 0.57, 1.15, 2.3, 4.6, and 9.4 mg a.i./L. 72-hour toxicity study.	72-hour **Cell density** EC_{50} = > 9.4 mg a.i./L NOAEC = 4.6 mg a.i./L **Biomass** EC_{50} = > 9.4 mg a.i./L NOAEC = 4.6 mg a.i./L The most sensitive endpoint could not be determined, as the EC_{50} values of the endpoints tested were greater than the highest test concentration.	MRID 47443263 Supplemental Page 146 (U.S. EPA/OPP 2010a)

Species	Exposure	Response	Reference
Freshwater green algae (*Pseudokircheriella subcapitata*)	Indaziflam – hydroxyethyl (96.5%) Nominal concentrations of 0 (negative control), 0.31, 0.63, 1.25, 2.5, and 5.0 mg a.i./L under static conditions. Mean-measured concentrations were < 0.03 (<LOQ, control), 0.33, 0.69, 1.38, 2.7, and 5.6 mg a.i./L. 72-hour toxicity study.	72-hour EC_{50} = 0.55 mg a.i./L (Cell Density) NOAEC: 0.33 mg a.i./L Most sensitive endpoint was cell density.	MRID: 47443264 Supplemental Page 147 (U.S. EPA/OPP 2010a)
Freshwater green algae (*Pseudokircheriella subcapitata*)	Indaziflam – olefin (96.0%) Nominal concentrations of 0 (negative control), 0.89, 2.86, 9.16, 29.3, 93.8, and 300 µg a.i./L under static conditions. Mean-measured concentrations were <0.10 (<LOQ, control), 1.01, 3.19, 10.2, 32.6, 103, and 336 µg a.i./L. 72-hour toxicity study.	72-hour EC_{50} = 54 µg a.i./L (Biomass) NOAEC: 10.2 µg a.i./L Most sensitive endpoint was biomass.	MRID 47443265 Supplemental Page 147 (U.S. EPA/OPP 2010a)
Freshwater green algae (*Pseudokircheriella subcapitata*)	Indaziflam – technical (95.7%) Nominal concentrations of 0 (negative and solvent control), 25, 50, 100, 200, and 400 µg a.i./L under static conditions. Mean-measured concentrations were < 2.5 (<LOQ, controls), 18, 38, 77, 151, and 222 µg a.i./L. 96-hour toxicity study.	96-hour EC_{50} = 77 µg a.i./L (Biomass) NOAEC = 38 µg a.i./L Most sensitive endpoint was biomass.	MRID 47743309 Acceptable Page 148 (U.S. EPA/OPP 2010a)
Freshwater green algae (*Pseudokircheriella*	Indaziflam 500 SC (45.08%) Nominal concentrations	72-hour EC_{50} = 51 µg a.i./L (Cell Density) NOAEC: < 34 µg a.i./L	MRID 47743310 Supplemental

Species	Exposure	Response	Reference
subcapitata)	of 0 (negative and solvent control), 26, 51, 103, 205, and 410 µg a.i./L under static conditions. Mean-measured concentrations were < 2.50 (<LOQ, controls), 34, 66, 132, 271, and 543 µg a.i./L. 72-hour toxicity study.	Most sensitive endpoint was cell density.	Page 149 (U.S. EPA/OPP 2010a)
Freshwater green algae (*Pseudokircheriella subcapitata*)	Indaziflam – 200 SC (19.2%) Nominal concentrations of the active ingredient component were 0 (negative control), 5.49, 17.6, 56.3, 180, and 576 µg a.i./L. Mean-measured concentrations were < 0.5365 (<LSC, negative control), 5.9, 16.8, 51.0, 162, and 520 µg a.i./L. 72-hour toxicity study.	72-hour EC_{50} = 53 µg a.i./L (cell density) NOAEC: 16.8 µg a.i./L More sensitive endpoint was cell density.	MRID 47743311 Supplemental Page 150 (U.S. EPA/OPP 2010a)
Freshwater Diatom (*Navicula pelliculosa)*	Indaziflam (94.5%) Nominal concentrations of 0 (negative control and solvent control), 2.0, 6.3, 20, 63, 200, 630, and 2,000 µg a.i./L under static conditions. 96-hour toxicity study.	96-hour EC_{50} = 87 µg total a.i./L (Biomass) NOAEC = 17.7 µg total a.i./L Most sensitive endpoint was biomass.	MRID 47443266 Supplemental Page 142 (U.S. EPA/OPP 2010a)
Marine Diatom (*Skeletonemia costatum*)	Indaziflam (94.5%) Nominal concentrations of 0 (negative and solvent control), 2.0, 5.1, 13, 32, 80, and 200 µg a.i./L under static conditions. 96-hour toxicity study.	96-hour EC_{50} = 27 µg a.i./L (Biomass) NOAEC = 5.1 µg a.i./L Most sensitive endpoint was biomass.	MRID 47443267 Acceptable Page 143 (U.S. EPA/OPP 2010a)
Freshwater Cyanobacteria (*Anabaena flos-*	Indaziflam (94.5%) Nominal concentrations	96-hour	MRID 47443268 Supplemental Page 144 (U.S.

Species	Exposure	Response	Reference
aquae)	of 0 (negative and solvent control), 13, 40, 127, 400, 1,270, and 4,000 µg a.i./L under static conditions. 96-hour toxicity study.	EC_{50} = 750 µg total a.i./L (Cell density) NOAEC = 115 µg total a.i./L Most sensitive endpoint was cell density.	EPA/OPP 2010a)

Table A8-2: Aquatic Vascular Plants Toxicity Studies Using Duckweed

Species	Exposure	Response	Reference
Freshwater Duckweed (*Lemna gibba*)	Indaziflam (94.5%) Nominal concentrations of 0 (negative and solvent controls), 3.92, 7.85, 15.7, 31.4, 62.8, and 126 ng a.i./L under static conditions. Mean-measured concentrations for the control, 31.4, 62.8, and 126 ng a.i/L test levels were <10.39, 30.9, 59.9, and 112 ng ai/L. 7-day toxicity study.	7-day EC_{50} =67 ng a.i./L (Frond area) NOAEC = 31.4 ng a.i./L Most sensitive endpoint was frond area.	MRID 47443250 Acceptable Page 152 (U.S. EPA/OPP 2010a)
Freshwater Duckweed (*Lemna gibba*)	Triazineindanone (96.1%) Nominal concentrations of 0 (negative and solvent controls) 6.25, 12.5, 25, 50, and 100 µg/L under static conditions. Mean-measured concentrations were <0.4716 (<lowest standard analyzed, controls), 6.09, 12.0, 22.5, 45.25, and 114.5 µg/L. 7-day toxicity study.	7-day EC_{50} = 12 µg/L (frond area) NOAEC: 6.09 µg/L Most sensitive endpoint was frond area.	MRID 47443251 Acceptable Page 153 (U.S. EPA/OPP 2010a)
Freshwater Duckweed (*Lemna gibba*)	Fluoroethyldiam Inotriazine (99.3%) Nominal concentrations of 0 (negative and solvent controls), 9.54, 30.5, 97.7, 313, and 1,000 µg/L under static conditions. Mean-measured concentrations were <1.026 (<lowest standard analyzed, controls), 11.1, 35.15, 110.5, 354.5, and	7-day **Frond number** EC_{50} =12 µg/L NOAEC = 6.09 µg/L **Frond area** EC_{50}: 12 µg/L NOAEC = 6.09 µg **Frond area based on growth rate** EC_{50}: 16 µg/L NOAEC = 6.09 µg/L	MRID 47443252 Supplemental Page 154 (U.S. EPA/OPP 2010a)

Species	Exposure	Response	Reference
	1,111 µg/L. 7-day toxicity study.	Most sensitive endpoint could not be determined.	
Freshwater Duckweed (*Lemna gibba*)	Indaziflam – carboxylic Acid (96.5%) Nominal concentrations of 0 (negative control), 1.00, 3.20, 10.0, 32.0, and 100 mg/L under static conditions. Mean-measured concentrations were <0.0037 (<lowest standard analyzed, control), 1.13, 3.67, 11.1, 35.8, and 113 mg/L. 7-day toxicity study.	7-day EC_{50} = 4.0 mg/L (Frond number) NOAEC = 1.13 mg/L Most sensitive endpoint was frond number.	MRID 47443253 Acceptable Page 155 (U.S. EPA/OPP 2010a)
Freshwater Duckweed (*Lemna gibba*)	Indaziflamhydroxyethyl (99.0%) Nominal concentrations of 0 (negative control and solvent controls), 62.5, 125, 250, 500, and 1000 ng/L under static conditions. Mean-measured concentrations were <0.054 µg/L (<lowest standard analyzed, controls), 101.1, 121.5, 250, 496, and 944.5 ng/L. 7-day toxicity study.	7-day EC_{50} = 510 ng/L (Frond area) NOAEC = 250 ng/L Most sensitive endpoint was frond area.	MRID 47443254 Acceptable Page 156 (U.S. EPA/OPP 2010a)
Freshwater Duckweed (*Lemna gibba*)	Indaziflam – olefin (96.0%) Nominal concentrations of 0 (negative control and solvent control), 0.095, 0.305, 0.977, 3.13, and 10.0 µg/L under static conditions. Mean-measured concentrations	7-day EC_{50} = 0.34 µg/L (Frond area) NOAEC = 0.09 µg/L Most sensitive endpoint was frond area.	MRID 47443255 Acceptable Page 158 (U.S. EPA/OPP 2010a)

Species	Exposure	Response	Reference
	were <0.0515 (<lowest standard analyzed, controls), 0.09, 0.32, 1.08, 3.68, and 11.4 µg/L. 7-day toxicity study.		
Freshwater Duckweed (*Lemna gibba*)	Indaziflam (94.5%) Nominal initial concentrations of 0 (negative and solvent controls), 26.8, 67.0, 167, 419, and 1,046 ng a.i./L under static conditions. Mean measured concentrations at day 0 were <10.39 (<lowest standard analyzed, controls), 76.2, 154, 329, and 889 ng a.i./L. 7-day toxicity study.	7-day EC_{50} = 350 ng a.i./L (Frond number) NOAEC = 167 ng a.i./L Most sensitive endpoint was frond number.	MRID 47443256 Supplemental Page 159 (U.S. EPA/OPP 2010a)
Freshwater Duckweed (*Lemna gibba*)	Indaziflam 500 SC (44.4%) Nominal concentrations of the active ingredient BCS AA 10717 were 0 (negative control), 5.55, 11.1, 22.2, 44.4, 88.8, and 177.7 ng ai/L. The mean-measured concentrations were <2.03 (<LOQ, negative control), 5.55, 11.1, 19.4, 46.1, 92.6, and 185 ng ai/L	7-day EC_{50} = 61 ng ai/L NOAEC = 19.4 ng ai/L Most sensitive endpoint was yield based on frond number.	MRID 47443308 Acceptable Page 159 (U.S. EPA/OPP 2010a)

Appendix 9: Indaziflam GLEAMS-Driver Modeling Results

Table 1: Effective Off-site Application Rate (lb/acre)

Site	*Central Clay*	*Lower Clay*	*Upper Clay*	*Central Loam*	*Lower Loam*	*Upper Loam*	*Central Sand*	*Lower Sand*	*Upper Sand*
Dry and Warm Location	5.23E-04	6.84E-06	1.51E-03	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	3.53E-03	4.59E-04	4.87E-03	6.90E-06	0.00E+00	2.54E-03	0.00E+00	0.00E+00	7.97E-04
Dry and Cold Location	7.79E-02	6.05E-02	1.03E-01	5.11E-02	3.84E-02	6.55E-02	4.67E-02	3.87E-02	6.90E-02
Average Rainfall and Warm Location	2.76E-02	1.16E-02	5.44E-02	3.09E-04	3.19E-05	6.07E-04	4.26E-06	1.68E-06	2.39E-05
Average Rainfall and Temperate Location	1.64E-02	4.84E-03	3.76E-02	1.54E-03	4.87E-04	3.07E-03	3.97E-04	1.40E-04	5.54E-04
Average Rainfall and Cool Location	3.03E-02	9.09E-03	5.23E-02	5.18E-03	3.13E-03	8.39E-03	1.15E-03	6.06E-04	1.69E-03
Wet and Warm Location	3.91E-02	2.24E-02	5.86E-02	1.85E-03	8.41E-04	5.72E-03	1.07E-04	6.34E-05	3.59E-04
Wet and Temperate Location	2.88E-02	2.27E-02	1.47E-01	1.10E-03	1.09E-04	1.32E-02	1.01E-04	1.66E-06	1.60E-03
Wet and Cool Location	3.63E-01	3.46E-01	3.72E-01	3.38E-01	2.81E-01	3.60E-01	2.64E-01	2.12E-01	3.07E-01
Summary									
								Average of Central Values	*4.81E-02*
								25th Percentile of Lower Bounds	*6.84E-06*
								Maximum Value	*3.72E-01*
								Summary of Values[1]	***0.0481 (0.00000684 - 0.372)***

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 2: Concentration in Top 12 Inches of Soil (ppm)

Site	*Central Clay*	*Lower Clay*	*Upper Clay*	*Central Loam*	*Lower Loam*	*Upper Loam*	*Central Sand*	*Lower Sand*	*Upper Sand*
Dry and Warm Location	2.07E-01	2.06E-01	2.07E-01	1.92E-01	1.91E-01	1.92E-01	1.92E-01	1.91E-01	1.92E-01
Dry and Temperate Location	2.19E-01	2.17E-01	2.20E-01	2.03E-01	2.01E-01	2.04E-01	2.02E-01	2.00E-01	2.04E-01
Dry and Cold Location	3.26E-01	3.17E-01	3.31E-01	3.07E-01	3.00E-01	3.10E-01	3.06E-01	2.99E-01	3.09E-01
Average Rainfall and Warm Location	2.07E-01	2.05E-01	2.07E-01	1.92E-01	1.91E-01	1.92E-01	1.92E-01	1.91E-01	1.92E-01
Average Rainfall and Temperate Location	2.16E-01	2.15E-01	2.18E-01	2.01E-01	2.00E-01	2.02E-01	1.99E-01	1.98E-01	2.01E-01
Average Rainfall and Cool Location	2.38E-01	2.35E-01	2.39E-01	2.22E-01	2.18E-01	2.24E-01	2.19E-01	2.16E-01	2.20E-01
Wet and Warm Location	2.07E-01	2.06E-01	2.07E-01	1.92E-01	1.91E-01	1.93E-01	1.92E-01	1.91E-01	1.92E-01
Wet and Temperate Location	2.29E-01	2.27E-01	2.29E-01	2.10E-01	2.09E-01	2.11E-01	1.99E-01	1.97E-01	2.01E-01
Wet and Cool Location	2.28E-01	2.12E-01	2.47E-01	2.27E-01	2.14E-01	2.40E-01	2.13E-01	2.06E-01	2.33E-01
Summary									
							Average of Central Values	*2.20E-01*	
							25th Percentile of Lower Bounds	*1.97E-01*	
							Maximum Value	*3.31E-01*	
							Summary of Values[1]	***0.220 (0.197 - 0.331)***	

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 3: Concentration in Top 36 Inches of Soil (mg/kg)

Site	*Central Clay*	*Lower Clay*	*Upper Clay*	*Central Loam*	*Lower Loam*	*Upper Loam*	*Central Sand*	*Lower Sand*	*Upper Sand*
Dry and Warm Location	6.89E-02	6.87E-02	6.90E-02	6.39E-02	6.37E-02	6.40E-02	6.39E-02	6.37E-02	6.40E-02
Dry and Temperate Location	7.28E-02	7.24E-02	7.33E-02	6.76E-02	6.70E-02	6.81E-02	6.75E-02	6.66E-02	6.79E-02
Dry and Cold Location	1.09E-01	1.06E-01	1.10E-01	1.02E-01	9.99E-02	1.03E-01	1.02E-01	9.97E-02	1.03E-01
Average Rainfall and Warm Location	6.90E-02	6.85E-02	6.90E-02	6.39E-02	6.35E-02	6.40E-02	6.39E-02	6.35E-02	6.40E-02
Average Rainfall and Temperate Location	7.21E-02	7.18E-02	7.26E-02	6.71E-02	6.66E-02	6.74E-02	6.68E-02	6.60E-02	6.70E-02
Average Rainfall and Cool Location	7.93E-02	7.83E-02	7.96E-02	7.40E-02	7.27E-02	7.47E-02	7.34E-02	7.23E-02	7.41E-02
Wet and Warm Location	6.91E-02	6.88E-02	6.91E-02	6.41E-02	6.38E-02	6.42E-02	6.42E-02	6.38E-02	6.42E-02
Wet and Temperate Location	7.67E-02	7.63E-02	7.69E-02	7.14E-02	7.12E-02	7.19E-02	7.14E-02	7.13E-02	7.17E-02
Wet and Cool Location	7.62E-02	7.08E-02	8.23E-02	7.62E-02	7.17E-02	8.01E-02	7.69E-02	7.23E-02	8.01E-02
Summary									
							Average of Central Values	*7.38E-02*	
							25th Percentile of Lower Bounds	*6.60E-02*	
							Maximum Value	*1.10E-01*	
							Summary of Values[1]	***0.0738 (0.0660 - 0.110)***	

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 4: Maximum Penetration into Soil Column (inches)

Site	*Central Clay*	*Lower Clay*	*Upper Clay*	*Central Loam*	*Lower Loam*	*Upper Loam*	*Central Sand*	*Lower Sand*	*Upper Sand*
Dry and Warm Location	12	8	12	12	8	12	18	12	18
Dry and Temperate Location	12	12	18	12	12	18	18	18	24
Dry and Cold Location	12	8	12	12	8	12	12	12	18
Average Rainfall and Warm Location	18	18	18	24	18	24	36	30	36
Average Rainfall and Temperate Location	18	18	18	24	18	24	30	24	36
Average Rainfall and Cool Location	18	18	18	18	18	24	30	30	36
Wet and Warm Location	18	18	18	30	30	30	36	36	36
Wet and Temperate Location	30	30	30	36	36	36	36	36	36
Wet and Cool Location	24	24	24	36	30	36	36	36	36
Summary									
								Average of Central Values	*22.89*
								25th Percentile of Lower Bounds	*12.00*
								Maximum Value	*36.00*
								Summary of Values[1]	***22.9 (12 - 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 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	1.58E-03	2.68E-05	3.03E-03	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	5.23E-03	1.54E-03	6.00E-03	1.91E-05	0.00E+00	4.67E-03	0.00E+00	0.00E+00	1.50E-03
Dry and Cold Location	5.05E-02	4.42E-02	7.75E-02	3.96E-02	2.80E-02	6.11E-02	3.30E-02	3.04E-02	6.66E-02
Average Rainfall and Warm Location	3.68E-02	1.77E-02	5.83E-02	2.51E-04	2.60E-05	1.44E-03	6.45E-06	1.38E-06	1.83E-05
Average Rainfall and Temperate Location	2.08E-02	7.84E-03	3.25E-02	1.26E-03	4.04E-04	1.54E-03	3.00E-04	1.10E-04	3.73E-04
Average Rainfall and Cool Location	2.88E-02	6.33E-03	3.86E-02	2.30E-03	2.04E-03	2.79E-03	5.34E-04	4.06E-04	8.67E-04
Wet and Warm Location	2.74E-02	1.84E-02	3.10E-02	1.86E-03	3.38E-04	3.53E-03	9.38E-05	2.30E-05	2.51E-04
Wet and Temperate Location	2.74E-02	1.70E-02	5.87E-02	1.04E-03	4.74E-05	4.93E-03	7.25E-04	3.86E-04	1.36E-03
Wet and Cool Location	1.19E-01	1.05E-01	1.35E-01	9.84E-02	8.41E-02	1.15E-01	9.32E-02	7.65E-02	1.13E-01
Summary									
							Average of Central Values		*2.19E-02*
							25th Percentile of Lower Bounds		*2.60E-05*
							Maximum Value		*1.35E-01*
							Summary of Values[1]		***0.0219 (0.000026 - 0.135)***

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 6: Stream, Average Annual Concentration in Surface Water (mg/L or ppm)

Site	*Central Clay*	*Lower Clay*	*Upper Clay*	*Central Loam*	*Lower Loam*	*Upper Loam*	*Central Sand*	*Lower Sand*	*Upper Sand*
Dry and Warm Location	6.26E-06	9.43E-08	1.12E-05	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	2.51E-05	9.91E-06	3.60E-05	6.11E-08	0.00E+00	1.80E-05	0.00E+00	0.00E+00	5.63E-06
Dry and Cold Location	9.96E-04	7.42E-04	1.39E-03	6.54E-04	4.83E-04	9.06E-04	5.62E-04	4.99E-04	9.40E-04
Average Rainfall and Warm Location	2.52E-04	1.26E-04	4.04E-04	1.19E-06	1.14E-07	4.85E-06	3.04E-08	6.02E-09	8.24E-08
Average Rainfall and Temperate Location	1.96E-04	8.83E-05	3.93E-04	1.61E-05	9.01E-06	2.53E-05	3.79E-06	2.41E-06	5.03E-06
Average Rainfall and Cool Location	2.87E-04	1.26E-04	4.15E-04	4.66E-05	2.99E-05	6.45E-05	1.11E-05	7.16E-06	1.38E-05
Wet and Warm Location	2.55E-04	2.17E-04	4.06E-04	7.62E-06	4.32E-06	2.10E-05	6.20E-07	3.77E-07	1.53E-06
Wet and Temperate Location	2.94E-04	1.60E-04	5.27E-04	4.44E-06	4.06E-07	3.49E-05	8.02E-05	3.69E-05	1.21E-04
Wet and Cool Location	2.33E-03	2.10E-03	2.52E-03	1.58E-03	1.53E-03	1.70E-03	1.16E-03	1.13E-03	1.32E-03
Summary									
								Average of Central Values	*3.25E-04*
								25th Percentile of Lower Bounds	*1.14E-07*
								Maximum Value	*2.52E-03*
								Summary of Values[1]	***0.000325 (0.000000114 - 0.00252)***

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 7: Pond, Maximum Peak Concentration in Surface Water (mg/L or ppm)

Site	*Central Clay*	*Lower Clay*	*Upper Clay*	*Central Loam*	*Lower Loam*	*Upper Loam*	*Central Sand*	*Lower Sand*	*Upper Sand*
Dry and Warm Location	4.56E-04	5.80E-06	1.37E-03	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	2.41E-03	3.94E-04	2.75E-03	5.91E-06	0.00E+00	1.71E-03	0.00E+00	0.00E+00	5.38E-04
Dry and Cold Location	2.52E-02	1.92E-02	3.33E-02	1.88E-02	1.42E-02	2.15E-02	1.44E-02	1.10E-02	2.32E-02
Average Rainfall and Warm Location	1.82E-02	7.72E-03	3.28E-02	1.55E-04	1.56E-05	5.30E-04	3.06E-06	8.13E-07	1.15E-05
Average Rainfall and Temperate Location	8.81E-03	2.50E-03	2.15E-02	5.85E-04	1.68E-04	8.05E-04	1.29E-04	4.16E-05	1.58E-04
Average Rainfall and Cool Location	1.45E-02	2.17E-03	2.09E-02	1.16E-03	1.02E-03	1.34E-03	2.33E-04	2.10E-04	3.51E-04
Wet and Warm Location	1.57E-02	7.35E-03	2.04E-02	1.05E-03	2.25E-04	2.01E-03	5.37E-05	1.39E-05	1.28E-04
Wet and Temperate Location	1.31E-02	9.85E-03	3.84E-02	5.81E-04	2.99E-05	3.69E-03	3.28E-04	1.76E-04	8.22E-04
Wet and Cool Location	5.12E-02	4.05E-02	5.29E-02	4.21E-02	3.15E-02	4.39E-02	3.57E-02	2.78E-02	4.03E-02
Summary									
								Average of Central Values	*9.81E-03*
								25th Percentile of Lower Bounds	*1.39E-05*
								Maximum Value	*5.29E-02*
								Summary of Values[1]	***0.00981 (0.0000139 - 0.0529)***

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 8: Pond, Average Annual Concentration in Surface Water (mg/L or ppm)

Site	*Central Clay*	*Lower Clay*	*Upper Clay*	*Central Loam*	*Lower Loam*	*Upper Loam*	*Central Sand*	*Lower Sand*	*Upper Sand*
Dry and Warm Location	9.10E-06	1.16E-07	2.49E-05	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Dry and Temperate Location	5.38E-05	1.39E-05	7.08E-05	1.03E-07	0.00E+00	3.65E-05	0.00E+00	0.00E+00	1.13E-05
Dry and Cold Location	1.35E-03	9.35E-04	1.83E-03	8.81E-04	5.91E-04	1.13E-03	7.51E-04	5.84E-04	1.17E-03
Average Rainfall and Warm Location	5.43E-04	2.81E-04	9.21E-04	3.83E-06	3.45E-07	1.03E-05	7.72E-08	1.78E-08	2.61E-07
Average Rainfall and Temperate Location	3.92E-04	1.50E-04	8.84E-04	2.90E-05	1.36E-05	4.65E-05	6.60E-06	3.63E-06	8.69E-06
Average Rainfall and Cool Location	5.99E-04	2.18E-04	9.38E-04	8.59E-05	5.13E-05	1.04E-04	1.77E-05	1.01E-05	2.37E-05
Wet and Warm Location	4.93E-04	4.36E-04	7.13E-04	2.04E-05	9.07E-06	4.39E-05	1.44E-06	7.68E-07	3.19E-06
Wet and Temperate Location	6.07E-04	2.87E-04	9.42E-04	1.05E-05	7.42E-07	6.58E-05	6.60E-05	3.50E-05	1.11E-04
Wet and Cool Location	1.66E-03	1.59E-03	1.74E-03	1.13E-03	1.07E-03	1.23E-03	8.48E-04	7.71E-04	1.01E-03
Summary									
								Average of Central Values	*3.54E-04*
								25th Percentile of Lower Bounds	*3.45E-07*
								Maximum Value	*1.83E-03*
								Summary of Values[1]	***0.000354 (0.000000345 - 0.00183)***

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.