



SERA TR-052-13-03a

Fluroxypyr
Human Health and Ecological Risk Assessment
FINAL REPORT

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USDA Forest Service Contract: **AG-3187-C-06-0010**
USDA Forest Order Number: **AG-43ZP-D-07-0013**
SERA Internal Task No. **52-13**

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June 12, 2009

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
AChE	acetylcholinesterase
AEL	adverse-effect level
a.i.	active ingredient
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
calc	calculated value
CBI	confidential business information
ChE	cholinesterase
CI	confidence interval
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
DER	data evaluation record
d.f.	degrees of freedom
EC _x	concentration causing X% inhibition of a process
EC ₂₅	concentration causing 25% inhibition of a process
EC ₅₀	concentration causing 50% inhibition of a process
EHE	2-ethylhexyl ester
EFED	Environmental Fate and Effects Division (U.S. EPA/OPP)
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
g	gram
GLP	Good Laboratory Practices
ha	hectare
HED	Health Effects Division (U.S. EPA/OPP)
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IREED	Interim Reregistration Eligibility Decision
IRIS	Integrated Risk Information System
k _a	absorption coefficient
k _e	elimination coefficient
kg	kilogram
K _{o/c}	organic carbon partition coefficient
K _{o/w}	octanol-water partition coefficient
K _p	skin permeability coefficient
L	liter
lb	pound
LC ₅₀	lethal concentration, 50% kill
LD ₅₀	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LOC	level of concern

ACRONYMS, ABBREVIATIONS, AND SYMBOLS *(continued)*

m	meter
M	male
MEI	most exposed individual
MHE	methylhepanol ester
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
mPa	millipascal, (0.001 Pa)
MOE	margin of exposure
MRID	Master Record Identification Number
MSDS	material safety data sheet
MSMA	monosodium methanearsonate
MW	molecular weight
NAWQA	USGS National Water Quality Assessment
NCI	National Cancer Institute
NCOD	National Drinking Water Contaminant Occurrence Database
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOS	not otherwise specified
NRC	National Research Council
NTP	National Toxicology Program
OM	organic matter
OPP	Office of Pesticide Programs
OPPTS	Office of Prevention, Pesticides and Toxic Substances
OSHA	Occupational Safety and Health Administration
Pa	Pascal
PBPK	physiologically-based kinetic
ppm	parts per million
QSAR	quantitative structure-activity relationship
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
TEP	typical end-use product
T.G.I.A.	Technical grade active ingredient
TIPA	Triisopropanolamine
UF	uncertainty factor
U.S.	United States
USDA	U.S. Department of Agriculture
U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey
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 (kg/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 (µg/cm ²)	11.21
pounds per gallon (lb/gal)	grams per liter (g/L)	119.8
square centimeters (cm ²)	square inches (in ²)	0.155
square centimeters (cm ²)	square meters (m ²)	0.0001
square meters (m ²)	square centimeters (cm ²)	10,000
yards	meters	0.9144

Note: All references to pounds and ounces refer to avoirdupois weights unless otherwise specified.

CONVERSION OF SCIENTIFIC NOTATION

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

EXECUTIVE SUMMARY

Fluroxypyr is a selective post-emergent systemic herbicide registered for the control of broadleaf weeds in rangeland, non-crop areas, and grazed areas as well as for the control of woody brush. Two formulations of fluroxypyr are specifically considered in this risk assessment: Vista Specialty Herbicide and Vista XRT. Both of these formulations contain the 1-methylheptyl ester of fluroxypyr, designated as fluroxypyr-MHE. Current application methods include backpack (selective foliar), hydraulic spray, and aerial applications. The Forest Service is likely to continue to use these methods in programs involving the application of fluroxypyr. Fluroxypyr is labeled for application rates that range from 0.12 to 0.5 lb a.e./acre.

Under normal conditions of use, fluroxypyr-MHE is not likely to cause adverse effects in humans. Moreover, for most of the accidental exposure scenarios presented in this risk assessment, the levels of exposure are below the level of concern. The two exceptions involve exposure scenarios after an accidental spill of fluroxypyr into a body of water. This extreme exposure scenario, which is standard in all Forest Service risk assessments, is designed to illustrate the potential consequences of a large spill of a pesticide into a small pond.

Fluroxypyr is an auxin mimicking herbicide. Like most auxin mimicking herbicides, fluroxypyr is more toxic to dicots (broadleaf plants) than to monocots (e.g. grasses). Any susceptible dicot, target or nontarget, that is directly sprayed with fluroxypyr at an effective application rate is likely to die. The hazards associated with drift will depend on the application method. Aerial applications are likely to be the most hazardous, followed by high boom ground broad cast, low boom ground broadcast, and backpack directed foliar applications. There is no basis for asserting that exposure to fluroxypyr is likely to cause adverse effects in terrestrial animals. Plausible effects in terrestrial animals, secondary to changes in vegetation, may be either beneficial or detrimental and are likely vary over time.

Applications of the fluroxypyr formulations considered in this risk assessment do not appear to present a risk to tolerant or sensitive species of fish, tolerant species of aquatic invertebrates (crustaceans), or tolerant species of algae and aquatic macrophytes. The HQ for sensitive species of aquatic algae is 0.6 (0.01 to 2)—i.e., only the upper bound of the HQ exceeds the level of concern. It is not clear that the modest excursion above the level of concern would result in any detectable adverse effects in aquatic algae. The most sensitive nontarget aquatic organism appears to be bivalves. This assessment, however, is based on a single study in a single species of bivalve. Based on an inhibition of shell deposition, the HQ based on peak expected concentrations is 6 (0.1 to 20). In other words, both the central estimate and the upper bound of the HQ exceed the level of concern. In the absence of any additional toxicity studies or any field studies on mollusks, the conservative assumption should be made that aquatic mollusks may be at risk of adverse effects from the application of fluroxypyr-MHE.

1. INTRODUCTION

Fluroxypyr is a post-emergent herbicide registered for the control of broadleaf weeds and woody brush. Although the Forest Service does not use fluroxypyr extensively in vegetation management programs, it is considering expanding the use of this herbicide. This document provides a human health and ecological effects risk assessment of the environmental consequences of using fluroxypyr in Forest Service programs.

The document consists of four chapters, including the introduction, program description, risk assessment for human health effects, and risk assessment for ecological effects or effects on wildlife species. Each of the two risk assessment chapters has four major sections, including an identification of the hazards associated with fluroxypyr and its commercial formulations, an assessment of potential exposure to the product, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure.

Although this is a technical support document and addresses some specialized technical areas, an effort was made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts, methods, and terms common to all parts of the risk assessment are described in plain language in a separate document (SERA 2007a).

The published literature on fluroxypyr was identified using TOXLINE (<http://toxnet.nlm.nih.gov/>), PubMed (<http://www.ncbi.nlm.nih.gov/entrez>), and AGRICOLA (<http://agricola.nal.usda.gov/>). Additional information on fluroxypyr was identified through standard Internet search engines.

The published literature on fluroxypyr has a fairly small impact on this risk assessment. There is a limited amount of published information regarding the toxicity of fluroxypyr to nontarget aquatic species (e.g. Ma 2002; Ma et al. 2001, 2002, 2003; Wan et al. 1992), and most of the published information on fluroxypyr pertains to environmental fate, analytical methods, and efficacy (Section 5). Since the open literature on fluroxypyr contains few reviews or risk assessments (e.g., European Commission 1990), open literature reviews are used in the current risk assessment only to ensure that all the relevant studies are covered. Fluroxypyr is not included in the U.S. EPA IRIS database (<http://www.epa.gov/iriswebp/iris/subst/index.html>), WHO INCHEM series (<http://www.inchem.org/>), the EXtension TOXicology NETwork series (<http://extoxnet.orst.edu/>), or the USDA/ARS Pesticide Properties Database (<http://www.ars.usda.gov/Services/docs.htm?docid=14199>). USGS (2003a) provides information on the agricultural use of fluroxypyr; however, monitoring data are not included in the USGS (2003b) National Water Quality Assessment Program.

Given the limitations of fluroxypyr data in the open literature, this risk assessment relies heavily on industry studies submitted to the U.S. EPA in support of the registration of fluroxypyr. These studies are typically classified as *Confidential Business Information*

(CBI) and are not typically released or available to individuals outside of the U.S. EPA Office of Pesticides.

In the preparation of this risk assessment, a Freedom of Information Act (FOIA) request (HQ-RIN-00463-08) was submitted to the U.S. EPA for a complete bibliography of all of the fluroxypyr studies submitted to the Agency, copies of all cleared fluroxypyr reviews (listed at <http://www.epa.gov/pesticides/foia/reviews/128959/index.htm>), and all fluroxypyr risk assessments/science chapters conducted by the Health Effects Division (HED) and the Environmental Fate and Effects Division (EFED) of the U.S. EPA Office of Pesticides.

The studies submitted to U.S. EPA in support of the registration of fluroxypyr are clearly the most relevant studies in terms of the quantitative risk assessment of fluroxypyr. As summarized in the addendum to the references (Section 5), the EPA provided 199 submitted studies, as cleared reviews, in response to the FOIA request. A cleared review typically refers to synopses of a submitted study and is usually based on data evaluation records (DERs) prepared by the Office of Pesticides. Cleared reviews differ from DERs in that information classified as CBI in the DER is removed in the preparation of a cleared review. While cleared reviews are helpful, they are available on only nine of the registrant submissions. Additional summaries of study submissions are available in two EPA E-Dockets (<http://www.regulations.gov/search/index.jsp>): EPA-HQ-OPP-2005-00536 and EPA-HQ-OPP-2007-0114. These summaries relate primarily to the toxicity of fluroxypyr in mammals (e.g., U.S. EPA/OPP 2006a,f) and the environmental fate of fluroxypyr (e.g., U.S. EPA/OPP 2007c).

Two additional studies (e.g., Domoradzki and Brzak 1996; Liberacki et al. 1996) were identified from cleared reviews provided by the Agency. Each submission is identified by a unique Master Record Identification (MRID) number. Not all of the submitted studies are germane to the current assessment. For example, MRID numbers ending in 00 (e.g., 44527200) are typically transmittal letters that do not contain relevant information.

In addition to the data provided by U.S. EPA, Dow AgroSciences, the registrant for fluroxypyr, provided full copies of 74 studies, as listed in Section 5 (References), as well as numerous DERs.

The Forest Service is aware of and is sensitive to concerns with risk assessments based chiefly on studies submitted to the U.S. EPA in support of product registration. The general concern can be expressed as follows:

If the study is paid for and/or conducted by the registrant, the study may be designed and/or conducted and/or reported in a manner that will obscure any adverse effects that the compound may have.

This concern is largely without foundation. Any study (published or unpublished) can be falsified; however, concerns about the design, conduct, or reporting of studies submitted to the EPA for pesticide registration are minor. There are strict EPA guidelines for designing, conducting, and reporting registrant-submitted studies. Full copies of the guidelines are available at <http://www.epa.gov/opptsfrs/home/guidelin.htm>. All studies are conducted under Good Laboratory Practices (GLPs). GLPs are an elaborate set of procedures involving documentation and independent quality control and quality assurance, which substantially exceed the levels typically seen in open literature publications. Finally, the EPA reviews each of the submitted studies for adherence to the relevant study guidelines. These reviews most often generate Data Evaluation Records (DERs), which are independent assessments of the studies to ensure that the EPA Guidelines are followed. In addition, each DER undergoes internal review (and sometimes several layers of review).

Almost no risk estimates presented in this document are given as single numbers. Usually, risk is expressed as a central estimate and a range, which is sometimes quite large. Because of the need to encompass many different types of exposure as well as the need to express the uncertainties in the assessment, this risk assessment involves numerous calculations. Most of the calculations are relatively simple, and they are included in the body of the document. For the more cumbersome calculations, an EXCEL workbook, consisting of a set of worksheets, is included as an attachment to the risk assessment. The worksheets, which provide the details for the estimates cited in the body of the risk assessment, are divided into the following sections: general data and assumptions, chemical specific data and assumptions, exposure assessments for workers, exposure assessments for the general public, and exposure assessments for effects on nontarget organisms. SERA (2008) provides documentation for the use of the EXCEL workbooks.

2. PROGRAM DESCRIPTION

2.1. OVERVIEW

Fluroxypyr is a selective post-emergent systemic herbicide. It is registered for the control of broadleaf weeds in rangeland, non-crop areas, and grazed areas and for the control of woody brush. Fluroxypyr is structurally similar to several other herbicides—i.e., aminopyralid, clopyralid, picloram, and triclopyr—and, like these other herbicides, fluroxypyr acts by mimicking indoleacetic acid, a plant growth hormone.

Two formulations of fluroxypyr are specifically considered in this risk assessment: Vista Specialty Herbicide and Vista XRT. Both of these formulations contain the 1-methylheptyl ester of fluroxypyr as well as two listed inerts: naphthalene and 1-methyl-2-pyrrolidinone. The Vista XRT formulation contains a greater concentration of the fluroxypyr ester and much lower concentrations of the listed inerts.

Fluroxypyr is not used extensively in Forest Service programs; however, the Forest Service is considering expanding its use as an alternative to some of the other structurally related herbicides noted above. In addition, the Forest Service is contemplating the use of fluroxypyr to control selected weed species, like *Ceanothus*, *Arbutus*, *Arctostaphylos*, and *Cytisus*. The most likely uses of fluroxypyr will involve applications to forest and rangelands, rights-of-way, and developed recreational areas such as campgrounds, picnic areas, and trails. Most likely, the methods of application will continue to include backpack (selective foliar), hydraulic spray, and aerial applications. Fluroxypyr is labeled for application rates ranging from 0.12 to 0.5 lb a.e./acre. The current risk assessment considers the full range of labeled application rates for broadleaf weeds as well as all labeled application methods.

2.2. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS

Fluroxypyr is a selective post-emergent systemic herbicide. It is registered for the control of broadleaf weeds in rangeland, non-crop areas, and grazed areas and for the control of woody brush. In addition to non-agricultural applications, fluroxypyr is registered for applications to wheat, barley, corn, and oats.

Fluroxypyr is the common name for 4-amino-3,5-dichloro-6-fluoro-2-pyridyloxyacetic acid. As illustrated in Figure 1, fluroxypyr is a pyridine carboxylic acid, a class of herbicides including aminopyralid, clopyralid, picloram, and triclopyr. Fluroxypyr differs structurally from these other herbicides in that the carbon in the 6-position on the pyridine ring contains fluorine rather than chlorine. In terms of alkyl substitution, fluroxypyr is similar to triclopyr—i.e., an acetic acid rather than a carboxylic acid in the 2-carbon position on the pyridine ring. Fluroxypyr is similar to picloram and aminopyralid in the occurrence of the amino group in the 4-carbon position. Fluroxypyr's mechanism of action is like that of other auxin mimicking herbicides (e.g., 2,4-D) and involves mimicking the auxin plant growth hormone, indoleacetic acid (Retzinger and Mallory-Smith 1997).

Fluroxypyr was developed by the Dow Chemical Company, now Dow AgroSciences, and released commercially in 1985 (Tomlin 2004). Fluroxypyr can be synthesized by reacting 4-amino-3,5-dichloro-2-(methylsulfonyl)pyridine with methylglycolate (Wiley-VCH 2007), although it is not clear that this method of synthesis is currently used to produce fluroxypyr.

There are numerous commercial pesticide formulations containing fluroxypyr, and the Pesticide Action Network lists 43 active commercial formulations (PAN 2008). All but two of these formulations, however, are mixtures of fluroxypyr with other herbicides, many of which contain 2,4-D, dicamba, clopyralid, and/or bromoxynil. The mixture formulations are not covered in the current risk assessment.

Starane and Vista are commercial formulations that contain fluroxypyr as the sole active ingredient. Vista is the only fluroxypyr formulation labeled for forestry applications, and is the only commercial formulation likely to be used in Forest Service programs. Starane formulations are labeled for agricultural use, and, therefore, not considered further in this risk assessment.

As summarized in Table 1, there are two available formulations of Vista: Vista Specialty Herbicide and Vista XRT (Ultra), both of which are produced by Dow AgroSciences. Vista Specialty Herbicide is less concentrated than Vista XRT and contains a much greater concentration of inerts. In the most recent product label on the U.S. EPA web site, the more concentrated formulation is named Vista Ultra, rather than Vista XRT. The EPA registration numbers for Vista Ultra and Vista XRT are identical—i.e., the formulations are identical. It appears that Dow AgroSciences simply decided to change the name of the formulation from Vista Ultra to Vista XRT. In the current risk assessment, only the name Vista XRT is used.

Vista Specialty Herbicide and Vista XRT each contain the 1-methylheptyl ester of fluroxypyr, sometimes referred to as fluroxypyr-meptyl. The fluroxypyr ester is rapidly absorbed by plants and then rapidly hydrolyzed to the acid form which has the herbicidal effect (Tomlin 2004). The product labels for Vista Specialty Herbicide and Vista XRT are virtually identical in terms of application rates and application instructions, when application rates are converted to units of lb a.e./acre.

The two commercial formulations of fluroxypyr addressed in this risk assessment differ substantially in the concentration of both the active ingredient and inerts. Vista Specialty Herbicide contains 26.2% (w/w) of the fluroxypyr 1-methylheptyl ester, which is equivalent to 1.5 lbs of fluroxypyr acid (a.e.) per gallon. The product label specifies that the formulation contains petroleum distillates. The material safety datasheet further specifies that the formulation contains <5.4% naphthalene and 5.1% 1-methyl-2-pyrrolidinone. The concentration of fluroxypyr 1-methylheptyl ester in Vista XRT is substantially greater—i.e., 45.2%, compared with the 26.2% in Vista Specialty Herbicide. More importantly, Vista XRT contains much lower concentrations of named inerts—i.e., 0.5% naphthalene and 0.1% 1-methyl-2-pyrrolidinone.

This difference in the concentrations of inert ingredients is important to the current risk assessment. The identity of these non-herbicidal ingredients must be listed on the MSDS for the fluroxypyr formulations because they are classified as having adverse effects: carcinogenicity in the case of naphthalene and developmental toxicity in the case of 1-methyl-2-pyrrolidinone. Naphthalene is a natural component of crude oil and occurs in the aromatic fraction of petroleum distillates (ATSDR 1999). For example, naphthalene and other related diaromatics constitute about 7% of diesel fuel oil (Potter and Simmons 1999). 1-Methyl-2-pyrrolidinone is a dipolar solvent that can be used to enhance penetration (Ash and Ash 2004). The significance of these components of the formulation is discussed further in Section 3.1.14 (Inerts and Adjuvants).

2.3. APPLICATION METHODS

The general use and application of herbicides in silviculture are discussed in the available literature (e.g., Cantrell and Hyland 1985) and in Environmental Impact Statements prepared by the Forest Service (e.g., USDA/FS 1989a,b,c). This risk assessment focuses on the aspects of herbicide application most germane to the exposure assessments for human health and ecological effects (Sections 3.2 and 4.2).

Although the Forest Service has not used fluroxypyr in vegetation management programs to date, its similarity to other herbicides used in Forest Service programs (e.g., clopyralid, picloram, and triclopyr), suggest that the methods of application would be similar, including backpack (selective foliar), hydraulic spray, and aerial applications. In general, small areas are treated by backpack application (selective foliar application or spot treatments), and relatively large areas are treated by either hydraulic spray (typically broadcast sprays using truck mounted equipment) or aerial application. In aerial applications, for which fluroxypyr is labeled, fixed-wing aircraft or helicopters may be used on pine plantations; however, only helicopters may be used in other non-cropland areas.

In backpack applications, the herbicide sprayer or container is carried by backpack, and the herbicide is applied to selected target vegetation. Application crews may treat up to shoulder high brush, which means that chemical contact with the arms, hands, or face is plausible. To reduce the likelihood of significant exposures, application crews are directed not to walk through treated vegetation. Usually, a worker treats approximately 0.5 acre/hour with a plausible range from 0.25 to 1.0 acre/hour.

Broadcast ground applications involve spray equipment, which may be mounted on trucks and will typically occur in areas such as rights-of-way or along roadsides. In truck-mounted applications, about 8 acres are treated in a 45-minute period (approximately 11 acres/hour) with approximately 200 gallons of the herbicide mixture (270 gallons/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) (USDA/FS 1989b, p 2-9 to 2-10).

In aerial applications, the herbicide is applied through specially designed spray nozzles and booms. The nozzles are designed to reduce turbulence and maintain a large droplet

size, both of which contribute to a reduction in spray drift. Aerial applications may only be made under meteorological conditions that minimize the potential for spray drift. The product labels for fluroxypyr specifically recommend that aerial applications be made at wind speeds of not less than 2 miles per hour and not greater than 10 miles per hour. As with most herbicides and other pesticides, application during temperature inversions is not recommended because of the high potential for drift. In aerial applications, approximately 40–100 acres may be treated per hour.

2.4. MIXING AND APPLICATION RATES

The range of application rates considered in typical risk assessments is based on labeled rates as well as application rates from past programs recorded in pesticide use reports (e.g., <http://www.fs.fed.us/foresthealth/pesticide/reports.shtml>) or other information provided by the Forest Service. Because, however, fluroxypyr was not used extensively in past Forest Service programs, the use rates considered in this risk assessment are based only on the labeled application rates.

The labeled application rates for Vista and Starane are virtually identical for non-cropland applications. The maximum labeled annual application rate is $2\frac{2}{3}$ pints formulation/acre, which corresponds to 0.5 lb a.e./acre [$(2\frac{2}{3}$ pints /8 pints per gallon) x 1.5 lbs a.e./gallon]. The lowest recommended application rate is $\frac{2}{3}$ pints formulation/acre, which corresponds to 0.12 lb a.e./acre [$(\frac{2}{3}$ pints /8 pints per gallon) x 1.5 lbs a.e./gallon]. With specific reference to the control of *Kochia*, the label cautions against application rates less than 0.12 lb a.e./acre because this may lead to a population shift to more tolerant biotypes of *Kochia*. As with any post-emergent herbicide, the label recommends that fluroxypyr should be applied only when the weeds are actively growing. The application rate range of 0.12 to 0.5 lb a.e./acre is also recommended for the control of weeds or woody brush on pine plantations. Multiple applications may be made in a single season so long as the total application rate for the season does not exceed 0.5 lb a.e./acre.

Spray adjuvants are not recommended for Starane applications to crops. For Vista applications intended to control *Kochia*, a methylated seed oil surfactant is recommended. Adjuvants for Vista are not recommended for the control of other weeds.

For this risk assessment, the typical application rate for fluroxypyr is taken as 0.25 lb a.e./acre or about $1\frac{1}{3}$ oz formulation/acre, which is one-half of the maximum application rate. The full range of the labeled rates—i.e., 0.012-0.5 lb a.e./acre—is considered as the lower and upper bounds on application rates that might be used in Forest Service programs.

In addition to application rates, this risk assessment considers specific application volumes—i.e., the number of gallons of material, including fluroxypyr and the material (primarily water) in which the fluroxypyr is mixed. For this risk assessment, the extent to which these formulations are diluted prior to application primarily influences dermal and direct spray scenarios, both of which depend on the ‘field dilution’ (i.e., the pesticide

concentration in the applied spray). Because of the nature of these scenarios, risk estimates are directly proportional to the pesticide concentration in the field solution.

The information on the product label for Vista indicates that recommended application volumes range from at least 3 gallons/acre for aerial applications to at least 5 gallons/acre for ground broadcast applications. The range of application rates used for this risk assessment is from 3 gallons/acre (the minimum volume that might be considered for aerial applications) to 10 gallons/acre (twice the minimum value recommended for ground applications) with a central value of 5 gallons/acre (the minimum value for ground applications).

The application rates and dilution volumes selected for use in this risk assessment reflect plausible estimates. For specific program activities, the Forest Service may use the worksheets included with this report to refine the assessment of potential risks associated with program-specific application rates.

2.5. USE STATISTICS

Most Forest Service risk assessments try to characterize herbicide or pesticide uses in Forest Service programs relative to their use in agricultural applications. Generally, the information about Forest Service uses comes from Forest Service pesticide use reports (<http://www.fs.fed.us/foresthealth/pesticide/reports.shtml>), and information about agricultural uses comes from use statistics compiled by the U.S. Geologic Survey (http://ca.water.usgs.gov/pnsp/pesticide_use_maps/) and/or detailed pesticide use statistics compiled by the state of California (<http://www.calepa.ca.gov/>).

Apparently, fluroxypyr has not been used or at least not used extensively in Forest Service programs, since its use is not documented in the pesticide use reports. As illustrated in Figure 2, agricultural uses of fluroxypyr are predominant in the north central region of the United States, primarily in North Dakota, South Dakota, and Montana with lesser amounts in Minnesota, Wyoming, Idaho, Washington, and Oregon. The areas of major agricultural use correspond roughly to Forest Service Region 1 (consisting primarily of Minnesota and North Dakota) and Forest Service Region 2 (which includes South Dakota and Wyoming).

It is unclear, however, if the agricultural uses of fluroxypyr would parallel the locations of forestry applications. The Pacific Northwest Weed Management Handbook (covering Forest Service Region 6) notes that fluroxypyr offers excellent control of several weed species that occur in FS Region 6 including *Ceanothus* and *Arbutus* species and offers good control of *Arctostaphylos* species (Peachey et al. 2007). These species are widely distributed in the United States; consequently, uses outside of the Pacific Northwest seem plausible. Fluroxypyr has also been evaluated for the control of Scotch Broom (*Cytisus scoparius*) in the southeast (FS Region 8) (Macdonald et al. 1993) and has been proposed for use in noxious weed control by Forest Service Region 3 (Southwest) (USDA/FS 2003). Thus, it seems plausible that fluroxypyr could be used in many areas of the United States in Forest Service programs.

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

Although fluroxypyr is not a new herbicide, there is not much information in the open literature directly relevant to its effects on human health. Thus, this hazard identification is based primarily on toxicity studies submitted to the U.S. EPA Office of Pesticides in support of the registration for fluroxypyr.

The mechanism of action of fluroxypyr and other pyridine carboxylic acid herbicides is fairly well characterized in plants, but not in mammals. Although fluroxypyr is absorbed and excreted rapidly, the mechanism of excretion involves active uptake by the kidneys resulting in high concentrations of fluroxypyr relative to concentrations in other organs. As with other weak acid herbicides, the concentration of fluroxypyr in the kidneys is associated with kidney damage, which can lead to renal failure.

Kidney damage and general weight loss in experimental mammals are the most common effects associated with high levels of exposure to fluroxypyr. The kidney appears to be the major target organ for fluroxypyr. Weight loss is a rather general sign of toxicity often seen in animals with serious diseases, including kidney damage. Forest Service risk assessments always try to identify specific effects of concern, including neurotoxicity, effects on immune function, and effects on the endocrine system. For each of these endpoints, specialized tests are conducted to assess whether a chemical is likely to cause direct adverse effects; however, no such tests were conducted with fluroxypyr. On the other hand, the potential of a chemical to elicit these effects of concern may be inferred from observations of behavioral changes, changes in reproductive capacity, or damage to specific tissues in standard subchronic and chronic toxicity studies. Such studies suggest that exposure to fluroxypyr may be associated with neurological, immune, or endocrine effects; however, these effects, like weight loss, are most likely to be secondary to kidney damage, general toxicity, or oxidative stress. In other words, if one vital organ, like the kidney, is severely damaged, many other organs may be damaged as the animal sickens, and these kinds of secondary effects are not signs that the chemical, in this case, fluroxypyr, directly damages these organs.

The only formulations of fluroxypyr considered in this risk assessment contain fluroxypyr-MHE, the octanol ester of fluroxypyr, not fluroxypyr acid. For the most part, the distinction between fluroxypyr acid and fluroxypyr-MHE has no substantial impact on the current risk assessment, because fluroxypyr-MHE is rapidly metabolized to fluroxypyr acid. In terms of the potential for dermal absorption, however, the distinction between fluroxypyr acid and fluroxypyr-MHE is an important one. Although the available data do not provide dermal absorption rates for either fluroxypyr acid or fluroxypyr-MHE, structure-activity relationships suggest that fluroxypyr-MHE is likely to be absorbed across the skin much more rapidly than fluroxypyr acid will be. Confidence in this assertion is diminished, however, by studies with 2,4-D acid and 2,4-D esters which indicate that 2,4-D esters are absorbed to about the same extent as 2,4-D

acid and salts of 2,4-D acid. In the absence of direct information on the dermal absorption rates of fluroxypyr acid and fluroxypyr-MHE, this risk assessment uses the more conservative and protective assumption that fluroxypyr-MHE will be absorbed relatively rapidly in dermal exposures.

The EPA determined that dermal absorption is not a significant pathway for fluroxypyr, and, therefore, does not consider dermal routes of exposure in their human health risk assessments. The EPA approach is based on a subchronic dermal NOAEL of 1000 mg/kg bw/day for 28 days. Nonetheless, upon further examination, this study suggests that the subchronic dermal NOAEL is consistent with subchronic oral toxicity data and that dermal exposures should be considered. As discussed further in the risk characterization, dermal exposure levels for workers wearing contaminated gloves is the scenario of greatest concern in the human health risk assessment of fluroxypyr.

3.1.2. Mechanism of Action

Fluroxypyr is a pyridine carboxylic acid herbicide, like picloram and clopyralid (SERA 2003a; SERA 2004). While the general mechanism of toxicity of this class of herbicides to plants is reasonably characterized—i.e., mimicking of the auxin plant growth hormone—the mechanism of toxicity to mammals is not as well characterized.

As discussed further in the following subsection (Section 3.1.3. Pharmacokinetics and Metabolism), fluroxypyr is a weak acid. Like a number of other weak acid herbicides, fluroxypyr is excreted by the kidneys via active transport processes. As part of these processes, fluroxypyr is actively taken up by and concentrated in the kidneys, causing damage which can lead to renal failure (Section 3.1.5). Nevertheless, the mechanism by which weak acid herbicides, including fluroxypyr, damage the kidneys is not well characterized.

3.1.3. Pharmacokinetics and Metabolism

Pharmacokinetics concerns the behavior of chemicals in the body, including their absorption, distribution, alteration (metabolism), and elimination as well as the rates at which these processes occur. This section of the risk assessment addresses the pharmacokinetic processes involved in fluroxypyr exposure, including a general discussion about metabolism (Section 3.1.3.1), with a focus on the kinetics of absorption (Section 3.1.3.2) and excretion (Section 3.1.3.3). Absorption kinetics, particularly the kinetics of dermal absorption, are important to this risk assessment because many of the included exposure assessments (Section 3.2) involve dermal exposure. Rates of excretion are generally used in Forest Service risk assessment to evaluate the likely body burdens associated with repeated exposure.

In addition to the general consideration about how fluroxypyr behaves in the body, another important consideration is the behavior of fluroxypyr in the environment and the extent to which the metabolism of fluroxypyr in the environment must be considered quantitatively in the risk assessment. The consideration of environmental metabolites is discussed in Section 3.1.15.1.

3.1.3.1. General Considerations

Pharmacokinetic studies have been conducted with fluroxypyr acid in rats (Veenstra and Herman 1983), cows (Hawkins et al. 1985; Roberts et al. 1986), and goats (Huskin 1996; Yackovich et al. 1990), and with fluroxypyr-MHE in rats (Hawkins et al. 1981a; Domoradzke and Brzak 1996). Table 4 provides an overview of the available pharmacokinetic studies.

As noted in Section 2.2 and illustrated in Figure 1, fluroxypyr is structurally similar to several other auxin mimicking herbicides, like aminopyralid (SERA 2007c), clopyralid (SERA 2004), picloram (SERA 2003a), and triclopyr (SERA 2003b). All of these compounds as well as other auxin herbicides, like 2,4-D (SERA 2006), are weak acids. This class of compounds is typically well absorbed after oral exposure, rapidly concentrated in the kidney, and excreted via a well-characterized active transport mechanism. As discussed in the 2,4-D risk assessment (SERA 2006a), this mechanism of active transport involves active secretion of the acid by the proximal tubules of the kidney in a manner similar to the excretion of paraminohippuric acid (PAH). Since this active transport mechanism can become saturated, the pharmacokinetics of weak acids tend to exhibit dose-dependent patterns in which the acid concentrations in blood and/or tissues increases disproportionately as the dose increases beyond the point at which excretion is saturated.

Generally, the patterns observed in metabolism studies with fluroxypyr acid are consistent with those observed in studies with other weak acid herbicides. Fluroxypyr is absorbed rapidly and excreted primarily in the urine via the kidney. Although the mechanism of urinary excretion is not addressed specifically in the fluroxypyr literature, it seems likely that it involves active secretion via the proximal tubules of the kidney. In the available studies involving multiple doses of fluroxypyr (i.e., Veenstra and Herman 1983, Roberts et al. 1986, and Yackovich et al. 1990) there is no indication that excretion was saturated over the range of doses tested. In other words, tissue residues (e.g., in the kidney) do not increase disproportionately with increasing dose. These results are not inconsistent with a mechanism for excretion prone to saturation; instead, they indicate that the doses used in the studies were not sufficiently high to saturate the excretion mechanism.

Several of the weak acid herbicides—e.g., 2,4-D and triclopyr—are available in both acid and ester formulations. While formulations of fluroxypyr acid are available—e.g., triisopropyl amine formulations (Lym and Messersmith 1991)—the only formulations considered in the current risk assessment involve the 2-octanol ester of fluroxypyr. As indicated in Table 4, fluroxypyr-MHE metabolism was studied in rats after single doses (Domoradzke and Brzak 1996) and multiple doses (Hawkins et al. 1981a). These studies indicate that fluroxypyr-MHE is rapidly hydrolyzed to fluroxypyr acid and 1-methyl-1-heptanol (Figure 3). The rapid hydrolysis of esters of weak acids to the corresponding acid and alcohol is seen with several other weak acid herbicides, like 2,4-D (SERA 2006) and triclopyr (SERA 2003b). As discussed further in Section 3.2.3.4, hydrolysis of the ester moiety is also an important component in the environmental fate of fluroxypyr-MHE.

The only substantial difference between the kinetics of fluroxypyr acid and fluroxypyr-MHE involves the formation of metabolites. As noted in the metabolism study in rats with fluroxypyr acid, most of the administered dose is excreted as the fluroxypyr, without the formation of significant metabolites (Veenstra and Herman 1983). The pattern with fluroxypyr-MHE is quite different: there is extensive metabolism resulting in the formation of about 20-22 metabolites, with a substantial proportion of the administered dose excreted in expired air—indicating complete mineralization—and most of the remaining dose excreted as urinary metabolites (Domoradzke and Brzak 1996). In the ester study, however, only the 2-octanol portion of fluroxypyr-MHE was labeled. Thus, the extensive metabolism observed in the study by Domoradzke and Brzak (1996) reflects the rapid hydrolysis of the ester with the subsequent and virtually complete metabolism of 2-octanol.

3.1.3.2. Absorption

As discussed in the previous section, fluroxypyr and fluroxypyr-MHE appear to be rapidly and almost completely absorbed after oral administration (Veenstra and Herman 1983). This is a common pattern for many pesticides and is consistent with the general assumption used in this risk assessment that fluroxypyr will be completely absorbed after oral administration.

Complete absorption, however, is not a reasonable assumption for dermal exposure scenarios. Dermal absorption is important in the current risk assessment because most of the occupational exposure scenarios and many of the exposure scenarios for the general public involve the dermal route of exposure. For these exposure scenarios, dermal absorption is estimated and compared to an estimated acceptable level of oral exposure based on subchronic or chronic oral toxicity studies in animals (SERA 2007a). Thus, it is necessary to assess the consequences of dermal exposure relative to oral exposure and the extent to which fluroxypyr is likely to be absorbed from the surface of the skin.

Relatively little experimental data are available on the dermal absorption fluroxypyr or fluroxypyr-MHE. Hewitt et al. (2000a) assayed the *in vitro* dermal absorption of fluroxypyr acid as well as fluroxypyr-MHE in ethanol and an emulsifiable concentrate formulation of fluroxypyr-MHE using both human and rat skin preparations. The formulation of fluroxypyr-MHE is not identified in the Hewitt et al. (2000a) publication but the paper does specify that the formulation was obtained from Dow AgroSciences (Wantage, UK). All compounds were ring-labeled – i.e., the radioactivity reflects the fluroxypyr ring rather than the ester in fluroxypyr-MHE. Hewitt et al. (2000a) noted complete metabolism of fluroxypyr-MHE to fluroxypyr acid during absorption, with no fluroxypyr-MHE detected in receptor fluid – i.e., the fluid containing the material that had penetrated through the *in vitro* skin preparations. In a subsequent study, the metabolism was associated with skin carboxyesterases (Hewitt et al. 2000b). Over a 48-hour incubation period, 0.4 to 0.5% of radioactivity of the fluroxypyr-MHE was recovered in the receptor fluid of human skin preparations and 5.1% to 5.9% was recovered in the receptor fluid of rat skin preparations. The reverse pattern was noted

with fluroxypyr acid, with 3.3% recovered in the human skin preparations and 1.9% recovered in rat skin preparations.

In the absence of experimental data, Forest Service risk assessments generally adopt estimates of dermal absorption rates based on quantitative structure activity relationships (QSAR), as documented in SERA (2007a). Using these methods with the molecular weight and $K_{o/w}$ for fluroxypyr-MHE, the estimated first-order dermal absorption rates are approximately 0.0040 (0.0013-0.012) hour⁻¹. The calculation of these rates is detailed in Worksheet B06-Ester in the EXCEL workbook that accompanies this risk assessment. Corresponding calculations using the molecular weight and $K_{o/w}$ (0.0575) for fluroxypyr acid are given in Worksheet B06-Acid and yield estimates of the dermal absorption rate that are more than 10 times less than the estimated rates for the ester—i.e., 0.00059 (0.00016-0.0021) hour⁻¹.

Another set of exposure scenarios used in this risk assessment involves the assumption of zero-order absorption (i.e., the dermal absorption rate is constant over time). This type of assumption is reasonable when the skin is in constant contact with the amount or concentration of the pesticide and is fundamental to exposure scenarios that involve wearing contaminated gloves. This scenario assumes that the amount of pesticide saturating the inside of the gloves is greater than the degree of dermal absorption. When experimental data are not available to estimate a zero-order dermal absorption rate (i.e., typically referred to as a K_p in units of cm/hour), Forest Service risk assessments generally use a QSAR algorithm developed by the EPA (U.S. EPA 1992, 2007). This approach is discussed in further detail in SERA (2007a). As detailed in Worksheet B05-Ester of the EXCEL workbook which accompanies this risk assessment, the QSAR algorithm developed by the EPA results in an estimated zero-order dermal absorption rate of 0.038 (0.016-0.089) cm/hour. The corresponding K_p values for fluroxypyr acid are given in Worksheet B05-Acid: 0.0000067 (0.0000024-0.000019) cm/hour. As with the estimated absorption rates for first-order absorption, the estimated K_p values for fluroxypyr acid are much lower than those for fluroxypyr-MHE.

In the current fluroxypyr risk assessment, all dermal exposure scenarios involve acute exposure to fluroxypyr-MHE formulations. In the absence of any experimental studies, the higher QSAR estimates of the first-order and zero-order dermal absorption rates for fluroxypyr-MHE would be used in this current Forest Service risk assessment. However, as noted above, the study by Hewitt et al. (2000a) suggest that the absorption of fluroxypyr-MHE will range from about 0.4% (based on human skin preparations) to nearly 6% (based on human skin preparations) over a 48-hour period. Based on the QSAR estimates for the first-order dermal absorption rate of fluroxypyr-MHE, the expected proportion absorbed over a 48-hour period would be about 84% (54% to 98%):

$$1 - E^{-0.038(0.016 \text{ to } 0.089) \times 48} = 0.836 (0.536 \text{ to } 0.986).$$

Using the corresponding estimates for fluroxypyr acid, the expected proportion absorbed over a 48-hour period would be about 2.8% (0.7% to 9.5%):

$$1 - E^{-0.00059(0.00016 \text{ to } 0.0021) \times 48} = 0.0279 (0.00765 \text{ to } 0.0959).$$

Clearly, the estimated first-order dermal absorption rates based on fluroxypyr acid provide a much closer correspondence to the experimental observations by Hewitt et al. (2000a) – i.e., proportions of 0.004 to 0.059. In addition, the studies by Hewitt et al. (2000a,b) also provide a plausible biological rationale for using the estimates based on fluroxypyr acid rather than the estimates based on fluroxypyr-MHE – i.e., fluroxypyr-MHE is rapidly converted to fluroxypyr acid during the process of dermal absorption.

Lastly, it may be worth noting little difference has been noted in the first-order dermal absorption rates of 2,4-D acid and 2,4-D esters. As discussed in SERA (2006), Moody et al. (1990) found no substantial differences regarding the rates of dermal absorption of 2,4-D acid, salts, or esters. Moody et al. (1990) assayed the dermal absorption of several forms of 2,4-D in different vehicles, using human volunteers and experimental mammals. In some instances—i.e., the application of 2,4-D amine and 2,4-D esters to the forehead of human volunteers—the amine salt of 2,4-D was absorbed to a greater extent than the isooctyl ester of 2,4-D using either an acetone or formulation blank solvent.

Occasionally, dermal toxicity studies are used to assess the plausibility of dermal absorption rates based on QSAR. As discussed further in Section 3.1.12, this is not the case for fluroxypyr. Fluroxypyr is not very toxic by either dermal or oral routes of exposure. Moreover, the available dermal toxicity data consists solely of NOAELs that are consistent with the oral NOAELs over the entire range of the estimated dermal absorption rates.

For the current Forest Service risk assessment, the estimates of both the first-order and zero-order dermal absorption rates are based on the QSAR estimates for fluroxypyr acid rather than fluroxypyr-MHE. While this is not the most conservative approach that could be taken, this approach is consistent with the available experimental data on the absorption of fluroxypyr-MHE from the study by Hewitt et al. (2000a).

3.1.3.3. Excretion

Although excretion rates are not used directly in either the dose-response assessment or risk characterization, excretion half-lives can be used to infer the effect of longer-term exposures on body burden, based on the *plateau principle* (e.g., Goldstein et al. 1974). The concentration of the chemical in the body after a series of doses (X_{Inf}) over an infinite period of time can be estimated based on the body burden immediately after a single dose, X_0 , by the relationship:

$$\frac{X_{Inf}}{X_0} = \frac{1}{1 - e^{-kt^*}}$$

where t^* is the interval between dosing and k is the first-order excretion rate.

In the study with ^{14}C -fluroxypyr-MHE in rats, Domoradzke and Brzak (1996) report a plasma half-life of 18.2 hours and a urinary half-life of 6 hours. The shorter urinary half-

life, relative to the plasma half-life, was attributed to the extensive metabolism of fluroxypyr-MHE (Section 3.1.3.1) and the incorporation of ^{14}C -residues into the carbon pool. This supposition is plausible.

In terms of applying the plateau principle to estimating body burden, however, the most relevant half-life involves total body burden. The study by Domoradzke and Brzak (1996) noted that only 7% of the total administered radioactivity was recovered in the animals by 48 hours after dosing—i.e., 93% of the radioactivity was excreted. Assuming a first-order excretion, the proportion (P_t) of the originally administered compound remaining in the body after a given time (t) is:

$$P_t = e^{-k t}$$

where k is the first-order whole-body excretion rate in units of reciprocal time. Solving for k ,

$$k = \frac{\text{Ln}(P_t)}{t}$$

and using 0.07 as the amount remaining at 48 hours, the value of the apparent first-order excretion rate is about $0.0554 \text{ hours}^{-1}$, corresponding to a half-life of about 12.5 hours [$t_{1/2} = \ln(2)/k$]. Converting the excretion rate to days—i.e., $0.0552 \text{ hours}^{-1} \times 24 \text{ hours/day}$ —the apparent excretion rate is about 1.32 days^{-1} , and the estimated plateau in the body burden after daily doses would be about 1.4 [$1 \div (1 - e^{-1.32}) = 1.36$].

The longer-term dietary exposure study in dairy cows by Roberts et al. (1986) may be used to assess the accuracy of the 1.4 estimate. In this study, residue levels in the milk of dairy cows were measured over a 28 day period of exposure to fluroxypyr in the diet. In the high dose group, the residue in milk after a single dose was 0.07 ppm and the residue on Day 28 was 0.25 ppm. This ratio is a factor of about 3.5, which is reasonably close to the 1.4 estimate based on the plateau principal. Furthermore, the modest difference probably reflects differences in total body burden versus concentrations excreted in milk.

The 1.4 estimate of the relative body burden (i.e., chronic to acute ratio) may also be assessed from the study by Hawkins et al. (1981) in which rats were administered fluroxypyr-MHE by gavage over a seven day period. No substantial differences are apparent in the peak plasma concentrations of fluroxypyr-MHE after a single dose (a peak of $24.7 \mu\text{g/mL}$) and the seventh dose (a peak of $24.9 \mu\text{g/mL}$).

Thus, based on the plateau principal as well as the studies by Roberts et al. (1986) and Hawkins et al. (1981), there is no basis for anticipating that fluroxypyr will accumulate in tissues over prolonged periods of exposure. As discussed further in Section 3.3, the lack of accumulation is consistent with the lack of a detectable dose-duration relationship in the toxicity of fluroxypyr.

3.1.4. Acute Oral Toxicity

The acute oral toxicity of fluroxypyr is addressed in standard acute studies: one on fluroxypyr acid (Lockwood et al. 1975), one on fluroxypyr-MHE (Cosse et al. 1992a), and one oral neurotoxicity study (Doczi et al. 1999). The neurotoxicity study is discussed further in Section 3.1.6 (Effects on the Nervous System).

The standard acute oral toxicity studies on fluroxypyr determined LD₅₀ values—i.e., the dose of the test material that is estimated to be lethal to 50% of the animals. LD₅₀ values are not used directly to derive toxicity values as part of the dose-response assessment in Forest Service risk assessments. Differences in LD₅₀ values, however, are useful measures of relative toxicity. Relative potency is particularly important for fluroxypyr acid and fluroxypyr-MHE. As discussed in Section 3.1.3.1, both fluroxypyr acid and fluroxypyr-MHE are rapidly absorbed and excreted; furthermore, the metabolism study by Domoradzke and Brzak (1996) indicates that the ester is rapidly cleaved from the fluroxypyr acid moiety. Thus, under the assumption that fluroxypyr acid is the agent of concern, the acute oral toxicity of fluroxypyr acid and fluroxypyr-MHE are expected to be fundamentally equivalent.

As summarized in Table 5, this toxicological equivalence appears to be the case with fluroxypyr. Based on the acute toxicity study by Lockwood et al. (1975), the acute oral LD₅₀ value for fluroxypyr acid in rats is 2405 mg/kg bw. The corresponding LD₅₀ for fluroxypyr-MHE is about 3450 mg/kg bw, the average value of the LD₅₀ in male (3738 mg/kg bw) and female (3162 mg/kg bw) rats. As indicated in Table 5, the relative toxicity of the acid with respect to the ester is about 1.43 [3450 mg ester/kg bw ÷ 2405 mg acid/kg bw]. On the basis of the comparison, U.S. EPA/OPP (2007f, p. 9) notes: *Based on the available acute toxicity data it appears that the fluroxypyr 1-methylheptyl ester (1-MHE) is less acutely toxic than the acid by the oral route of exposure.* Correcting for differences in the molecular weights of the acid and ester—i.e., a conversion factor of 0.694 from Table 3—the adjusted relative potency is about 0.992 [1.43 x 0.694]. Using either the mass ratio or the molar ratio results in a fundamentally equivalent toxicity for fluroxypyr acid and fluroxypyr ester.

Table 5 also summarizes acute toxicity values from acid and ester forms of both 2,4-D and triclopyr, other weak acid herbicides available as ester formulations. Similar to the case with fluroxypyr, the relative toxicities of the acid and ester forms of these other herbicides are also fundamentally equivalent. Thus, consistent with the approach taken in the EPA human health risk assessment of fluroxypyr (U.S. EPA//OPP 2003a, 2006a, 2007a,d,f), fluroxypyr is the toxic agent of concern for assessing risks associated with the use of fluroxypyr-MHE. This is an extremely important point in the current risk assessment. As detailed further in the following subsection, all of the chronic studies, particularly the study that serves as the basis for the RfD (Section 3.3) are based on exposures to fluroxypyr acid rather than fluroxypyr-MHE.

3.1.5. Subchronic or Chronic Systemic Toxic Effects

As discussed in SERA (2007a, Section 3.1.5), *subchronic* and *chronic* are somewhat general terms that refer to studies involving repeated dosing. The distinction between subchronic and chronic studies, as these terms are commonly used in risk assessment, is somewhat vague and inconsistent. For rodents (i.e., mice and rats), chronic studies generally involve exposures over the lifetime, or at least a substantial proportion of the lifetime. Typical chronic studies with rodents involve 18-month exposure durations for mice and 2-years exposure durations for rats. Since the lifespan of dogs is much longer than that of rodents, lifetime exposure studies are generally not conducted with dogs. Instead, *chronic studies* with dogs generally involve repeated dosing for only about 1 year. By convention, the term *subchronic* typically refers 90-day studies with mammals. In keeping with this convention, there are several subchronic studies involving rodent exposure to fluroxypyr. The 28-day canine exposure study (Ehard et al. 1983) was designed as a range finding study for the subsequent chronic toxicity study (Kinkel et al. 1984).

Repeated dose studies are sometimes designed to detect toxicities that are specific in nature, like reproductive toxicity or neurotoxicity, which are discussed in detail in subsequent sections of the hazard identification. The current subsection focuses on toxicity studies designed to detect more general signs of systemic toxicity and to quantify no-observable-adverse-effect levels (NOAELs) for the identified endpoints.

The available subchronic and chronic studies on fluroxypyr are summarized in Table 6 and presented in greater detail in Appendix 2. Table 6, which is organized by species and duration, provides the NOAEL and LOAEL values as well as the key endpoints on which they are based. Furthermore, Table 6 includes data from the standard subchronic studies (\approx 90 days), chronic studies (1-2 years), developmental studies (\approx 10 to 14 days), and two multigeneration studies (Koeter et al. 1984; Vedula et al. 1996). The multigeneration studies do not specify the precise duration and are designated simply as *Multigen* in the duration column of Table 6. As discussed further in Section 3.1.9.2, multigeneration studies involve complex dosing schedules for parents and offspring, but are generally regarded as subchronic. The inconsistent results from the studies summarized in Table 6 are to be expected given the number of relatively complex studies conducted at different times and by different investigators.

The most obvious inconsistency in Table 6 concerns the subchronic study in mice by Perry et al. (1984) in which adverse effects are reported at an estimated dose of 2.7 mg/kg bw/day. As summarized in Appendix 2, the study involved exposing groups of 10 male and 10 female mice to dietary concentrations of 0 (control), 20, 80, and 320 ppm (mg fluroxypyr/kg diet). The DER for this study does not specify rates of food consumption but does specify that there were no observed changes in food consumption or body weight, relative to controls. The dose of 2.7 mg/kg bw for the 20 ppm dose group is based on food consumption values from the subchronic study in mice by Shirasu et al. (1988), which also noted no significant differences in food consumption or body weights between control and treated mice.

The inconsistency of the Perry et al. (1984) study may be more clearly expressed in terms of dietary concentrations. Perry et al. (1984) noted adverse effects (i.e., increased testes and spleen weights in male mice and ovarian lesions in female mice) at dietary concentrations of 20, 80, and 320 ppm over a 91-day period of exposure. Over the same period of exposure, the subchronic mouse study by Shirasu et al. (1988) noted no adverse effects at dietary concentrations: 200, 500, 2500, or 10,000 ppm. Thus, Shirasu et al. (1988) report a NOAEL at dietary concentrations that are up to 500 times greater than the 20 ppm LOAEL reported by Perry et al. (1984).

Furthermore, in the chronic mouse feeding study by Cosse et al. (1993), doses of up to 300 mg/kg bw/day caused no adverse effects. Notably, the chronic study by Cosse et al. (1993) is also a dietary exposure study; however, the dietary concentration was continuously adjusted during the course of the study to keep the dose, expressed as mg/kg bw/day, constant. The NOAEL of 300 mg/kg bw/day is more than a 100 times greater than the estimated dose of 2.7 mg/kg bw/day from the study by the Perry et al. (1984) [$300 \text{ mg/kg bw/day} \div 2.7 \text{ mg/kg bw/day} = 111.11\dots$].

U.S. EPA/OPP bases the chronic RfD for fluroxypyr on the NOAEL of 100 mg/kg bw/day from the chronic rat feeding study by Quest and McGuirk (1995), which suggests an apparent lack of regard for the Perry et al. (1984) study. The U.S. EPA/OPP risk assessments (i.e., U.S. EPA/OPP 1998a,b, 2003a, 2006a,b,c, 2007c,d,e,f) do not discuss or cite the Perry et al. (1984) study. Nonetheless, based on the U.S. EPA/OPP DER for the Perry study, it is clear that U.S. EPA/OPP was aware of and carefully reviewed the study. This is not an unusual circumstance. The EPA process of deriving RfDs is highly deliberative and not often discussed in EPA risk assessments.

It is not appropriate for the current Forest Service risk assessment to speculate about the deliberative processes of the EPA; however it is important to provide a rationale for not quantitatively considering the LOAEL in the Perry et al. (1984) study. First, a distinction must be made between matched and historical controls. Matched controls designate a group of animals that are assayed but not dosed along with the dose groups. Perry et al. (1984) used relatively small groups of animals (i.e., 10 of each sex in both the matched control groups and each of the treated groups). As discussed in the DER, the study authors suggest that the observed increases in testes and spleen weights among treated males were perhaps due to abnormally low spleen and testes weights in the control group males. Nevertheless, the EPA reviewer of this study indicates that historical control data were not provided. The only effect observed in female mice was an increase in ovarian lesions, including cystic endometrial hyperplasia and ovarian cysts. Although the number of animals in each group is relatively small, the incidence of ovarian lesions is dose-related. Moreover, the incidence of lesions in the high dose group is significantly greater than that in the control group, based on the Fisher Exact test ($p=0.035$). Again, the observed responses may have been random in nature; however, the organ pathology (i.e., spleen and testes in males and ovaries in females) seems to undermine that argument.

A more compelling basis for arguing that the adverse effects reported by Perry et al. (1984) may not be attributable to fluroxypyr involves the weight of evidence. As summarized in Table 6, the fluroxypyr data include 10 subchronic or chronic studies: three mouse studies, five rat studies and two dog studies. Jonker et al. (1987) report pathological changes in the testes of rats; however, the effects were observed only at very high doses (i.e., >1000 mg/kg bw) and in animals that evidenced extreme kidney damage. Similarly, Grandjean et al. (1992) report decreased testes weights in rats, but, again, the effect was observed at a dose of 1000 mg/kg bw/day. Ovarian lesions are not reported in any of the other subchronic or chronic studies; furthermore, these lesions are also not reported in any of the developmental or reproduction studies. Thus, the other longer-term toxicity studies on fluroxypyr do not support the argument that the adverse effects noted by Perry et al. (1984) at low doses were likely due to fluroxypyr.

The results of other studies summarized in Table 6 are reasonably consistent. The most common effects associated with longer-term exposure to fluroxypyr involve a decrease in body weight (a very general adverse effect caused by many chemicals) and kidney damage. Kidney damage is commonly seen with many weak acid herbicides, like 2,4-D (SERA 2006), clopyralid (SERA 2004), picloram (SERA 2003a), and triclopyr (SERA 2003b). As discussed in Section 3.1.3.1, the toxicity of many weak acids to the kidney is probably associated with active transport mechanisms. Although weak acids are rapidly excreted by the kidney, also via active transport mechanisms, the transiently high concentrations of weak acids in the kidney are often associated with kidney damage.

Apart from the results of the Perry et al. (1984) study, other inconsistencies in the available subchronic and chronic studies are relatively minor. Excluding the reproductive and developmental studies, which are discussed further in Section 3.1.9, reported NOAELs range from 50 to greater than 1000 mg/kg bw/day, and reported LOAELs range from 150 to 1000 mg/kg bw/day. Again, this type of variability is not uncommon for pesticides for which numerous studies are available. It is notable that the NOAEL of 100 mg/kg bw/day selected by U.S. EPA to derive the RfD is lower than any reported LOAEL.

Another notable characteristic of the available fluroxypyr subchronic and chronic mammalian studies pertains to the relative sensitivity of dogs. As discussed in the risk assessments of 2,4-D (SERA 2006a) and triclopyr (SERA 2003b), dogs have an impaired capacity to excrete weak acids; accordingly, they are sometimes much more sensitive than other mammals to weak acids. On the other hand, the degree of dog sensitivity to some weak acid herbicides, like aminopyralid (SERA 2007c), is no greater than that of other mammals. Fluroxypyr appears to fall in the latter category. The 28-day NOAEL for dogs is 50 mg/kg bw/day (Ehard et al. 1983), only modestly below the lowest subchronic NOAEL of 80 mg/kg bw/day in rats. The chronic dog NOAEL of 150 mg/kg bw/day (Kinkel et al. 1984) is actually somewhat higher than the 100 mg/kg bw/day in rats (Quast and McGuirk 1995).

Finally, there is no consistent indication of a dose-duration relationship for fluroxypyr. In mice, the 91-day NOAEL of 1342 mg/kg bw/day (Shirasu et al. 1988) is somewhat

higher than the chronic LOAEL of 1000 mg/kg day, offering the suggestion (albeit weak) of a dose-duration relationship. Nonetheless, the greatest number of available studies are rat studies, and the relatively short-term LOAELs of 250-750 mg/kg bw/day from the reproduction studies (Schroeder 1994a,b; Bottomley et al. 1983) are actually less than the subchronic LOAELs of 750-1000 mg/kg bw/day (Jonker et al. 1987; Grandjean et al. 1992) and are in the range of the chronic LOAEL of 500 mg/kg bw/day (Quast and McGuirk 1995). As discussed in Section 3.1.3.3, the lack of a clear dose-duration relationship for fluroxypyr exposure is consistent with its rapid excretion and consequent lack of substantial accumulation in the body from longer-term exposures.

3.1.6. Effects on Nervous System

As discussed in Durkin and Diamond (2002), a neurotoxicant is a chemical that disrupts the function of nerves, either by interacting with nerves directly or by interacting with supporting cells in the nervous system. This definition of a neurotoxicant distinguishes agents that act directly on the nervous system (direct neurotoxicants) from those agents that might produce neurological effects secondary to other forms of toxicity (indirect neurotoxicants). Virtually any chemical will cause signs of neurotoxicity in severely poisoned animals and can be classified as an indirect neurotoxicant. The data on fluroxypyr indicate indirect effects that might be associated with neurotoxicity; however, there is no indication of specific neurotoxicity.

Several acute and subchronic fluroxypyr studies report adverse effects consistent with signs of indirect neurotoxicity (e.g., salivation, lacrimation, incoordination, weakness in the extremities) (Bottomley et al. 1983; Cosse et al. 1992a; Ehard et al. 1983; Schroeder 1994b; Tesh et al. 1984). In all cases, these effects were observed in severely poisoned animals that exhibited a number of other signs of toxicity, including death. All of these studies were evaluated by U.S. EPA/OPP (2007f) which concluded that:

There are no neurotoxicity concerns from the acute and subchronic neurotoxicity studies, and the weight of the evidence indicates a lack of concern for developmental neurotoxicity.

- U.S. EPA/OPP (2007f, p. 9)

The open literature includes one study (i.e., Doczi et al. 1999) concerning the potential neurological effects of fluroxypyr, and this study is not reviewed in the EPA human health risk assessments (U.S. EPA/OPP 1998a,b, 2003a, 2006a,b,c, 2007c,d,e,f). Doczi et al. (1999) examined the effect of fluroxypyr on seizure susceptibility induced by 4-aminopyridine. Aminopyridine is a compound used to induce seizures in experimental mammals in order to evaluate drugs that might be useful in treating diseases like epilepsy (e.g., Watts and Jefferys 1993). Oral exposure to fluroxypyr in drinking water or food significantly reduced the frequency of epileptic discharges in the brain; however, the effect was accompanied by an increase in the duration of discharges. As discussed by Doczi et al. (1999), the mechanism and significance of this effect is not clear. In terms of the current Forest Service risk assessment, the most relevant information from the study is that there was no indication that fluroxypyr crossed the blood-brain barrier. Thus, this

study does not contradict the EPA assessment that there is no basis for asserting that fluroxypyr will cause direct neurotoxic effects.

3.1.7. Effects on Immune System

There are various methods for assessing the effects of chemical exposure on immune responses, including assays of antibody-antigen reactions, changes in the activity of specific types of lymphoid cells, and assessments of changes in the susceptibility of exposed animals to resist infection from pathogens or proliferation of tumor cells. With the exception of skin sensitization studies (Section 3.1.11.2), specific studies regarding the effects of pesticides on immune function are not required for pesticide registration.

Although specific studies regarding immunological effects from exposure to fluroxypyr are not available, limited information is available from the standard subchronic and chronic studies (Section 3.1.5). Typical subchronic or chronic animal bioassays conduct morphological assessments of the major lymphoid tissues, including bone marrow, major lymph nodes, spleen and thymus (organ weights are sometimes measured as well), and blood leukocyte counts. These assessments can detect signs of inflammation or injury indicative of a direct toxic effect of the chemical on the lymphoid tissue. Changes in morphology/cellularity of lymphoid tissue and blood, indicative of a possible immune system stimulation or suppression, can also be detected.

There is very little indication that fluroxypyr causes effects associated with an impairment of immune function. As discussed in Section 3.1.5, Perry et al. (1984) report an increase in spleen weights in a subchronic toxicity study in rats but this effect has not been confirmed or noted in other subchronic studies conducted at much higher doses or in any of the chronic toxicity studies, all of which were also conducted at much higher doses (Table 6). The only other report concerning the potential effect of fluroxypyr on immune function is Jonker et al. (1987), which notes pathological changes in the thymus accompanied by lymphocyte necrosis and lymphoid depletion. These effects were apparent only at very high doses (≥ 750 mg/kg bw/day) in severely intoxicated animals. The specific pathological changes are characterized as “*stress involution.*” This type of pathological lesion is often observed in animals in very poor health due either to chemical stress or aging (Jonker et al. 1987; Beers 2006). Thus, as with potential neurological effects, the effects noted by Jonker et al. (1987) are consistent with an effect on immune function but do not necessarily reflect a direct immunotoxic mechanism.

In terms of the current risk assessment, any effect on immune function, direct or otherwise, is less relevant. Nonetheless, the toxicity values selected for risk characterization (Section 3.3) are well below the doses of 750 mg/kg bw/day from the Jonker et al. (1987) study.

3.1.8. Effects on Endocrine System

Assessment of the direct effects of chemicals on endocrine function are most often based on mechanistic studies on estrogen, androgen, or thyroid hormone systems (i.e., assessments on hormone availability, hormone receptor binding, or post-receptor processing). U.S. EPA has not yet adopted a specific set of protocols for assessing the

potential for endocrine disruption. As noted in the most recent EPA human health risk assessment for fluroxypyr:

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, fluroxypyr may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

- U.S. EPA/OPP 2007f, p. 12

Inferences concerning the potential for endocrine disruption can sometimes be made from responses seen in standard toxicity tests—i.e., changes in the structure of major endocrine glands (i.e., the adrenal, hypothalamus, pancreas, parathyroid, pituitary, thyroid, ovary, and testis) or changes in growth rates. As with effects on the nervous system and immune function, however, effects on organs associated with endocrine function may be secondary to other toxic effects, like kidney damage. Thus, in the absence of information on specific endocrine mechanisms, pathological changes in endocrine tissues do not necessarily indicate a direct effect on endocrine function.

As noted in Table 6, several longer-term toxicity studies report decreases in body weight (Cosse et al. 1993; Grandjean et al. 1992; Schroeder 1994a,b, Vedula et al. 1996). These effects are commonly observed in toxicity studies and may not be directly attributable to effects on the endocrine system. As discussed in Section 3.1.5, Perry et al. (1984) report ovarian lesions and increased testes weights at very low subchronic exposure levels; however, these effects are not confirmed in other subchronic studies or chronic studies involving much higher doses. Grandjean et al. (1992) reports a decrease in testes weights, which is more likely than increased testes weight to indicate an adverse effect of exposure. The magnitude of the decrease in testes weight (i.e., 4.3% less than controls) was slight and was also accompanied by a decrease in body weight of about the same magnitude (i.e., 5% less than controls). Jonker et al. (1987) indicates pathological changes in the testes, but only at very high doses (1000 and 1500 mg/kg bw) and only in rats with severe kidney damage. Decreases in adrenal and thyroid weights were noted in female rats at doses of 100 and 500 mg/kg bw/day; however, this effect was not accompanied by histological changes. Fluroxypyr doses of 1000 and 1500 mg/kg bw/day caused histopathological changes (hypertrophy and vacuolation) in the adrenals of male rats and female rats in the subchronic study by Jonker et al. (1987). This effect was, however, reversible over a 24-week recovery period. Jonker et al. (1987) speculate that the changes in adrenal tissue may be secondary to an effect of fluroxypyr on electrolyte balance. While all of these changes noted in individual studies suggest a potential for an impact on endocrine function, the major effect observed consistently in the majority of the subchronic and chronic studies involves kidney pathology, and not a direct or consistent impact on organs directly associated with endocrine function.

Disruption of the endocrine system during development may give rise to effects on the reproductive system, and the effects may be expressed only after maturation. Consequently, multigeneration exposures are recommended for toxicological assessment of suspected endocrine disruptors. Since the endocrine system is also important in

normal growth and development, changes in growth can be indicative of effects on the endocrine system. As discussed in Section 3.1.9.2, adverse effects on the reproductive system are not indicated in either of the two available multigeneration studies.

3.1.9. Reproductive and Developmental Effects

3.1.9.1. Developmental Studies

Developmental studies are used to assess whether a compound has the potential to cause birth defects—also referred to as teratogenic effects—as well as other effects during development or immediately after birth. These studies typically entail gavage administration to pregnant rats or rabbits on specific days of gestation. Teratology assays as well as studies on reproductive function (Section 3.1.9.2) are generally required for the registration of pesticides. Very specific protocols for developmental studies are established by U.S. EPA/OPPTS and are available at http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized.

As summarized in Table 6 and detailed further in Appendix 2, six developmental studies involving gavage dosing were submitted to the EPA in support of the registration of fluroxypyr: three studies in rabbits (Liberacki et al. 1996a,b; Tesh et al. 1984) and three studies in rats (Schroeder 1994a,b; Bottomley et al. 1983). For both rats and rabbits, studies are available on fluroxypyr-MHE (Liberacki et al. 1996a,b; Schroeder 1994a,b) as well as fluroxypyr acid (Bottomley et al. 1983; Tesh et al. 1984).

None of the available studies report the occurrence of fetal malformations. The only suggestion of a potential developmental effect is from the Liberacki et al. (1996a) study in which the incidence of abortions was increased in the high dose (1000 mg/kg bw/day) group. Specifically, 3 of 20 dams aborted in the high dose group compared with 0 of 20 dams in the control group. While the increase in the incidence of abortions, relative to the matched control, is not statistically significant, using the Fisher Exact test ($p=0.1154$), this response was considered to be biologically significant, based on historical controls. The NOAEL for developmental toxicity was 500 mg fluroxypyr-MHE/kg or about 346 mg a.e./kg bw. As discussed further in Section 3.3 (Dose-Response Assessment), the developmental LOAEL is substantially above the dose of 100 mg/kg bw/day used to derive the RfD.

3.1.9.2. Reproduction Studies

Reproduction studies involve exposing one or more generations of the test animal to a chemical compound. Generally, the experimental method involves dosing the parental (P or F₀) generation (i.e., the male and female animals used at the start of the study) to the test substance prior to mating, during mating, after mating, and through weaning of the offspring (F₁). In a 2-generation reproduction study, this procedure is repeated with male and female offspring from the F₁ generation to produce another set of offspring (F₂). During these types of studies, standard observations for gross signs of toxicity are made. Additional observations often include the length of the estrous cycle, assays on sperm and other reproductive tissue, and number, viability, and growth of the offspring.

As summarized in Table 6, two multigeneration studies were submitted to the EPA in support of the registration of fluroxypyr (Koeter et al. 1984; Vedula et al. 1996). Both studies involve dietary exposures to fluroxypyr acid. The initial study by Koeter et al. (1984) is classified by U.S. EPA/OPP as *Supplemental*, rather than *Acceptable*, because of insufficient histopathology. The subsequent study by Vedula et al. (1996) addresses this deficiency and is classified by U.S. EPA/OPP as *Acceptable*. As with the chronic study by Cosse et al. (1993), the dietary studies by Koeter et al. (1984) and Vedula et al. (1996) involve adjustments to the dietary concentrations of fluroxypyr over the course of the study in order to maintain a constant dose level in terms of mg/kg bw/day. At the highest dose—i.e., 500 mg/kg bw/day—a reduced fertility index was apparent; however, the EPA did not consider the effect to be toxicologically significant because it appeared to be secondary to maternal toxicity. In the Vedula et al. (1996) study, higher doses of fluroxypyr—i.e., 1000 mg/kg bw/day for females and 750 mg/kg bw/day for males—resulted in signs of systemic toxicity (Section 3.1.5) but no effects on reproductive capacity.

3.1.10. Carcinogenicity and Mutagenicity

In terms of a quantitative significance to the human health risk assessment, carcinogenicity is an issue only if the data are adequate to support the derivation of a cancer potency factor. The derivation of a cancer potency factor is typically based on a dose-related increase in malignant tumors from a chronic toxicity study that encompasses a significant portion of the test animals' lifespan. As discussed in Section 3.1.5, cancer bioassays are typically limited to chronic studies in rodents.

Four lifespan bioassays for carcinogenicity are available on fluroxypyr: two 18-month studies in mice (Cosse et al. 1993; Perry et al. 1984) and two 24-month studies in rats (Quast and McGuirk 1995; Til et al. 1985). In terms of assessing potential carcinogenic effects, the earlier studies (Perry et al. 1984; Til et al. 1985) are of relatively little use for assessing carcinogenicity. These studies are classified by U.S. EPA/OPP as *Supplemental* because the highest dose was not associated with an adverse effect, because histopathology was limited, and because reporting details were insufficient. The two later studies (Cosse et al. 1993; Quast and McGuirk 1995) are classified as *Acceptable*, because both studies can be used to determine a clear LOAEL—i.e., the maximum tolerated dose was identified—and because both studies provide complete histopathology and adequate reporting. As detailed in Appendix 2, none of the cancer bioassays report any indication of carcinogenic activity. The lack of carcinogenic activity is consistent with several *in vitro* screening assays for mutagenicity using fluroxypyr-MHE (Lawlor 1995; Lick et al. 1996; Linscombe and Engle 1996; Linscombe and Ormand 1996; Linscombe 1998). Based on the lack of activity the *in vivo* assays for carcinogenicity and *in vitro* assays for mutagenicity, U.S. EPA/OPP (2007f, p. 4) reports that fluroxypyr is “not likely to be carcinogenic.”

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

3.1.11.1. Skin Irritation

The fluroxypyr literature includes two standard skin irritation assays, one using fluroxypyr acid (Lockwood et al. 1975) and the other using fluroxypyr-MHE (Cosse et al. 1992d). Neither study reports any indication of skin irritation; accordingly, fluroxypyr acid and fluroxypyr-MHE are classified as Category IV—the lowest categorization of irritancy in the ranking scheme used by U.S. EPA (U.S. EPA/OPP 2007f, p. 26).

3.1.11.2. Skin Sensitization

There are two standard skin sensitization studies in which guinea pigs are exposed to fluroxypyr (Berdasco 1990; Cosse and Berdasco 1992). Neither study notes any indication of skin sensitization.

3.1.11.3. Ocular Effects

Only one study is available on the potential of fluroxypyr-MHE to cause eye irritation (Cosse et al. 1992c). This study involved the instillation of a 25.6% solution of fluroxypyr-MHE into the right eye of a rabbit, with the left eye serving as a control. Notably the fluroxypyr-MHE concentration is about the same as in Vista Specialty Herbicide (26.2%) but less than that in the newer Vista XRT formulation (45.52%). Observed effects included reddening of the eye as well as corneal opacity, which was reversible in 14 days. Based on the effects on the cornea, the DER for this study classifies fluroxypyr-MHE as Category II, the second most hazardous category in the ranking scheme employed by U.S. EPA.

The Cosse et al.(1992c) study is designated by the EPA as MRID 44080332. The MRID (Master Record Identification) number is an EPA designation to uniquely identify studies submitted by registrants. The most recent human health risk assessment from the Office of Pesticide Programs (U.S. EPA/OPP 2007f) cites MRID 40354007. The study associated with MRID 40354007 was not included in the list of studies obtained from U.S. EPA/OPP under the Freedom of Information Act during the preparation of this Forest Service risk assessment. Based on the summary in U.S. EPA/OPP (2007f, p. 26), fluroxypyr is classified fluroxypyr acid as a Category III eye irritant—i.e., only mildly irritating to the eyes with no corneal opacity.

Because the current risk assessment addressed the use of fluroxypyr-MHE formulations, the Category II designation for fluroxypyr-MHE from the study by Cosse et al. (1992c) is used in the current risk assessment, and the potential for eye irritation is discussed further in Section 3.4.2 (Risk Characterization for Workers).

3.1.12. Systemic Toxic Effects from Dermal Exposure

The potential for systemic effects from dermal exposure to fluroxypyr is important in the current risk assessment because many of the exposure scenarios for workers and members of the general public are based on dermal exposure. Nonetheless, U.S. EPA/OPP (2007b) dismisses the hazards that may be associated with dermal exposure:

A dermal endpoint was not selected for fluroxypyr because no toxicity was observed at the limit dose of 1,000 mg/kg/day in the dermal toxicity study in rabbits, and there was no concern for developmental toxicity in rats or rabbits. Therefore, the occupational risk assessment was based on inhalation exposure only.

- U.S. EPA/OPP 2007f, p. 22

Notably, the limit dose of 1000 mg/kg bw/day refers to the subchronic dermal toxicity study by Cosse et al. (1991a) in which rabbits were treated with 100, 300, or 1000 mg/kg bw/day fluroxypyr-MHE 6 hours/day for 28 days with no apparent signs of toxicity. This dose regimen corresponds to acid equivalent doses of about 69.4, 208, or 694 mg a.e./kg bw/day. Single dose studies with fluroxypyr-MHE also noted no signs of toxicity at a dose of 2000 mg/kg bw or 1,388 mg a.e./kg bw. [As indicated in Table 2, the conversion factor for fluroxypyr-MHE to fluroxypyr acid is 0.694.]

Although none of the above information suggests that fluroxypyr is highly toxic after dermal administration, the potential hazards of dermal exposure to fluroxypyr should not be dismissed. As discussed in Section 3.1.5, fluroxypyr is not highly toxic after oral administration, and the longer term NOAEL of 100 mg/kg bw/day is the basis for the EPA RfD (Section 3.3).

As discussed in Section 3.1.3.2, the estimated first-order dermal absorption rate for fluroxypyr acid is 0.00059 (0.00016-0.0021) hour⁻¹. Based on standard first-order absorption kinetics, the proportion of the dose (P) that is absorbed by time t is:

$$P=1-e^{-k t}$$

Thus, over the course of a 6-hour exposure, the proportion of applied dose estimated to be absorbed is about 0.00353 (0.000960 to 0.0125). At the maximum dose of 1000 mg/kg bw/day used in subchronic dermal study by Cosse et al. (1991a), the maximum absorbed dose in units of acid equivalents and based on the upper bound of the estimated proportion for fluroxypyr-MHE (≈ 0.0125) would be about 9 mg/kg bw/day [1000 mg ester/kg bw/day $\times 0.0125 \times 0.694 \approx 8.675$ mg a.e./kg bw/day]. Thus, assuming 100% oral absorption and considering the well-documented oral NOAEL of 100 mg a.e./kg bw/day, the absorbed dermal dose of about 9 mg a.e./kg bw/day would be expected to be a dermal NOAEL.

In other words, fluroxypyr is not highly toxic after dermal exposure, but it is also not highly toxic after oral exposure. The dermal NOAEL is consistent with the oral NOAEL, and the dermal NOAEL should not be used as a basis for dismissing the potential hazards from dermal exposure. Accordingly, the current Forest Service risk assessment considers dermal exposure a route of potential concern.

3.1.13. Inhalation Exposure

As summarized in Appendix 2, the acute inhalation toxicity of fluroxypyr is addressed in three studies: one study on the acid (Appelman 1979) and two studies on fluroxypyr-

MHE (Jones 1983; Beekman and Yano 1993). No studies identify an LC₅₀ for inhalation exposure—i.e., all LC₅₀ values cited by the EPA are expressed as greater than a particular concentration. Nonetheless, the Appelman (1997) study involves a relatively low concentration (269 mg/m³), and fluroxypyr acid is classified for inhalation exposure as Category II—the second most hazardous category used in the EPA classification system.

As noted in the previous section, the EPA identifies inhalation exposures as a route of concern. The limited nature of the inhalation toxicity values—i.e., only >LC₅₀ estimates—is irrelevant to the EPA risk assessments on fluroxypyr because the Agency elected to use the oral toxicity value of 100 mg/kg bw/day with the assumption of 100% inhalation absorption. This is a common and sensible practice for most pesticides because the inhalation toxicity data on most pesticides is very limited, as is the case with fluroxypyr. Using the much more extensive oral toxicity data with a conservative estimate of absorption is likely to be protective. As with all Forest Service risk assessments, inhalation exposure is taken into consideration in estimating worker exposure (Section 3.2.2.1), and, in keeping with the EPA risk assessments, the toxicity value is based on oral toxicity data.

3.1.14. Inerts and Adjuvants

3.1.14.1. Inerts

U.S. EPA is responsible for regulating inerts and adjuvants in pesticide formulations. As implemented, these regulations affect only pesticide labeling and testing requirements. The term *inert* was used to designate compounds that do not have a direct toxic effect on the target species. While the term *inert* is codified in FIFRA, some inerts can be toxic, and the U.S. EPA now uses the term *Other Ingredients* rather than *inerts* (<http://www.epa.gov/opprd001/inerts/>). For brevity, the following discussion uses the term *inert*, recognizing that *inerts* may be biologically active and potentially hazardous.

The identities of inerts in pesticide formulations are generally considered trade secrets and need not be disclosed to the general public. Nonetheless, all inert ingredients as well as the amounts of the inerts in the formulations are disclosed to and reviewed by the U.S. EPA as part of the registration process. Some inerts are considered potentially hazardous and are identified as such on various lists developed by the federal government and state governments. The identity of these inerts must be listed on the Material Safety Data Sheet for the formulation. As summarized in Table 1, the fluroxypyr formulations considered in this risk assessments contain two listed inerts: naphthalene and 1-methyl-2-pyrrolidinone.

Naphthalene is both an inert in some formulations as well as active ingredient in other formulations. As detailed in U.S. EPA/OPP (2008b), naphthalene is registered as a pesticide used as an insecticide and insect repellent. For example, naphthalene is the active ingredient in mothballs.

1-Methyl-2-pyrrolidinone is not a registered insecticide. It is a solvent used in pesticide formulations as well as in various chemical operations related to the production of petroleum and plastics (U.S. EPA/OPP 2006d). Both naphthalene and 1-methyl-2-pyrrolidinone are approved for use in pesticide formulations in both food crop and

nonfood crop products. In order for an inert to be used in pesticide formulations applied to food crops, pesticide tolerances must be established or a waiver for tolerances must be granted by the EPA. Because naphthalene is a registered pesticide, pesticide tolerances are established (U.S. EPA/OPP 2008b). The toxicology data on 1-methyl-2-pyrrolidinone were reviewed by the EPA, and the requirement for pesticide tolerances was waived (U.S. EPA/OPP 2006d). In other words, the EPA determined that the use of 1-methyl-2-pyrrolidinone in pesticide formulations applied to food crops or other vegetation does not constitute an unreasonable risk. Specifically, the EPA concludes:

...it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to NMP [1-methyl-2-pyrrolidinone] when used as an inert ingredient in pesticide formulations when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information.

- U.S. EPA/OPP 2006d, p. 2

The EPA assessments on naphthalene are extensively documented in the Reregistration Eligibility Decision (RED) for naphthalene (U.S. EPA/OPP 2008b) as well as related EPA assessments of naphthalene (U.S. EPA 1990, 1998). These assessments are consistent with the ATSDR review of naphthalene (ATSDR 2005). While the literature on 1-methyl-2-pyrrolidinone is less extensive than that on naphthalene, the inert reassessment made by U.S. EPA/OPP (2006d) is well-documented with information from the open literature as well as studies submitted to the EPA by pesticide registrants.

3.1.14.2. Adjuvants

No specific adjuvants are recommended in the product labels for Vista Specialty Herbicide or Vista XRT (Ultra).

3.1.15. Impurities and Metabolites

3.1.15.1. Metabolites

The *in vivo* mammalian metabolism of fluroxypyr-MHE is considered in Section 3.1.3. This section is concerned with the metabolism of fluroxypyr-MHE in the environment. The environmental metabolism of a pesticide is considered quantitatively, if the metabolites are more toxic and more persistent than the parent compound.

Fluroxypyr-MHE is rapidly hydrolyzed by microorganisms to fluroxypyr acid and 2-octanol (Lehmann 1991; Lehmann and Miller 1989). Rapid hydrolysis may also occur under basic (i.e., pH \geq 11) conditions; however, it is not likely to be a significant environmental pathway (U.S. EPA/OPP 1998a). As in mammalian metabolism, 2-octanol will be rapidly mineralized via beta oxidation to CO₂ or will be incorporated into the general carbon pool (Lehmann 1991). In plants and soils, the major metabolites of fluroxypyr acid are 4-amino-3,5-dichloro-6-fluoro-pyridin-2-ol and 4-amino-3,5-dichloro-6-fluoro-2-methoxy-pyridine (Hawkins et al. 1981b; Lehmann 1991; Lehmann and Miller 1989b).

The fluroxypyr literature does not include data regarding the mammalian toxicity of either the pyridinol or pyridine metabolites. As discussed in Section 4.1.3.4 (Hazard Identification for Aquatic Plants), these metabolites are from 3 to 100 times less toxic than fluroxypyr to aquatic plants. It is not possible, however, to extrapolate the mammalian toxicity of the environmental metabolites from the available toxicity data on aquatic plants. Nonetheless, based on the available information, there is no basis for asserting that the environmental metabolites of fluroxypyr pose a greater risk to human health than fluroxypyr itself. Like all of the EPA human health risk assessments of fluroxypyr (U.S. EPA/OPP 1998a,b, 2003a, 2006a,b,c, 2007c,d,e,f), this Forest Service risk assessment addresses fluroxypyr itself as the agent of concern, and the metabolites are not considered quantitatively.

3.1.15.2. Impurities

Virtually no chemical synthesis yields a totally pure product. Technical grade fluroxypyr, like other technical grade products, undoubtedly contains some impurities. To some extent, concern for impurities in technical grade fluroxypyr is reduced by the fact that the existing toxicity studies on fluroxypyr were conducted with the technical grade product itself or the technical grade product in formulation. Thus, if toxic impurities are present in the technical grade product, they are likely to be encompassed by the available toxicity studies on the technical grade product.

Impurities can be a substantial concern in a risk assessment, if the impurities pose risks that are qualitatively different from the active ingredient. For example, both picloram (SERA 2003a) and clopyralid (SERA 2004) contain hexachlorobenzene as an impurity. Hexachlorobenzene is a concern in the risk assessments on picloram and clopyralid because hexachlorobenzene is a persistent carcinogen. Thus, full exposure assessments, dose-response assessments, and risk characterizations are given for the hexachlorobenzene impurity in the risk assessments on picloram and clopyralid. There is, however, no evidence in the available literature to suggest that technical grade fluroxypyr contains impurities which differ qualitatively from fluroxypyr itself.

3.1.16. Toxicological Interactions

No information is available on the interactions of fluroxypyr with other compounds. In terms of the mechanism of action, it is likely that fluroxypyr would influence and be influenced by other weak acids that are excreted by the kidney. These influences, however, would be significant only at relatively high doses that saturated the active transport processes involved in excretion by the kidney.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview

All exposure assessments for fluroxypyr are summarized in Worksheet E01 for workers and Worksheet E03 for the general public in the EXCEL workbook that accompanies this risk assessment. All exposure assessments are based on the maximum application rate of 0.5 lb a.e./acre.

For workers applying fluroxypyr, three types of application methods are modeled: directed ground spray, broadcast ground spray, and aerial spray. In non-accidental scenarios involving the normal application of fluroxypyr, central estimates of exposure for workers are approximately 0.007 mg/kg/day for aerial and backpack workers and about 0.01 mg/kg/day for broadcast ground spray workers. Upper ranges of exposures are approximately 0.04 mg/kg/day for backpack and aerial workers and 0.08 mg/kg/day for broadcast ground spray workers. All of the accidental exposure scenarios for workers involve dermal exposures. The accidental exposure scenarios lead to dose estimates that are comparable to the general exposure levels estimated for workers. The upper bound estimate of the absorbed dose is about 0.005 mg/kg bw if contaminated gloves are worn for 1 hour.

For the general public (Worksheet E03), acute levels of exposures range from minuscule (e.g., 1×10^{-6} mg/kg/day) to about 1 mg/kg bw at the maximum application rate of 0.5 lb a.e./acre. The upper bound of exposure, 1 mg/kg bw, is associated with the consumption of contaminated fish by subsistence populations shortly after an accidental spill. This exposure scenario is highly arbitrary. The upper bound of the dose associated with the consumption of contaminated vegetation, a more plausible but still extreme exposure scenario, is about 0.6 mg/kg bw. The other acute exposure scenarios lead to much lower dose estimates. The lowest acute exposure levels are associated with swimming in or drinking contaminated water.

The chronic or longer-term exposure levels are much lower than the estimates of corresponding acute exposures. The highest longer-term exposure levels are associated with the consumption of contaminated vegetation, and the upper bound for this scenario is about 0.065 mg/kg/day, which is followed by the scenario for the longer-term consumption of contaminated fruit with an upper bound of 0.008 mg/kg/day. As with the acute exposures, the lowest longer-term exposures are associated with the consumption of surface water.

3.2.2. Workers

Exposure assessments for workers are summarized in Worksheet E01 of the EXCEL workbook that accompanies this risk assessment (Attachment 1). This workbook contains a set of worksheets on fluroxypyr that detail each exposure scenario discussed in this risk assessment as well as summary worksheets for both workers and members of the general public. Documentation for these worksheets is presented in SERA (2008). This section on workers and the following section on the general public provide a plain

language description of the worksheets and discuss the fluroxypyr specific data used in the worksheets.

Two types of exposure assessments are considered: general and accidental/incidental. The term *general exposure* is used to designate exposures involving absorbed dose estimates based on handling a specified amount of chemical during specific types of applications. The accidental/incidental exposure scenarios involve specific events that may occur during any type of application. All exposure assessments (i.e., those for workers, members of the general public, and ecological receptors) are based on the maximum application rate of 0.5 lb a.e./acre. The consequences of using lower application rates are considered in the risk characterization (Section 3.4).

3.2.2.1. General Exposures

The worker exposure assessments in the current risk assessment are based on a standard set of exposure scenarios used for other herbicides with similar uses and application methods—i.e., aminopyralid (SERA 2007c), 2,4-D (SERA 2006), clopyralid (SERA 2004c), picloram (SERA 2003a), and triclopyr (SERA 2003b). As described in SERA (2007a), worker exposure rates in Forest Service risk assessments are expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical handled. Based on analyses of several different pesticides using a variety of application methods, default exposure rates are estimated for three different types of applications: directed foliar (backpack), boom spray (hydraulic ground spray), and aerial. A summary of these exposure rates, taken from Table 3-3 in SERA 2007a, is given below:

<u>Application Method</u>	<u>Exposure Rate (mg/kg bw per lb a.i.)</u>
Directed foliar	0.003 (0.0003 to 0.01)
Broadcast foliar, boom spray	0.0002 (0.00001 to 0.0009)
Aerial	0.00003 (0.000001 to 0.0001)

Sometimes, Forest Service pesticide risk assessments incorporate an adjustment to the worker exposure rates to consider the use of personal protective equipment (PPE). For fluroxypyr, the use of extraordinary PPE is neither required on the product label nor specified by the Forest Service. Consequently, the worksheets for worker exposures (i.e., C01 series) use a clothing protection factor of 0 (i.e., no protection). As documented in Section 3.4.2 (Risk Characterization for Workers), all of the HQ values for general worker exposure are substantially below the level of concern, and the use of extraordinary PPE does not have an impact the risk characterization.

Typical occupational exposures involve multiple routes of exposure (i.e., oral, dermal, and inhalation). The exposure rates used in the current Forest Service risk assessment are all based on estimates of absorbed doses during field applications. Thus, the general exposure assessments for workers encompass all routes of exposure. Generally, dermal exposure is the predominant route of exposure for pesticide applicators (Ecobichon 1998; van Hemmen 1992). As discussed in Section 3.1.12, the U.S. EPA/OPP (2007f) did not consider dermal exposures for workers. Dermal exposures are considered in the current Forest Service risk assessment.

3.2.2.2. *Accidental Exposures*

Accidental exposures, on the other hand, are most likely to involve splashing a solution of the pesticide into the eyes or contaminating the surface of the skin. Quantitative exposure scenarios for eye exposures are not developed in this or other Forest Service risk assessments. As discussed in Section 3.1.11.3 (Ocular Effects), fluroxypyr-MHE, at concentrations very close to those in Vista Specialty Herbicide (26.2%) is shown to cause eye damage in rabbits. The newer Vista XRT formulation contains a higher concentration of fluroxypyr-MHE (45.52%), and, presumably, would cause more severe damage to the eyes. This effect is considered qualitatively in the risk characterization for workers (Section 3.4.2).

Dermal exposure to fluroxypyr is considered quantitatively in this risk assessment. The two types of dermal exposure that are modeled include direct contact with a pesticide solution and accidental spills of the pesticide onto the surface of the skin. Furthermore, two exposure scenarios are developed for each of the two types of dermal exposure, and the estimated absorbed dose for each scenario is expressed in units of mg chemical/kg body weight. Both sets of exposure scenarios are summarized in Worksheet E01, which references other worksheets in which the calculations are specified.

Exposure scenarios involving direct contact with solutions of fluroxypyr are characterized either by immersion of the hands in a field solution for 1 hour or wearing pesticide contaminated gloves for 1 hour. The assumption 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 may seem unreasonable; however, it is quite plausible that the gloves or other articles of clothing worn by a worker may become contaminated with a pesticide. For these exposure scenarios, the key assumption is that wearing gloves grossly contaminated with a chemical solution is equivalent to immersing the hands in the solution. In both cases, the chemical concentration in contact with the skin and the resulting dermal absorption rate are essentially constant.

For both scenarios (hand immersion and contaminated gloves), the assumption of zero-order absorption kinetics is appropriate. For these types of exposures, the rate of absorption is estimated, based on a zero-order dermal absorption rate (K_p). Details regarding the derivation of the K_p value for fluroxypyr are provided in Section 3.1.3.2. The amount of the pesticide absorbed per unit time depends directly on the concentration of the chemical in solution. As discussed in Section 2.4, the current risk assessment uses an application volume of 5 gallons/acre with a range of 3-10 gallons per acre, which encompasses the potential range of application to be used in ground and aerial applications. At an application rate of 0.5 lb/acre, the estimated concentrations in a field solution are 12 mg/mL with a range of 6 to 20 mg/mL (Worksheet A01).

Exposure scenarios involving chemical spills onto the skin are characterized by a spill on to the lower legs as well as a spill on to the hands and are based on the assumption that a certain amount of the chemical adheres to the skin. The absorbed dose is then calculated as the product of the amount of chemical on the surface of the skin (i.e., the amount of liquid per unit surface area multiplied by the surface area of the skin over which the spill

occurs and the chemical concentration in the liquid), the first-order absorption rate, and the duration of exposure. As with the zero-order dermal absorption rate, the first-order absorption rate (k_a) is derived in Section 3.1.3.2. There is uncertainty concerning the appropriate dermal absorption rate for fluroxypyr-MHE. Based on the study by Hewitt et al. (2000a), this risk assessment uses the dermal absorption rates based on the molecular weight and $K_{o/w}$ of fluroxypyr acid.

Numerous exposure scenarios could be developed for direct contact or accidental spills by varying the amount or concentration of the chemical on, or in contact with, the skin surface, the surface area of the affected skin, and the duration of exposure. The impact of these variables on the risk assessment is discussed further in the risk characterization (Section 3.4.2).

3.2.3. General Public

3.2.3.1. General Considerations

3.2.3.1.1. Likelihood and Magnitude of Exposure

The likelihood that members of the general public will be exposed to fluroxypyr in Forest Service applications is highly variable. In some Forest Service applications, fluroxypyr could be applied in recreational areas, including campgrounds, picnic areas, and trails. Because of the conservative exposure assumptions used in the current risk assessment, neither the probability of exposure nor the number of individuals who might be exposed has a substantial impact on the risk characterization presented in Section 3.4. As noted in Section 1 (Introduction) and detailed in SERA (2007, Section 1.2.2.2), the exposure assessments developed in this risk assessment are based on *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 plausible exposures.

This Extreme Value approach is essentially an elaboration on the concept of the *Most Exposed Individual* (MEI), sometime referred to as the *Maximum Exposed Individual*. As this name implies, exposure assessments that use the MEI approach attempt to characterize the extreme but still plausible upper limit on exposure. This common approach to exposure assessment is used by U. S. EPA, other government agencies, and the International Commission on Radiological Protection (e.g., ATSDR 2002; ICRP 2005; Payne-Sturges et al. 2004). In the current risk assessment, all upper bounds on exposure are based on the MEI.

In addition to this upper bound MEI value, the Extreme Value approach used in this risk assessment provides a central estimate of exposure as well as a lower bound on exposure. Although not germane to assessing the upper bound risk, using the central estimate and especially the lower bound estimate is not intended to lessen concern. To the contrary, the central and lower estimates of exposure are used to assess the prospect of mitigation—e.g., protective measures to limit exposure. If lower bound exposure estimates exceed a level of concern (which is not the case in the current risk assessment),

there is strong indication that the pesticide cannot be used in a manner that will lead to acceptable risk.

In addition to concern for the most exposed individual, there is concern for individuals who may be more sensitive than most members of the general population to fluroxypyr exposure. This concern is considered in the dose-response assessment (Section 3.3) in which exposures are based on the most sensitive endpoint in the most sensitive species and an uncertainty factor for sensitive individuals is used. Atypical sensitivities—i.e., special conditions that might increase an individual's sensitivity to a particular agent—are also considered separately in the risk characterization (Section 3.4.4).

Thus, the use of extreme values in the exposure assessment is part of an integrated approach designed to encompass plausible upper limits of risk for the most exposed and most sensitive individuals, regardless of the specific probability or number of exposures. In the event that an extreme value risk assessment triggers concern, there are probabilistic methods that deal more explicitly with the likelihood of exposure, the number of exposed individuals, and many other quantitative considerations (e.g., SERA 2007A, Section 1.2.2.1). Nonetheless, as discussed further in Section 3.4, there is no evidence of substantial risk in this risk assessment of fluroxypyr.

3.2.3.1.2. Summary of Assessments

The exposure scenarios developed for the general public are summarized in Worksheet E03 of the EXCEL workbook that accompanies this risk assessment. As with the worker exposure scenarios, details about the assumptions and calculations used in these assessments are given in the worksheets that accompany this risk assessment (Worksheets D01–D11).

As summarized in Worksheet E03, the kinds of exposure scenarios developed for the general public include acute accidental, acute non-accidental, and longer-term or chronic exposures. The accidental exposure scenarios assume that an individual is exposed to the compound of concern either during or shortly after its application. What is more, the nature of the accidental exposures is intentionally extreme. Non-accidental exposures involve dermal contact with contaminated vegetation as well as the consumption of contaminated fruit, vegetation, water, and fish. The longer-term or chronic exposure scenarios parallel the acute exposure scenarios for the consumption of contaminated fruit, water, and fish. All of the non-accidental exposure scenarios are based on levels of exposure to be expected in the routine uses of fluroxypyr at the maximum application rate. Nonetheless, the upper bounds of the exposure estimates for the non-accidental scenarios involve conservative assumptions intended to reflect exposure for the MEI (*Most Exposed Individual*).

3.2.3.2. Direct Spray

Direct sprays involving ground applications are modeled similarly to accidental spills for workers (Section 3.2.2.2). In other words, the scenarios assume that an individual is sprayed with a chemical solution, some of which remains on the skin and is absorbed by

first-order kinetics. Two direct spray scenarios are included in this risk assessment: one for a young child (D01a) and the other for a young woman (D01b).

The exposure scenario involving the young child assumes that a naked child is sprayed directly with a chemical during a ground broadcast application and is completely covered (i.e., 100% of the surface area of the body is exposed). This exposure scenario is intentionally extreme. As discussed in Section 3.2.3.1.1, the upper limits of this exposure scenario are intended to represent the *Extreme Value* upper limits of exposure for the *Most Exposed Individual* (MEI).

The exposure scenario involving the young woman (Worksheet D01b) is somewhat less extreme but more plausible. In this scenario, it is assumed that the woman is accidentally sprayed over the feet and lower legs. The preference for using a young woman rather than an adult male in many of the exposure assessments relates to concerns for both the *Most Exposed Individual* (MEI) as well as the most sensitive individual. Based on general allometric considerations, the smaller the individual, the greater will be the chemical doses per unit body weight (e.g., Boxenbaum and D'Souza. 1990). According to standard reference values used in exposure assessments (e.g., U.S. EPA/ORD. 1989), the female body size is smaller than that of males. Thus, in direct spray exposure scenarios, females are subject to somewhat higher doses than males. More significantly, reproductive effects are a major concern in all Forest Service risk assessments. Consequently, exposure levels for a young woman of reproductive age are used in order to better assess the potential for adverse effects in the population at risk from potential reproductive effects—i.e., the most exposed and the most sensitive individual.

For this exposure scenario, assumptions are made regarding the surface area of the skin and the body weight of the individual, as detailed in Worksheet A03. The rationale for and sources of the specific values used in these and other exposure scenarios is given in the documentation for the worksheets (SERA 2008) as well as the documentation for the preparation of Forest Service risk assessments (SERA 2007a).

3.2.3.3. Dermal Exposure from Contaminated Vegetation

The exposure scenario involving contaminated vegetation assumes that the herbicide is sprayed at a given application rate and that a young woman comes in contact with the sprayed vegetation or with other contaminated surfaces sometime after the spray operation (D02). This exposure scenario depends on estimates of dislodgeable residue (a measure of the amount of the chemical that could be released from the vegetation) and the availability of dermal transfer rates (i.e., the rate at which the chemical is transferred from the contaminated vegetation to the surface of the skin).

Dermal transfer rates are reasonably consistent for a number of different pesticides (Durkin et al. 1995). In addition, the methods and rates derived in Durkin et al. (1995) are used as defined in Worksheet D02. Most Forest Service risk assessments use a default dislodgeable residue rate of 0.1 of the application rate, based on a field simulation study which measured dermal exposure levels in humans after an application of 2,4-D (Harris and Solomon 1992). For fluroxypyr-MHE, however, Robert and Foster (2000) suggest much lower dislodgeable residues rates (i.e., on the order of 0.0003-0.0074 of the application rate). The study is highly relevant to this risk assessment because it involved the application of Vista Specialty Herbicide to turf at three different sites under field conditions. The highest dislodgeable residue rate of 0.74% (a proportion of 0.0074) was assayed 1.5 hours after application from a site in Pennsylvania (Robert and Foster 2000, Table 9, p. 28).

The rapid absorption of fluroxypyr-MHE by plants is documented in other studies (e.g., Lym 1992); moreover, fluroxypyr does appear to be more rapidly absorbed than other related herbicides, like clopyralid (Orfanedes et al. 1993). Thus, the low dislodgeable residues reported by Robert and Foster (2000) are well documented in the study itself and consistent with the results of other studies.

Although the assumptions in Forest Service risk assessments tend to be conservative and sometimes highly conservative, there is no justification for using the default value 0.1 for the dislodgeable residue rate. Accordingly, the highest value reported by Robert and Foster (2000)—i.e., 0.0074—is used in the current risk assessment, which does not have a substantial impact, since the highest HQ for this scenario would be 0.01, even if the default value of 0.1 were used.

This exposure scenario assumes both a contact period of 1 hour and that the chemical is not effectively removed by washing for 24 hours. Other estimates used in this exposure scenario involve estimates of body weight, skin surface area, and first-order dermal absorption rates, as discussed in the previous section.

3.2.3.4. Contaminated Water

3.2.3.4.1. Accidental Spill

Two exposure scenarios are presented for the acute consumption of contaminated water: an accidental spill into a small pond (0.25 acres in surface area and 1 meter deep) and the contamination of a small stream by runoff or percolation.

The accidental spill scenario assumes that a young child consumes contaminated water shortly after an accidental spill of a field solution into a small pond. The specifics of this scenario are given in Worksheet D05. Because this scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation or degradation is considered. Since this exposure scenario is based on assumptions that are somewhat arbitrary and highly variable, it may overestimate exposure. The actual chemical concentrations in the water will vary according to the amount of compound spilled, the size of the water body into which it is spilled, the time at which water consumption occurs relative to the time of the spill, and the amount of contaminated water consumption. To reflect the variability

inherent in this exposure scenario, a spill volume of 100 gallons (range of 20-200 gallons) is used to reflect plausible spill events. The fluroxypyr concentrations in the field solution are also varied to reflect the plausible range of concentrations in field solutions—i.e., the material that might be spilled—using the same values as in the accidental exposure scenarios for workers (Section 3.2.2.2). Based on these assumptions, the estimated concentration of fluroxypyr in a small pond ranges from about 0.45 to 15 mg/L, with a central estimate of about 4.5 mg/L (Worksheet D05).

3.2.3.4.2. Accidental Direct Spray/drift for a Pond or Stream

These exposure scenarios involving drift are less severe but more plausible than the accidental spill scenario described above. U.S. EPA typically uses a 2-meter-deep pond to develop exposure assessments (SERA 2007b). If such a pond is directly sprayed with fluroxypyr at the central estimate of the application rate (0.5 lb a.e./acre), the peak concentration in the pond would be about 0.056 mg/L, equivalent to 56 µg/L or 56 ppb (Worksheet D10a). This concentration is a factor of about 80 below the upper bound of the peak concentration of 4.5 mg/L after the accidental spill (Section 3.2.3.4.1, Worksheets D05). Worksheet D10a also models concentrations at distances of 25-900 feet down wind based on standard values adapted from AgDrift (SERA 2008). Based on these estimates, fluroxypyr concentrations in a small pond contaminated by drift would range from about 0.00006 mg/L (60 part per trillion) to 0.002 mg/L (2 parts per billion).

Similar calculations can be made for the direct spray of or drift into a stream. For this scenario, the resulting water concentrations depend on the surface area of the stream and the rate of water flow in the stream. The stream modeled using GLEAMS (see below) is about 6 feet wide (1.82 meters), and it is assumed that the pesticide is applied along a 1038 foot (316.38 meters) length of the stream with a flow rate of 710,000 L/day. Using these values, the concentration in stream water after a direct spray is estimated at about 0.05 mg/L (50 parts per billion). Much lower concentrations, ranging from about 0.00005 mg/L (50 part per trillion) to 0.0016 mg/L (1.6 part per billion) are estimated based on drift at distances of 25-900 feet (Worksheet D10b).

3.2.3.4.3. GLEAMS Modeling

The Forest Service developed a program, Gleams-Driver, to estimate expected peak and longer-term pesticide concentrations in surface water. Gleams-Driver serves as a preprocessor and postprocessor for GLEAMS (Knisel and Davis 2000). GLEAMS is a field scale model developed by the USDA/ARS and has been used for many years in Forest Service and other USDA risk assessments (SERA 2007b).

Gleams-Driver offers the option of conducting general exposure assessments using site-specific weather files from Cligen, a climate generator program developed and maintained by the USDA Agricultural Research Service (<http://horizon.nserl.purdue.edu/Cligen>). Gleams-Driver was used in the current risk assessment to model fluroxypyr concentrations in a small stream and small pond. The generic site parameters used in the Gleams-Driver runs are summarized in Table 6, and additional details are available in the documentation for Gleams-Driver (SERA 2007b).

Table 7 summarizes the chemical-specific values used in GLEAMS, which, for the most part, are similar to those used by U.S. EPA (U.S. EPA/OPP 2007c). The EPA modeling efforts are discussed below (Section 3.2.3.4.4). In the current risk assessment, the modeling input values are based on the environmental fate studies submitted to the EPA by the registrant as well as standard values for GLEAMS modeling recommended by Knisel and Davis (2000). The notes to Table 7 indicate the sources of the chemical-specific values used in the GLEAMS modeling effort.

The locations selected for modeling include a total of nine sites, as summarized in Table 8. As discussed in SERA (2007b), these locations are standard sites for the application of Gleams-Driver in Forest Service risk assessments and are intended to represent combinations of precipitation (dry, average, and wet) and temperature (hot, temperate, and cool). For each site, Gleams-Driver was used to simulate 100 applications of fluroxypyr at a unit application rate of 1 lb/acre, and each of the simulations was followed for a period of more than 1½ years post application.

For each of the nine sites, three sets of simulations were conducted for a field with soil characteristics for clay, loam, and sand. The concentrations of fluroxypyr were estimated in both a pond and a stream. The characteristics of the field, pond, and stream are summarized in Table 9.

Details of the results for the Gleams-Driver runs are provided in Appendix 9. A summary of the results for the Gleams-Driver runs are presented in Table 10, along with a summary of other modeling efforts and monitoring data, both of which are discussed further in the following subsections.

3.2.3.4.4. Other Modeling Efforts

In an early EPA risk assessment on fluroxypyr (U.S. EPA/OPP 1998b), two Tier 1 screening models were used, GENEEC and SCIGROW. In a more recent drinking water assessment (U.S. EPA/OPP 2007c), the Agency used a more complex Tier 2 model, PRZM/EXAMS. The results of the EPA modeling are summarized at the bottom of Table 9 and are normalized for an application rate of 1 lb a.i./acre so that the results are comparable to the other values summarized in Table 10. A comparison of the EPA modeling to the modeling conducted with Gleams-Driver is considered further in Section 3.2.3.4.6 (Concentrations in Water Used for Risk Assessment).

3.2.3.4.5. Monitoring Data

As summarized in Table 10, very little information is available on the monitored levels of fluroxypyr in surface water. In the only available monitoring study, Krueger (1998) report fluroxypyr concentrations of from 1.8 to 7 ppb in streams in an agricultural region of Sweden. As indicated in Table 10, the central estimate of the peak concentrations in a small stream modeled using Gleams-Driver is 6.33 ppb, which coincidentally is very close to the upper bound concentration of 7 ppb from the Krueger (1998) study. Nonetheless, since the monitored values reported by Krueger (1998) cannot be associated with defined applications or application rates, they really are not comparable to the modeled surface water concentrations provided in Table 10.

3.2.3.4.6. Concentrations in Water Used for Risk Assessment

Table 11 summarizes the surface water concentrations of fluroxypyr used in this risk assessment. The concentrations are specified as water contamination rates (WCRs)—i.e., the concentrations in water expected at a normalized application rate of 1 lb a.i./acre, converted to units of ppm or mg/L per lb a.i./acre. In Table 10, units of exposure are expressed as ppb or $\mu\text{g/L}$, as a matter of convenience. In Table 11, however, ppb is converted to ppm because ppm and mg/L are the units of measure used in the EXCEL workbook for contaminated water exposure scenarios in both the human health and ecological risk assessments. The water contamination rates are entered in Worksheet B04 in each of the EXCEL workbooks that accompany this risk assessment. The values in Worksheet B04 are linked to the appropriate scenario-specific worksheets in the EXCEL workbooks.

The surface water concentrations summarized in Table 11 are based on Gleams-Driver simulations as well as the modeled estimates from U.S. EPA/OPP (1998b, 2007c). As summarized in Table 10, Gleams-Driver simulations resulted in somewhat higher estimates of surface water concentrations, relative to the simulations based on PRZM-EXAMS or the Tier 1 screening models used by U.S. EPA (i.e., GENEEC, FIRST, and SCIGROW). This pattern is a quite common in Forest Service risk assessments. While the estimates based on Gleams-Driver are comparable to estimates from the other models, the estimates from Gleams-Driver tend to be higher than those based on applications of other models owing to the highly conservative input values used for clay (i.e., a very high runoff potential) and sand (i.e., a very high potential for percolation). The upper bound estimates also tend to be higher than those of other modeling efforts simply because of the nature of the simulations. The Gleams-Driver runs are all based on 100 simulations per run, and the upper bound of the concentrations given in Appendix 8 reflect the empirical 0.05 upper bound from each simulation. The simulations using the PRZM-EXAMS shell are based on a single 20-year simulation. As indicated in Table 11, the upper bound of the peak concentration in surface water is taken as 0.08 mg/L, equivalent to 80 ppb.

The upper bound concentration of 80 ppb is selected to encompass the highest modeled peak concentration—i.e., 79 ppb for streams, based on Gleams-Driver simulations. As summarized in Table 7 of Appendix 9, this concentration is associated with the peak concentration in streams in areas with clay soils, average rainfall, and moderate temperatures. As also noted in Table 7 of Appendix 9, areas with clay soils and greater rainfall rates will have modestly lower peak concentrations, ranging from about 45 to 70 ppb. Again, this is a common pattern and reflects the higher dilution of the pesticide in runoff when rainfall rates are very high.

The central and lower bound estimates of peak concentrations in surface water are taken as 0.022 and 0.0005 mg/L, respectively. The selection of these values is judgmental and somewhat arbitrary. As indicated in Table 5 (pond) and Table 6 (stream), the modeled peak concentrations in surface water will vary substantially according to soil texture and weather conditions. Furthermore, within each of the simulations for these variable factors, peak concentrations will vary substantially with year-to-year differences in

rainfall. For example, the peak concentration of 79 ppb for a small stream is simply the highest concentration modeled in the 100 simulations of a small stream in an area with clay soils, average rainfall, and moderate temperatures. For the same site and soil type, the lowest modeled concentration is 0.7 ppb (Appendix 9, Table 7, column 2, row 5). Thus, selecting a single value for a typical concentration is difficult and must, to some extent, be arbitrary.

The central estimate of the peak concentration, 0.022 mg/L, provided in Table 11 is modestly higher than the central estimate of 18.7 ppb from U.S. EPA/OPP (2007c) and is the approximate geometric mean of the average and upper bound stream concentrations from Gleams-Driver $[(3.18 \text{ ppb} \times 79 \text{ ppb})^{0.5} = 22.36 \text{ ppb}]$. The lower bound of the peak concentration, 0.00005 mg/L or 0.5 ppb, is the upper bound of the peak concentration for a small pond with sandy soil, average rainfall, and warm temperatures (Appendix 9, Table 5). As indicated in Appendix 9, modeled concentrations of 0 ppb—i.e., no detectable contamination—are anticipated in areas with very low rainfall rates.

As indicated in Table 11, the longer-term concentrations of fluroxypyr in surface water are taken as 0.001 (0.0001-0.011) mg/L. As with peak concentrations, the selection of central and lower bound estimates are somewhat judgmental. The central estimate of 0.001 mg/L or 1 ppb is essentially the central estimate from Gleams-Driver pond simulations (0.52 ppb) rounded upward to a single significant digit. The lower bound of the average concentration is simply the central estimate divided by 10. The maximum longer-term concentration of 0.011 mg/L is based on the maximum modeled concentration of 10.9 ppb, rounded to two significant places.

As discussed further in Section 3.4.3 (Risk Characterization for the General Public), the selection of central estimates and lower bounds of the fluroxypyr concentrations in surface water has no impact on the interpretation of risk, because all of the upper bound concentrations result in hazard quotients that are below the level of concern by factors of at least 200.

3.2.3.5. Oral Exposure from Contaminated Fish

This risk assessment includes three sets of exposure scenarios for the consumption of contaminated fish, and each set includes separate estimates for the general population and subsistence populations. These exposure scenarios consist of one set for acute exposures following an accidental spill (Worksheets D08a and D08b), another set for acute exposures based on expected peak concentrations (Worksheets D08c and D08d), and the third set for chronic exposures based on estimates of longer-term concentrations in water (Worksheets D09a and D09b). The two worksheets in each of these three sets are intended to account for different rates of wild-caught fish consumption in both general and subsistence populations. Details of exposure scenarios involving the consumption of contaminated fish are provided in Section 3.2.3.5 of SERA (2007a).

The water concentrations of fluroxypyr are based on the accidental spill scenario (Section 3.2.3.4.1) for Worksheets D08a and D08b, and the peak and longer-term expected

concentrations in water are based on the Gleams-Driver modeling, as summarized in Table 11 and discussed in Section 3.2.3.4.6.

The concentration of the pesticide in fish (C_F) is taken as the product of the concentration of the chemical in water (C_W) and the bioconcentration factor (BCF):

$$C_{Fish_{mg/kg}} = C_{W_{mg/L}} \times BCF_{L/kg}$$

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 and the concentration in the water is 1 mg/L, the BCF is 5 L/kg [5 mg/kg ÷ 1 mg/L]. As with most absorption processes, bioconcentration depends initially on the duration of exposure but eventually reaches steady state.

The only available study regarding the bioconcentration of fluroxypyr-MHE in fish (Rick et al. 1996b) involves the exposure of trout to ¹⁴C-2,6 pyridine ring-labelled fluroxypyr-MHE at a nominal concentration of 0.31 ppb (µg/L) for 28-days under flow-through conditions with a 17-day depuration period. Based on a simple and relatively standard two-compartment model (e.g., Calabrese and Baldwin 1993), bioconcentration factors were estimated at 167 L/kg in whole fish and 21 L/kg in fish muscle. As with other studies on fluroxypyr-MHE, rapid and extensive metabolism of fluroxypyr-MHE to fluroxypyr acid was noted. To account for the rapid conversion of fluroxypyr-MHE to fluroxypyr acid, Rick et al. (1996b) used a relatively simple four compartment model, consisting of the standard two-compartment model for fluroxypyr-MHE linked (via an irreversible first-order rate) to a two-compartment model for fluroxypyr acid. Using this approach, the estimated bioconcentration factors were 26 L/kg for whole fish and 0.6 L/kg for muscle tissue.

As with dermal absorption rates (Section 3.1.3.2), various algorithms are available for estimating the BCF based on the structure and physical properties of a chemical. One such program, EPI Suite, was developed by the EPA (Meylan and Howard 2007). As summarized in Table 2, the estimated BCF for fluroxypyr acid is 3.16. As summarized in Table 3, the estimated BCF for fluroxypyr-MHE is 613.9.

The U.S. EPA/OPP (1998b, p. 10) has reviewed the bioconcentration study by Rick et al. (1996b) and noted several deficiencies including substantial variability in the measured concentrations of fluroxypyr-MHE in the water over the course of exposures – i.e., 0.168 to 0.42 ppb compared to the targeted nominal concentration of 0.31 ppb. The variability in water concentrations is specifically addressed by Rick et al. (1996b, pp. 24 and 28) in that the modeled estimates are based on measured (and variable) concentrations of fluroxypyr in water. The U.S. EPA/OPP (1998b) indicates that a new study on bioconcentration should be conducted. A newer study, however, was not identified in the listing of studies obtained from the U.S. EPA under FOIA.

For the current Forest Service risk assessment, the higher BCF values of 167 L/kg in whole fish and 21 L/kg in fish muscle are used. The BCF factor for muscle is used in the

human health risk assessment under the assumption that human will consume only the fish fillet. The BCF factor for whole fish is used in the ecological risk assessment (Section 4.2.2.3).

As noted above, these BCF values are based on the simpler two-compartment model used by Rick et al. (1996b), which does not account for the rapid hydrolysis of fluroxypyr-MHE to fluroxypyr acid. This more conservative approach probably overestimates actual exposures and the overestimates may be substantial. In the absence of a newer study that is acceptable to the U.S. EPA, this more conservative approach seems justified.

3.2.3.6. Dermal Exposure from Swimming in Contaminated Water

Some geographical sites maintained by the Forest Service or Forest Service cooperators contain surface water in which members of the general public might swim. To assess the potential risks associated with swimming in contaminated water, an exposure assessment is developed for a young woman swimming in surface water for 1 hour (Worksheet D11).

Conceptually and computationally, this exposure scenario is virtually identical to the contaminated gloves scenario used for workers (Section 3.2.2.2)—i.e., a portion of the body is immersed in an aqueous solution of the compound at a fixed concentration for a fixed period of time. As with the worker exposure scenario, the K_p values used for the swimming scenario are based on estimated values for fluroxypyr-MHE. Because of the rapid hydrolysis of fluroxypyr-MHE to fluroxypyr acid and the much lower K_p values for fluroxypyr acid, relative to fluroxypyr-MHE, this approach is likely to overestimate exposures substantially for periods greater than a few days after application. As discussed further in the risk characterization (Section 3.4.3), the possibility of overestimating exposure levels has no impact on this risk assessment, since the HQ values associated with this scenario are far below the level of concern.

There are major differences between the two dermal exposure scenarios. For the worker wearing contaminated gloves, the basic assumption is that both hands are exposed to the field solution—i.e., the concentration of the compound in the applied solution. For the swimmer, the basic assumption is that the entire surface area of the body is exposed to the expected peak concentrations in ambient water (Table 11). Yet, like the contaminated glove scenario, the swimming scenario is conservative in that it assumes zero-order absorption directly from the water to the systemic circulation. The swimmer will not be immersed in contaminated water for 1 hour; however, the entire body surface is used both as a conservative approximation (i.e., the MEI) and because the entire body may be wetted and the water wetting the body will be continually replenished during most swimming activities.

As in the corresponding worker exposure scenario, the 1-hour period of exposure is somewhat, but not completely, arbitrary, given that longer periods of exposure are plausible. Nonetheless, the 1-hour period is intended as a unit exposure estimate. In other words, the exposure and consequently the risk will increase linearly with the duration of exposure, as indicated in Worksheet D11. Thus, a 2-hour exposure would lead to a hazard quotient that is twice as high as that associated with an exposure period

of 1 hour. In cases in which this or other similar exposures approach a level of concern, further consideration is given to the duration of exposure in the risk characterization (Section 3.4). As noted above, the levels of exposure to fluroxypyr-MHE are well below the level of concern, and the duration of the swimming event does not have a substantial impact on this risk assessment.

3.2.3.6. Oral Exposure from Contaminated Vegetation

Although none of the Forest Service applications of fluroxypyr will involve crop treatment, Forest Service risk assessments typically include standard exposure scenarios for the acute and longer-term consumption of contaminated vegetation. Two sets of exposure scenarios are provided: one for the consumption of contaminated fruit and the other for the consumption of contaminated vegetation. These scenarios are detailed in Worksheets D03a and D03b for acute exposure and Worksheets D04a and D04b for chronic exposure.

The concentration of the pesticide on contaminated fruit and vegetation is estimated using the empirical relationships between application rate and concentration on different types of vegetation (Fletcher et al. 1994). The rates provided by Fletcher et al. (1994) are based on a reanalysis of data originally compiled by Hoerger and Kenaga (1972) and represent estimates of pesticide concentration in different types of vegetation (mg chemical/kg vegetation) after a normalized application rate of 1 lb a.i./acre. Although the human health risk assessments conducted by the EPA do not consider this exposure scenario, the residue rates recommended by Fletcher et al. (1994) are used by U.S. EPA/OPP in their ecological risk assessment of fluroxypyr (U.S. EPA/OPP 1998b, p. 13).

The residue rates recommended by Fletcher et al. (1994) are given in Table 12 of the current Forest Service risk assessment. Fletcher et al. (1994) and Hoerger and Kenaga (1972) provide only central and upper bound estimates of residue rates. Accordingly, the lower bound estimates in Table 12 are made under the assumption that the ratio of the central estimate to the upper bound estimate is identical to the ratio of the lower bound estimate to the central estimate (i.e., the variability is log-symmetrical).

For longer-term exposures, the time-weighted average exposure is estimated using the initial pesticide concentration and its half-life on vegetation (Worksheet D04a and D04b). These worksheets accommodate a central estimate and the lower and upper bounds on the half-life. The half-life of fluroxypyr residue on vegetation is not reported in the available literature, including the published literature or the studies submitted to the EPA in support of registration. This data gap is somewhat unusual for a herbicide. Robert and Foster (2000) estimated half-lives ranging from about 1.4 to 2.5 days; however, these half-lives are based on dislodgeable residues (i.e., $\mu\text{g}/\text{cm}^2$) from turf rather than total residues (i.e., mg chemical/kg vegetation) on consumable vegetation.

Based on an analysis for 41 pesticides, Juraske et al. (2008) proposes a simple approximation for estimating either dislodgeable foliar residues or total residues based on soil half-lives—i.e., plant surface half-lives can be estimated as the soil half-life divided by 4, and the half-life of total residues can be estimated as the soil half-life divided by 16.

Although these relationships are not intuitive, a summary of the soil and vegetation half-lives for a far greater number of pesticides (Knissel and Davis 2000) suggests that soil half-lives are usually much greater than foliar half-lives.

As summarized in Table 7, soil half-lives of 7, 13, and 23 days are used for Gleams-Driver modeling, based on studies reviewed and accepted by U.S. EPA/OPP (2007c). The turf half-lives of 1.4 to 2.5 days for dislodgeable foliar residue reported by Robert and Foster (2000) are reasonably consistent with the estimation method proposed by Juraske et al. (2008)—i.e., $13 (7-23) \text{ days} \div 4 = 3.25 (1.75 - 5.75) \text{ days}$.

Rather than estimating total residue half-lives as one-sixteenth of the soil half-lives, as recommended by Juraske et al. (2008), the current risk assessment takes a more conservative approach and divides the soil-lives by 4. Thus, the half-lives for total residues on contaminated vegetation or fruit are taken as 3 (2-6) days—i.e., $13 (7 \text{ to } 23) \text{ days} \div 4$ and rounded to the nearest day.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

Table 13 provides an overview of the toxicity values used in the current Forest Service risk assessment for human health effects. When the EPA adopts toxicity values for human health, which is the case for fluroxypyr, those values are typically adopted and used directly in Forest Service risk assessments. The EPA has not derived an acute RfD for fluroxypyr, which is understandable, given the lack of a clear dose-duration relationship for fluroxypyr. The chronic RfD of 1 mg/kg bw/day derived by the EPA is based on a NOAEL of 100 mg/kg bw/day for kidney damage in rats and an uncertainty factor of 100. This RfD is used in the current Forest Service risk assessment to characterize human risks associated with both acute and chronic exposures to fluroxypyr. The EPA does not derive RfDs for occupational exposure. Instead, the EPA recommends an experimental toxicity value and a margin of exposure (MOE), which is analogous to an uncertainty factor. For fluroxypyr, the EPA uses the same NOAEL as for the chronic RfD with a MOE of 100. Thus, the surrogate RfD used for workers in the current Forest Service risk assessment is identical to the chronic RfD—i.e., 1 mg/kg bw/day.

To help interpret the risks associated with exposure levels that exceed the RfD, Forest Service risk assessments try to characterize dose-severity relationships based preferably on human data, or systematic and consistent differences in species sensitivity among mammals, or, at very least, consistent dose-response and/or dose-severity relationships in mammals. These data, however, are not available on fluroxypyr. In other words, there are no data regarding the toxicity or kinetics of fluroxypyr, with respect to human exposure. Moreover, the mammalian data from experimental studies are not consistent. Therefore, a dose-severity relationship for fluroxypyr is not proposed in this risk assessment.

3.3.2. Acute RfD

U.S. EPA/OPP sometimes derives an acute RfD for pesticide exposures that occur in a single day. Accordingly, acute RfDs are usually based on developmental studies in which an adverse effect is associated with a single dose of a pesticide. U.S. EPA/OPP elected not to derive an acute RfD for fluroxypyr because an ... *endpoint attributable to a single exposure was not identified* (U.S. EPA/OPP 2007f, p. 4). As summarized in Table 6, the developmental NOAELs for fluroxypyr range from 100 mg a.e./kg bw/day (Tesh et al. 1984) to 424 mg a.e./kg bw/day (Liberacki et al. 1996b). An acute RfD, if derived, would likely be based on the dose of 100 mg a.e./kg bw/day from the Tesh et al. (1984) study, because the LOAEL of 250 mg a.e./kg bw/day in that study is lower than NOAELs reported in other developmental studies. In other words, there does not appear to be a dose-duration relationship for fluroxypyr, which is consistent with its rapid excretion suggesting that fluroxypyr body burdens are not likely to increase as the duration of exposure increases (Section 3.1.3.3). Thus, the characterization of all acute exposure scenarios in the current Forest Service risk assessment are based on the chronic RfD, as discussed in the following subsection.

3.3.3. Chronic RfD

The EPA human health risk assessments of fluroxypyr characterizes risks to members of the general public, based on a chronic RfD of 1 mg a.e./kg bw/day (U.S. EPA/OPP 1998a,b, 2003a, 2006a,b,c, 2007c,d,e,f). This chronic RfD is based on a NOAEL of 100 mg a.e./kg/day from the 24-month feeding study in rats (Quast and McGuirk 1995).

As summarized in Appendix 2, this study involved dietary exposure levels equivalent to doses of 0 (control), 100, 500, and 1000 mg a.e./kg bw/day over a 2-year period. Reasonably consistent doses (averaging 93 to 98% of the targeted doses) were maintained by varying the dietary concentrations of fluroxypyr over the course of the study. Adverse effects were observed only at doses greater than 100 mg/kg bw/day, as discussed in Section 3.3.5 (Dose-Severity Relationships).

The RfD of 1 mg a.e./kg/day was derived by dividing the NOAEL of 100 mg a.e./kg bw/day by an uncertainty factor of 100. This uncertainty factor consists of two components: a factor of 10 for extrapolating from animals to humans and a factor of 10 for extrapolating to sensitive individuals within the human population. Using the same conversion factor, the 500 mg a.e./kg bw/day dose corresponds to an estimated functional human LOAEL of 5 mg a.e./kg/day. At this functional LOAEL, moderately adverse effects might be anticipated.

As summarized in Table 6, the NOAEL of 100 mg/kg bw/day is supported by a number of other NOAELs, many at higher doses than the 100 mg/kg bw/day NOAEL from Quast and McGuirk (1995). The NOAEL of 80 mg/kg bw/day from the subchronic study by Jonker et al. (1987) does not contradict the NOAEL of 100 mg/kg bw/day; rather, it reflects the somewhat lower dose used in the study. The only study that suggests a risk below the NOAEL of 100 mg/kg bw/day is the dietary study by Perry et al. (1984) in which the LOAEL is 20 ppm, based on increased testes and spleen weights and ovarian lesions in mice. As discussed in some detail Section 3.1.5, the study appears to be an outlier since the results are contradicted by several other toxicity studies, including the chronic study in mice by Perry et al. (1985).

3.3.4. Surrogate RfD for Occupational Exposures

U.S. EPA/OPP does not derive an RfD explicitly for occupational exposures. Instead, the EPA typically uses a NOAEL from an experimental study in mammals to define a target margin of exposure (MOE). Then, if the worker exposure level is less than the NOAEL by a factor equal to or greater than the MOE, the exposure is concerned below the EPA level of concern.

Typically, the NOAEL selected for workers is identical to the NOAEL used to derive the chronic RfD and the MOE is identical to the uncertainty factor used to derive the RfD. This is the case for fluroxypyr for which the occupational NOAEL is taken as 100 mg/kg bw/day and the MOE is taken as 100 (U.S. EPA/OPP 2007f).

Forest Service risk assessments do not use the MOE approach for workers, and, instead, use a surrogate RfD, which is usually based on the NOAEL divided by the EPA MOE for

workers. This approach is mathematically equivalent to the EPA method and is consistent with other numerical expressions of risk (i.e., the hazard quotient), as discussed further in Section 3.4 (Risk Characterization). Thus, worker risks are assessed with a surrogate RfD of 1 mg a.e./kg bw/day, which is identical to the chronic RfD. As with the acute RfD, this approach is consistent with the lack of a detectable dose-duration relationship for fluroxypyr and the expectation that fluroxypyr will not accumulate in the body as the period of exposure increases.

3.3.5. Dose-Severity Relationships

Unless all hazard quotients are below the level of concern (HQ=1), Forest Service risk assessments attempt to define dose-severity relationships in order to more fully interpret the plausible consequences of exceeding the RfD. As discussed further in Section 3.4, one hazard quotient does modestly exceed the level of concern – i.e., the upper bound HQ of the scenario for subsistence populations consuming fish after an accidental spill (HQ=3). Thus, a discussion of dose-severity is warranted. When possible, dose-severity relationships are based on comparisons of human data to data from experimental animal studies; systematic patterns of toxicity for various species; and dose-response and/or dose-severity relationships in mammals. For fluroxypyr, there are no human data; furthermore, as discussed in Section 3.1 (Hazard Identification), there appear to be no systematic differences in sensitivity among species.

The only remaining basis for the discussion of dose-severity relationships is the comparison of NOAELs and LOAELs from experimental animal studies, which is a relatively weak basis for assessing dose-severity relationships. That is because NOAEL and LOAEL values from a toxicity study are essentially artifacts of the experimental doses selected prior to the start of the study. As discussed in Section 3.3.3 (Chronic RfD), the RfD of 1 mg/kg bw/day is based on the NOAEL of 100 mg/kg bw/day from the chronic feeding study in rats by Quast and McGuirk (1995) in which adverse effects were noted only at higher doses. At 500 mg/kg bw/day, adverse effects included increased kidney weight and kidney pathology in both sexes, and an increased incidence of atrophy, adipose tissue (mesenteric tissues) in males. These effects would be regarded as a serious basis for concern in a human population—i.e., mitigation and medical attention would be clearly required.

At doses of 1000 mg/kg bw/day, kidney effects were more severe and were characterized by Quast and McGuirk (1995) as renal failure. Substantial mortality was noted in both male and female rats. In females, 42% mortality was noted and 48% of the deaths were attributed to renal failure. In males, severe signs of toxicity were noted at 1000 mg/kg bw/day with 12% of the animals dying by Day 112 of the study and the remaining animals sacrificed on Day 118 of the study.

The doses of 500 and 1000 mg/kg bw/day are factors of 5 and 10, respectively, greater than the NOAEL of 100 mg/kg bw/day on which the RfD is based. This circumstance suggests that an HQ of 5 might be associated with serious adverse effects and that an HQ of 10 might be associated with lethal effects.

The inherent uncertainty associated with this interpretation of hazard quotients is substantial. As summarized in Table 6, there are two subchronic studies in which the NOAELs are equal to or greater than 1000 mg/kg bw/day (Shirasu et al. 1988; Cosse et al. 1991b). The NOAELs from many other subchronic, developmental, or reproduction studies range 125 to 750 mg/kg bw/day. Consequently, some of these studies suggest that adverse effects might not be noted at HQ values of up to 10. Conversely, some studies suggest that the ratio of the LOAEL to the NOAEL is as low as 2—e.g., the NOAEL of 212 mg/kg bw and LOAEL of 424 mg a.e./kg bw from the Liberacki et al. (1996a) study. Accordingly, an HQ of 2 could be regarded with serious concern, given that the Liberacki et al. (1996a) study reports an increased number of abortions at the LOAEL, which corresponds to an HQ of 2 using the NOAEL from the Liberacki et al. (1996a) study.

Given the variability in the experimental mammalian data and the absence of human data, no specific dose-severity relationship for fluroxypyr is proposed or used in the current risk assessment. This limitation is discussed further in Section 3.4 (Risk Characterization).

3.4. RISK CHARACTERIZATION

3.4.1. Overview

The quantitative risk characterization in both the human health and in the ecological risk assessment is based on the hazard quotient (HQ), which is defined as the anticipated exposure divided by the toxicity value. For both workers and members of the general public, the chronic RfD of 1 mg a.e./kg bw/day is used to characterize risks associated with both acute and longer-term exposures. As discussed in the exposure assessment (Section 3.2.2), all exposure assessments are based on the application of Vista XRT at the maximum application rate of 0.5 lb a.e./acre. A quantitative summary of the risk characterization for worker exposure to fluroxypyr is presented in Worksheets E02. A quantitative summary of risks to members of the general public is presented in Worksheet E04. Because the HQs are based on the RfD, an HQ of 1 or less suggests that exposures are below the level of concern. HQ values greater than 1 indicate that the exposure exceeds the level of concern.

Under normal conditions of use, fluroxypyr-MHE is not expected to cause adverse human health effects. One accidental exposure scenario, however, results in an HQ exceeds the level of concern – i.e., subsistence populations consuming fish after an accidental spill which has an upper bound HQ of 3. This exposure scenario, which is standard in all Forest Service risk assessments, is extreme, but designed to illustrate the potential consequences of a large spill into a small pond.

3.4.2. Workers

3.4.2.1. General Exposures

In terms of general exposures—i.e., daily exposure levels anticipated during a prolonged application program—the hazard quotients range from 0.0001 (aerial spray) to 0.08 (ground broadcast spray), which are below the level of concern (1.0) by factors ranging from 12.5 to 10,000. Thus, under normal conditions, even at the highest application rate, exposure levels of fluroxypyr-MHE are substantially below the level of concern.

Qualitatively, the risk characterization for workers given in the current Forest Service risk assessment is consistent with that given in the most recent EPA risk assessments:

The MOEs range from 40,000 for mixing/loading liquids for aerial application to 720,000 for flagging for aerial sprays. These MOEs are above the LOC of 100, and therefore, are not of concern.

- U.S. EPA/OPP (2007f)

The term *MOE* refers to the margin of exposure. As discussed in Section 3.3.4, the EPA does not use an RfD, using instead the animal NOAEL of 100 mg/kg bw/day with the stipulation that worker exposure levels should be below the NOAEL by the MOE, which is 100 for fluroxypyr. Mathematically, this approach is equivalent to using the RfD, which is based on an uncertainty factor of 100.

Quantitatively, the current Forest Service risk assessment is somewhat more conservative than the EPA risk assessment of fluroxypyr. The highest MOE noted by the EPA is 720,000. Given the MOE of 100, this MOE is below the level of concern by a factor of 7200 [720,000 ÷ 100]. The lowest MOE is about 40,000, which is below the level of concern by a factor of 400. Thus, based on the U.S. EPA/OPP (2007f) risk assessment for workers, exposure levels are below the level of concern by factors ranging from 400 to 7200. As noted above, the HQs for the current Forest Service risk assessment are below the level of concern by factors from 12.5 to 10,000.

The differences in the upper bound values (factors of 7000 vs 10,000 below the level of concern) are inconsequential. The lower bound values—i.e., 12.5 vs 400—reflect the consideration of dermal exposure. As discussed in Section 3.2.2.1 (General Exposures for Workers), the exposure assessment for workers is based on studies in which absorbed doses are estimated from field exposures to herbicide applications that consider all routes of exposure. As discussed in Section 3.1.3.2 (Absorption), the EPA dismissed the dermal route of exposure based on a dermal NOAEL of 1000 mg/kg bw/day in rats (U.S. EPA/OPP 2007f, p. 22). Thus, in the exposure assessment for workers, the EPA considers only the inhalation route (U.S. EPA/OPP 2007f, p. 23).

3.4.2.2. Dermal Exposures

As with general exposures discussed in the previous sections, the consideration of accidental dermal exposure scenarios in the current Forest Service risk assessment result in risk characterizations that are essentially consistent with those of the U.S. EPA. As noted above, the U.S. EPA dismissed concern for the dermal route of exposure based on a dermal NOAEL of 1000 mg/kg bw/day in rats (U.S. EPA/OPP 2007f, p. 22). The current Forest Service risk assessment does explicitly consider accidental dermal exposures in a manner consistent with other Forest Service risk assessments. Nonetheless, the upper bounds of the hazard quotients for the different exposure scenarios range from 0.00008 to 0.01, below the level of the concern by factors of 100 to 12,500. Thus, the current Forest Service risk assessment is consistent with the conclusions reached in the risk assessment by the U.S. EPA/OPP (2007f) – i.e., dermal exposures to fluroxypyr are not likely to pose a risk to workers.

3.4.2.3. Damage to the Eyes

During the application of any pesticide, care should be taken to avoid accidentally splashing the pesticide formulation into the eyes. As discussed in Section 3.1.11.3 (Ocular Effects), there is some uncertainty concerning the studies on ocular effects submitted to U.S. EPA/OPP; furthermore, studies concerning the irritant effects of Vista XRT formulation, the more concentrated formulation of fluroxypyr-MHE are not available. Based on the DER for the study by Cosse et al. (1992c), in which a formulation corresponding to Vista Specialty Herbicide (26.2% a.e.) is classified as Category II for eye damage, normal precautions for protecting the eyes during applications of fluroxypyr-MHE seem warranted. While somewhat speculative, the more highly concentrated Vista XRT formulation (45.52% a.e.) may pose a greater risk of eye damage to workers than a diluted formulation would pose.

3.4.3. General Public

Worksheet E04 summarizes the risk characterization for members of the general public based on the exposure assessments developed in Section 3.2.3 using the maximum application rate of 0.5 lb a.e./acre. As with the risk characterization for workers, the quantitative risk characterization is based on chronic RfD of 1 mg/kg bw/day. Three sets of HQ values are given in Worksheet E03: accidental, acute non-accidental, and longer-term.

The risk characterizations for all non-accidental exposure scenarios are easily interpreted, and there is no basis for assuming plausible risks to the general public. The upper bound of the highest hazard quotient for longer-term exposure scenarios is 0.06 (the longer-term consumption of contaminated vegetation), which is below the level of concern by a factor of about 16. The upper bound HQ values for the other longer-term exposure scenarios are associated with upper bound hazard quotients of 0.00002-0.009, which are below the level of concern by factors of about 100 to 50,000.

The highest HQ for non-accidental acute exposure scenarios is 0.7, and is associated with the consumption of contaminated vegetation shortly after application. This upper bound value is based on very conservative assumptions which are likely to overestimate risk. This exposure scenario essentially involves the direct spray of a home garden and assumes that the vegetation is not washed prior to consumption. The upper bound of the other non-accidental acute exposure scenarios range from 0.0007 to 0.09, below the level of concern by factors from about 10 to greater than 1400.

All of the accidental exposure scenarios are intentionally extreme. Nonetheless, only two exposure scenarios result in upper bound HQ values that exceed the level of concern—i.e., the consumption of contaminated water by a child after an accidental spill with HQ values of 0.3 (0.02-1.7) and the consumption of fish by subsistence populations after an accidental spill with HQ values of 1.0 (0.1-3). In the event of an accidental spill of a fluroxypyr-MHE formulation into a small pond, measures should be taken to limit or mitigate potential exposures to members of the general public. Such mitigation measures would be standard practice in any properly conducted pesticide application.

3.4.4. Sensitive Subgroups

With all chemicals, exposure is of particular concern for children, women who are pregnant or may become pregnant, the elderly, or diseased individuals. Although fluroxypyr may be associated with adverse effects on several organ systems (Section 3.1), the kidneys seem to be the primary target organ. While somewhat speculative, individuals with kidney diseases might be less able to excrete fluroxypyr and could be more sensitive to kidney damage associated with exposure to fluroxypyr.

Some individuals report a high degree of sensitivity to multiple chemicals, resulting in a broad-spectrum of effects, many of which are similar to allergic reactions. This condition is generally referred to as Multiple Chemical Sensitivity (e.g., ATSDR 1995). No reports have been encountered that associate exposures with fluroxypyr with adverse effects in individuals who report having Multiple Chemical Sensitivity.

3.4.5. *Connected Actions*

The Council on Environmental Quality (CEQ), which provides the framework for implementing NEPA, defines connected actions (40 CFR 1508.25) as actions which occur in close association with the action of concern; in this case, pesticide use. Actions are considered to be connected if they: (i) Automatically trigger other actions which may require environmental impact statements; (ii) Cannot or will not proceed unless other actions are taken previously or simultaneously, and (iii) Are interdependent parts of a larger action and depend on the larger action for their justification. Within the context of this risk assessment, “connected actions” include actions or the use of other chemicals which are necessary and occur in close association with use of fluroxypyr.

As discussed in detail in Sections 3.1.14 (Inerts and Adjuvants) and 3.1.15 (Impurities and Metabolites), fluroxypyr formulations contain inert components, and the metabolism of fluroxypyr may involve the formation of other compounds. Given the low HQ values associated with non-accidental exposure scenarios and the generally conservative assumptions on which these HQ values are based, there does not appear to be a plausible basis for suggesting that inerts, impurities, or metabolites will have an impact on the risk characterization for potential human health effects.

Adjuvants are a much more difficult issue to address, and it is beyond the scope current risk assessment to address adjuvants in detail. This is a general issue in all Forest Service risk assessments.

3.4.6. *Cumulative Effects*

Similar to the issues involved in assessing the use of adjuvants, it is beyond the scope of the current risk assessment to identify and consider all agents that might interact with, or cause cumulative effects with fluroxypyr, and to do so quantitatively would require a complete set of risk assessments on each of the other agents to be considered.

Addressing cumulative effects, within the context of the Food Quality Protection Act, requires the assessment of chemicals with a similar mode of action. In the recent human health risk assessment on fluroxypyr, the EPA states:

...EPA has not made a common mechanism of toxicity finding for fluroxypyr and any other substances, and fluroxypyr does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that fluroxypyr has a common mechanism of toxicity with other substances..

– U.S. EPA/OPP, 2004e, p. 73.

Notwithstanding the above statement, fluroxypyr is a relatively typical weak-acid auxin herbicide. As illustrated in Figure 1 and discussed in Section 3.1, fluroxypyr, aminopyralid (SERA 2007c), clopyralid (SERA 2004), picloram (SERA 2003a), and triclopyr (SERA 2003b) are similar with respect to their structure, pharmacokinetics, and

toxicity. It is reasonable to anticipate that exposure to fluroxypyr and other weak acid herbicides would result in essentially additive risks.

The current Forest Service risk assessment does consider the effect of repeated exposures to fluroxypyr for both workers and members of the general public. The chronic RfD is used as an index of acceptable acute and longer-term exposures. Consequently, the risk characterizations presented in this risk assessment specifically address and encompass the potential impact of the cumulative effects of repeated exposures to fluroxypyr.

4.0 ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

Fluroxypyr acid and fluroxypyr-MHE appear to be relatively non-toxic to terrestrial animals. No field studies are available on the effects of fluroxypyr applications on populations of mammalian wildlife; furthermore toxicity studies have not been conducted on mammalian species other than the standard studies in mice, rats, rabbits, and dogs generally required for pesticide registration. Thus, the hazard identification for mammalian wildlife is based on the same data used in the human health risk assessment. Fluroxypyr is not highly toxic to mammals, and there is no indication of systematic differences in sensitivity among different groups of mammals. The most likely primary target organ for fluroxypyr in mammalian wildlife is the kidney. Toxicity studies in birds are not as detailed as those in mammals. In addition, the avian studies focus on estimates of acute toxicity and the impact of longer-term exposure on reproductive capacity. Nonetheless, the available studies indicate that fluroxypyr is relatively nontoxic to birds. The U.S. EPA Office of Pesticide Programs classifies fluroxypyr, including fluroxypyr-MHE, as *Practically Nontoxic* to birds and mammals. As with most herbicides, very little information is available on the toxicity of fluroxypyr to insects. The NOEC for honeybees is about 270 mg/kg bw, which is similar to the longer-term NOEC values reported in studies on mammals and birds.

Fluroxypyr is an effective herbicide, as demonstrated in several field studies. In addition, the fluroxypyr literature includes a standard set of toxicity studies on terrestrial plants. Fluroxypyr is a typical auxin-binding herbicide, and like similar herbicides (e.g., 2,4-D and triclopyr), fluroxypyr is more toxic to broadleaf plants than to grasses. The maximum labelled application rate for fluroxypyr is 0.5 lb/acre, which is much higher than the EC₂₅ values for broadleaf plants exposed to fluroxypyr—i.e., from about 0.002 to 0.01 lb/acre. In other words, at application rates recommended for weed control, fluroxypyr will be toxic to susceptible broadleaf vegetation.

The toxicity of fluroxypyr to aquatic organisms follows a pattern similar to that observed in studies with terrestrial organisms. There is little indication that fluroxypyr poses a hazard to most species of aquatic animals; moreover, fluroxypyr is classified as slightly toxic to practically nontoxic to fish and most aquatic crustaceans (daphnids and shrimp). Based on a standard toxicity study in Eastern oysters, however, fluroxypyr-MHE is highly toxic to that species. Studies on the effects of fluroxypyr-MHE to freshwater bivalves and other species of saltwater bivalves are not available. In the absence of information to the contrary, it is reasonable to assume that fluroxypyr-MHE may be highly toxic to bivalves and perhaps to other molluscs. As with many herbicides, fluroxypyr-MHE is toxic to aquatic vegetation. Fluroxypyr-MHE, however, undergoes rapid hydrolysis to fluroxypyr acid, and the limited data available on fluroxypyr acid indicates that it is much less toxic to aquatic vegetation than the ester. Similarly, the available data indicate that the major pyridinol and pyridine metabolites are less toxic

than fluroxypyr-MHE. In addition, most studies indicate that the metabolites are much less toxic.

4.1.2. Toxicity to Terrestrial Organisms

4.1.2.1. Mammals

Several standard toxicity studies were conducted with experimental mammals as part of the registration process for fluroxypyr. As summarized in Table 6 and discussed in Sections 3.1.4 and 3.1.5, the most common effects noted in these studies include kidney pathology and decreased body weight.

No field studies are available in which the impact of fluroxypyr applications were assessed on mammalian wildlife communities. In standard experimental studies, the acute toxicity of oral exposure to fluroxypyr is low. A common measure of acute oral toxicity is the LD₅₀, the estimate of the dose that may be lethal to 50% of the exposed animals. As summarized in Section 3.1.4, the acute oral LD₅₀ in rats is greater than 2000 mg a.e./kg for both fluroxypyr acid and fluroxypyr-MHE. As also discussed in Section 3.1, a standard series of bioassays in mammals is available for subchronic and chronic toxicity (Section 3.1.5) as well as developmental and reproductive effects (Section 3.1.9). Based on these studies, the longer-term NOAEL in mammals is on the order of 100 mg a.e. /kg bw/day.

Because fluroxypyr is a weak acid, there is concern for the potential increased sensitivity of dogs and other canid species. As discussed in the risk assessments of 2,4-D (SERA 2006a) and triclopyr (SERA 2003b), dogs have an impaired capacity to excrete some weak acids and, as a result, are sometimes much more sensitive than other mammals to weak acids. With some other weak acid herbicides, like aminopyralid (SERA 2007c), there is no indication that dogs are more sensitive than other mammalian species. Fluroxypyr appears to be more like aminopyralid with respect to dog sensitivity. The 28-day NOAEL for dogs is 50 mg/kg bw/day (Ehard et al. 1983), only modestly below the lowest subchronic NOAEL of 80 mg/kg bw/day in rats. The chronic dog NOAEL of 150 mg/kg bw/day (Kinkel et al. 1984) is actually somewhat higher than the 100 mg/kg bw/day in rats (Quast and McGuirk 1995). Thus, there appears to be no basis for asserting that dogs and other canid species are more sensitive than other mammals to fluroxypyr. Thus, as discussed further in Section 4.3.2, no separate dose-response assessment is conducted for dogs and other canids.

As also summarized in Table 6 and discussed in Section 3.3.5 (Dose-Severity Relationships), there are no apparent systematic differences among groups of mammals, based on body size. Repeated dosing studies are available in four species: mice, rats, rabbits, and dogs. In rats, rabbits, and dogs, the lower bound of the NOAELs are about 100 mg/kg bw/day. The data in mice are somewhat complicated by a subchronic study by Perry et al. (1984) which reports a LOAEL of 2.7 mg/kg bw/day. The Perry et al. (1984) study is discussed in some detail in Section 3.1.5 and appears to be a clear outlier that is inconsistent with three other studies in mice, including the subsequent chronic study by Perry et al. (1985). Notwithstanding the Perry et al. (1984) study, the NOAELs reported in mice are about 300 mg/kg bw/day, well within the range of NOAELs reported

in rats. Consequently, the variability in sensitivities among mammals does not appear to be substantial. As with concerns for canid species, the lack of the systematic difference in sensitivity to fluroxypyr among mammals does not support a dose-response assessment for mammals of differing body sizes (Section 3,4.2).

4.1.2.2. Birds

The available avian toxicity studies are summarized in Appendix 3. Field studies are not available to address the effects of fluroxypyr applications on bird populations. What is more, the available avian studies looked only at gross signs of toxicity and pathology (acute studies) and reproductive endpoints (longer-term studies).

It is not clear that the avian target tissue for fluroxypyr exposure is the same as that for mammals—i.e., the kidney. The only information on organ damage comes from the acute gavage study in mallards (Roberts and Phillips 1984a), in which groups of five male and five female mallards were given gavage doses of 0 (control), 500, 1000, or 2000 mg/kg bw fluroxypyr acid. After a 14-day observation period, the mallards were sacrificed, and a gross examination of tissues was conducted. No mortality and no signs of toxicity were noted. On post mortem examination, however, orange-yellow livers characterized as *hard to the touch* were noted in 4/10 birds at 500 mg/kg bw ($p=0.043$), 3/10 birds at 1000 mg/kg bw ($p=0.11$), and 2/10 birds at 2000 mg/kg bw ($p=0.24$). No discoloration of the liver was noted in the control group. The effect on the liver is clearly not dose-related, and the differences between the control and dose groups, using the Fisher exact test, is significant only at 500 mg/kg bw. Roberts and Phillips (1984a) do not offer an interpretation of the liver effects, which are not discussed in the U.S. EPA/OPP (1998b) ecological risk assessment on fluroxypyr.

Liver changes are not noted in any of the 5-day dietary studies conducted with quail (Roberts and Phillips 1983c; Roberts and Phillips 1983b) or mallards (Grimes et al. 1991; Grimes and Jaber 1988). As noted in Appendix 3, food consumption rates varied highly among treated quail, as commonly observed in acute dietary studies with quail and mallards. Based on food consumption rates for quail, which ranged from 0.15 to 0.3 (weight of food consumed per day per unit bodyweight), according to a review of the full studies, dietary concentrations of up to 5000 ppm would be associated with doses ranging from about 750 to 1500 mg/kg bw/day. In the absence of confirming observations in these dietary studies, the liver effects in mallards, observed by Roberts and Phillips (1984a), cannot be clearly attributed to treatment. In the acute dietary study in bobwhites by Roberts and Phillips (1983b,c) low mortality rates (1/10 to 2/10) were noted at intermediate dietary concentrations (from 988 to 5000 ppm) but not at the lowest concentration (658 ppm), the highest concentration (5000 ppm), or in the control group.

As with mammals, the acute oral toxicity of fluroxypyr to birds is very low. LD₅₀ values are greater than 2000 mg a.e./kg bw for both fluroxypyr acid and fluroxypyr-MHE. Based on the available acute toxicity studies, U.S. EPA/OPP (1998b, p. 14) classifies fluroxypyr acid and fluroxypyr-MHE as *Practically Nontoxic* to birds. In birds, as in mammals, there is no great potential for fluroxypyr accumulation (Yackovich et al. 1989).

Longer-term avian toxicity studies are relatively few (n=2), compared with the number of repeated dosing studies in mammals (n=19 as summarized in Table 6). The two longer-term studies in birds are standard reproduction studies, both of which involve dietary exposure to fluroxypyr-MHE conducted with bobwhite quail (Beavers et al. 1989a) and mallard ducks (Beavers et al. 1989b). These are standard toxicity studies required for pesticide registration and are both classified as Core by U.S. EPA/OPP (1998b)—i.e., the studies are acceptable and satisfy the guideline requirements set by the EPA. There are minor differences in the effects noted in the two studies, namely that the mallards appeared to be more sensitive to exposure. In the mallard study, the dietary NOEC was 250 ppm with a corresponding LOEC of 500 ppm for reduced egg production; while in the quail study, no adverse effects were noted at dietary concentrations up to 1000 ppm. Based on these studies, U.S. EPA/OPP (1998b, p. 17) classifies fluroxypyr-MHE as *Practically Nontoxic* to birds based on longer-term exposures.

4.1.2.3. Reptiles

Fluroxypyr toxicity to reptiles and amphibians is not represented in the database maintained by Pauli et al. (2000). Furthermore, no other sources for such data were identified in the fluroxypyr literature. Generally, in the absence of toxicity data concerning reptile exposure to pesticides, the EPA recommends the use of birds as suitable surrogates (e.g., U.S. EPA/OPP 2001).

4.1.2.4. Terrestrial Invertebrates

The EPA requirements for testing the effects of herbicides on terrestrial invertebrates are relatively modest. Accordingly, for many herbicides, the dominant source of toxicity data comes from honeybee assays. For fluroxypyr, the standard contact bioassays in bees involve exposure to fluroxypyr acid (Lynn and Hoxter 1991a) and fluroxypyr-MHE (Lynn and Hoxter 1991b). Apparently, for honeybees, as for mammals, there is not a substantial difference in the toxicity of fluroxypyr acid and fluroxypyr-MHE. The LD₅₀ values for both forms of fluroxypyr are >25 µg/bee. The greater than (>) designation indicates that at this dose less than 50% of the animals died. As indicated in Appendix 4, mortality rates in the treated groups were not dose-related and within the range of control group mortality rates. In other words, 25 µg/bee is considered a NOEC.

Moreby (1991) applied a dose of 0.5 µg/insect fluroxypyr-MHE (Starane) to potato bug nymphs—i.e., *Calocoris norvegicus*, a nontarget invertebrate. Treatment significantly increased mortality (14.1% in 135 insects) at 24 hours, compared with controls (1.3%). Moreby (1991) does not provide the body weight of the insects, and this information is not otherwise available.

The only other publication identified in the open literature is the paper by Samsøe-Petersen (1995) which summarizes bioassays on the rove beetle for several pesticides. The publication cites fluroxypyr, but does not provide toxicity data.

4.1.2.5. Terrestrial Plants (Macrophytes)

Fluroxypyr is a typical auxin-binding herbicide (Fuerst et al. 1996; Hull and Cobb 1998; MacDonald et al. 1993; Orfanedes and Liebl 1993; Sanders and Pallett 1987a,b). In this respect, fluroxypyr is similar to other carboxylic acid herbicides, like clopyralid, picloram, and triclopyr and is mechanistically similar to other auxin-like herbicides, like 2,4-D, dichlorprop, mecoprop, dicamba, and quinclorac (Retzinger and Mallory-Smith 1997). As discussed in risk assessments of clopyralid, picloram, and triclopyr (SERA 2003a,b; SERA 2004c), the pyridine carboxylic acid herbicides mimic indole auxin plant growth hormones and cause uncontrolled growth in plants. At sufficiently high levels of exposure, the abnormal growth is so severe that vital functions cannot be maintained and the plant dies.

While the uptake and metabolism of fluroxypyr is different from the uptake and metabolism of other auxin herbicides (e.g., Orfanedes and Liebl 1993), the efficacy of fluroxypyr has been assayed in numerous target species, including the field bindweed (*Convolvulus arvensis*) (MacDonald et al. 1993), the highbush blackberry (*Rubus argutus*) (McCarty et al. 1996), and mixed weed populations in wheat fields (Malik et al. 1992). Some weeds, such as chickweed (*Stellaria media*), are more susceptible to fluroxypyr than are other weeds such as the field pansy (*Viola arvensis*). Moreover, the sensitivity differences are apparently due to a combination of different rates of translocation and metabolism (Sanders and Pallett 1987a). Cross resistance can be an issue for any pesticide, including herbicides. For fluroxypyr, cross-resistance was observed in yellow starthistle (*Centaurea solstitialis*) populations that are resistant to picloram (Fuerst et al. 1996).

The testing requirements for the effects of herbicides on terrestrial plants are relatively rigorous since terrestrial vegetation is the typical target group for herbicides. The testing requirements (U.S. EPA/OPPTS 2007g) involve bioassays for seedling germination and emergence (soil exposures) as well as vegetative vigor (foliar exposures) in several species of dicots and monocots. Consistent with these requirements, the registrant submitted a complete set of studies on seedling germination, seedling emergence, and vegetative vigor (Schwab 1996). As summarized in Appendix 5, the complete set of studies includes a series of plant bioassays on six dicots (cotton, cucumber, radish, soybean, sunflower, and tomato) and four species of monocots (corn, onion, ryegrass, and wheat). This set of studies is classified Core by the EPA (U.S. EPA/OPP 1998b)—i.e., it meets EPA requirements.

As indicated in Appendix 5, dicots (i.e., broadleaf plants) are substantially more sensitive than monocots (e.g., grasses) to fluroxypyr treatment, with EC₂₅ values in the range of 2.2-13.1 grams a.i./ha (\approx 0.002-0.01 lb a.i./acre) for dicots and 112 to more than 280 grams a.i./ha for monocots. This observation is consistent with the uses of fluroxypyr, and the quantitative aspects of this difference in sensitivity are discussed further in Section 4.3.2.4 (Dose-Response Assessment for Terrestrial Plants).

As discussed in 3.1.15.1. (Metabolites), two predominant metabolites are formed in the environmental degradation of fluroxypyr: a pyridinol metabolite (4-amino-3,5-dichloro-

6-fluoro-2-pyridinol) and a pyridine (4-amino-3,5-dichloro-6-fluoro-2-methoxypyridine). Both metabolites were assayed in a Tier 1 seedling emergence and vegetative vigor assay at a limit rate of 560 grams a.i./ha. For both metabolites, the values of the EC₂₅ for all effects were greater than the limit rate. Thus, the environmental and/or *in vivo* metabolism of fluroxypyr is a detoxification reaction for phytotoxicity – i.e., the metabolites are less toxic than the parent compound.

4.1.2.6. Terrestrial Microorganisms

Studies on the toxicity of herbicides to terrestrial microorganisms are not generally required for registration, and no such studies were submitted to the EPA. Soil metabolism studies (e.g., Bergstrom et al. 1990; Hawkins et al. 1981b; Lehmann and Miller 1989b; Lehmann et al. 1990a) do not include assays of microbial populations that might be used to infer an adverse effect of fluroxypyr on soil microorganisms. Nonetheless, if fluroxypyr was highly toxic to soil microorganisms, the effect might be reflected in degradation studies as a rapid decline in degradation rates. No such pattern is reported in the available literature.

A summary report by the European Commission (1999) indicates that no negative effects were observed on nitrogen or carbon metabolism in a bioassay of soil microorganisms at an exposure to fluroxypyr and another unidentified substance equivalent to 2 kg/ha. This report provides no experimental detail.

4.1.3. Aquatic Organisms

4.1.3.1. Fish

Data on the toxicity of fluroxypyr-acid and fluroxypyr-MHE to fish are summarized in Table 14 and presented in further detail in Appendix 6. The data on fluroxypyr acid are relatively simple. Based on the LC₅₀ values ranging from about 14.3 mg/L (Weinberg et al. 1991b) to greater than 100 mg/L (Willis 1984a,b), U.S. EPA/OPP (1998b, p. 18, Table 7) classifies fluroxypyr-acid as slightly toxic to practically nontoxic to fish, based on acute toxicity. Because of the low acute toxicity of fluroxypyr acid to fish, the EPA did not require an early life-stage or a fish life-cycle toxicity study on fluroxypyr acid.

As with the mammalian database (e.g., Table 6), there are apparent inconsistencies and variability in the fish toxicity studies conducted with fluroxypyr acid (Table 14). For example, Hill et al. (1984) report a NOEC of 1.8 mg/L with a corresponding LOEC of 10 mg/L in trout. In a summary of a study by Willis (1984a), however, U.S. EPA/OPP (1998b) reports a NOEC of 100 mg/L. The reason for this discrepancy is not apparent. Dow AgroSciences provided a full copy of the study by Hill et al. (1984) which indicates clearly that study was conducted under flow-through conditions. No details are available for the Willis (1984a) study—i.e., there seems to be no DER, and U.S. EPA/OPP (1998b) does not discuss any of the study details. The Willis (1984b) golden orfe study was conducted under static conditions, making it seem likely that the Willis (1984a) trout study was also a static study. This difference in exposure regime could account for the differences in NOEC values reported by Hill et al. (1984) in the flow-through study and Willis (1984a) in the presumably static study.

The studies on fluroxypyr-MHE are somewhat more complicated to discuss because of the vast differences in *nominal concentration* versus *measured concentration*. Within the context of discussing the aquatic toxicity studies on fluroxypyr-MHE, the term *nominal concentration* refers to the concentration calculated as the amount of compound added to the water, such as the amount in mg, divided by the volume of water, in liters, to which the compound is added. Thus, if 100 mg of fluroxypyr-MHE is added to one liter of water, the nominal concentration is 100 mg/L.

As noted in Table 3, the water solubility of fluroxypyr-MHE is about 0.09 mg/L in pure water and 0.136 mg/L in water buffered at pH 7. Thus, if 100 mg of fluroxypyr-MHE is added to one liter of water, not all of the fluroxypyr-MHE will dissolve and the excess fluroxypyr-MHE will form a film on the surface of the water (as discussed further below). As discussed below and detailed further in Appendices 6 through 8, many aquatic toxicity studies report nominal concentrations that exceed and often substantially exceed the solubility of fluroxypyr-MHE in water. Most of these studies will also assay the concentration of fluroxypyr-MHE and these concentrations are referred to as *measured concentrations*.

With the exception of the toxicity study by Manning (1998a), the toxicity studies on fluroxypyr-MHE (Table 14) were conducted at nominal concentrations that greatly exceed the solubility of fluroxypyr-MHE in water—i.e., nominal concentrations of 5-100 mg/L. Of these studies, all except the study by Wan et al. (1992) report both nominal and measured concentrations of fluroxypyr-MHE in water, and the measured concentrations (i.e., 0.087-0.7 mg/L) are far below the nominal concentrations.

For example, the static-renewal study by Rick et al. (1996a) reports a NOEC for bluegills of 100 mg/L based on the nominal concentration and a NOEC >0.629 mg/L based on the mean measured concentration. Actual mean measured concentrations ranged from 0.549 to 0.745 mg/L, equivalent to from 0.295 to 0.331 mg a.e./L (Rick et al. 1996a, Table 4, p. 30). Notably, the concentrations ranging from 0.549 to 0.632 mg ester/L are above the solubility of fluroxypyr-MHE in water—i.e., 0.136 mg/L in buffered water. This supersaturation may be due to the use of acetone as a solvent in the Rick et al. (1996a) study—i.e., approximately 20 g of fluroxypyr-MHE were dissolved into 100 mL of acetone, and this stock solution was then added to water to achieve the desired concentration. The acetone may have enhanced the water solubility of fluroxypyr in the test solution.

The assessment of fluroxypyr-MHE toxicity to fish is somewhat ambiguous in U.S. EPA/OPP (1998b). In the summary table of fish toxicity values (U.S. EPA/OPP 1998b, Table 7), the toxicity category for fluroxypyr-MHE is listed as *not determined*. In the discussion, however, the EPA states:

Since fluroxypyr MHE is not acutely toxic at its solubility limit, it is also considered practically nontoxic to freshwater fish on an acute basis (U.S. EPA/OPP 1998b, p. 18).

In other words, several bioassays summarized by U.S. EPA/OPP (1998b) report no apparent adverse effects in fish at nominal concentrations that substantially exceed the solubility of fluroxypyr-MHE in water. As noted above, the levels of exposure for the fish were actually above the solubility limit. The selection of the toxicity values for fluroxypyr-MHE is discussed further in Section 4.3.3.1 (Dose-Response Assessment for Fish). As with fluroxypyr acid, the EPA did not require a longer-term toxicity study in fish because of the low acute toxicity of fluroxypyr-MHE to fish.

U.S. EPA/OPP (1998b) notes that:

A degradation product of fluroxypyr is pyridinol. Wan et al. (1987) found that the 96 hr LC₅₀ of pyridinol for juveniles of six salmonid species ranged from 1.5 to 2.7 mg/L. This classifies pyridinol as moderately toxic to fish on an acute basis.

U.S. EPA/OPP (1998b, p. 18)

Apparently, Wan et al. (1987) conducted fish bioassays only on 3,5,6-trichloro-2-pyridinol, a metabolite of triclopyr. It seems that Wan et al. (1987, Table 1, p. 722) elected, for the sake of brevity, to refer to the 3,5,6-trichloro-2-pyridinol metabolite of triclopyr simply as *pyridinol*, and this designation is used in several tables in the Wan publication. The toxicity of 2-pyridinol (CAS No. 142-08-5) to trout is not addressed in the available literature, and it is not clear that 2-pyridinol is a metabolite of either triclopyr or fluroxypyr. Nevertheless, 3,5,6-trichloro-2-pyridinol is clearly a metabolite of triclopyr but not fluroxypyr (see Figure 1).

4.1.3.2. Amphibians

As with reptiles, the EPA does not generally require toxicity studies on amphibians for pesticide registration. Accordingly, amphibian studies were not identified in the FOIA of fluroxypyr studies submitted to the EPA for registration. In addition, information regarding the toxicity of fluroxypyr to amphibians was not identified in the open literature or in the reptile and amphibian database maintained by Pauli et al. (2000). In the absence of toxicity data concerning amphibian exposure to pesticides, the EPA typically assumes that fish are useful surrogates for aquatic life-stages of amphibians (e.g., e.g., U.S. EPA/OPP 2001).

4.1.3.3. Aquatic Invertebrates

The toxicity of fluroxypyr-acid and fluroxypyr-MHE to aquatic invertebrates is summarized in Table 15 and detailed further in Appendix 7. As is the case with fish, U.S. EPA/OPP (1998b, p.19) classifies fluroxypyr acid as *practically nontoxic* to freshwater invertebrates, based on the acute NOEC of 100 mg/L in *Daphnia magna* from the study by Jones and Willis (1984). For saltwater invertebrates, fluroxypyr acid is classified as *practically nontoxic* to grass shrimp, based on the NOEC of 120 mg/L from the study by Boeri et al. (1994c) and *slightly toxic* to oysters based on the LC₅₀ of 51 mg/L from the study by (Boeri et al. 1994b). The EPA did not require a chronic study in aquatic invertebrates because of the low toxicity of fluroxypyr acid to this group of organisms; however, Jones (1984a) conducted a standard life cycle study which was

submitted to the EPA in support of the registration of fluroxypyr. This study reports an effect on reproduction parameters but does not identify an LOEC based on immobility at 100 mg. The NOEC reported in the study is 56 mg/L.

The toxicity data on fluroxypyr-MHE are somewhat more complicated owing to the distinction between nominal and measured concentration. As noted in Table 15, all of the acute studies on fluroxypyr-MHE, except for the study by Manning (1998b), used nominal concentrations substantially greater than the measured concentrations, and there is no indication that fluroxypyr-MHE is toxic to daphnids or shrimp. Based on nominal NOEC values of 100 mg/L, fluroxypyr-MHE is classified as practically nontoxic to these organisms. Eastern oysters, however, appear to be more sensitive to fluroxypyr-MHE. Based on the EC₅₀ of 0.068 mg ester/L [measured concentration equivalent to 0.042 mg a.e./L] for shell deposition (Boeri et al. 1996b), fluroxypyr-MHE is classified as *very highly toxic* (U.S. EPA/OPP 1998a, p. 20).

Boeri et al. (1996b) is the only study suggesting the fluroxypyr-MHE is highly toxic to aquatic invertebrates and this study does have several limitations. Based on the EPA DER for this study, the test solutions at the three highest concentrations were visibly cloudy throughout the test. Since oysters are filter feeders, the suspended material was part of the exposure concentration, but the analytical chemistry studies were done on water filtered through a 0.45- μ filter. Therefore, the actual exposure concentrations that were effective in reducing growth may not be accurately reflected in the analytical concentrations that were used to calculate the EC₅₀. Nonetheless, this is the only study available on bivalves and the study was considered acceptable by the U.S. EPA as the basis for classifying fluroxypyr-MHE as highly toxic to bivalves.

Even though the EPA classifies fluroxypyr-MHE as very highly toxic to some saltwater invertebrates, based on acute toxicity, a chronic study in saltwater invertebrates was not required of the registrant. The EPA provides the following rationale for waiving this requirement:

Fluroxypyr MHE has high acute toxic to marine/estuarine mollusks, but is predicted to rapidly degrade to the much less toxic fluroxypyr acid in saltwater.

-U.S. EPA/OPP (1998b, p. 21)

In other words, chronic exposures to fluroxypyr-MHE are not a concern because fluroxypyr-MHE will rapidly hydrolyze to fluroxypyr acid; consequently, chronic levels of exposure to fluroxypyr-MHE will not occur. This assertion is reasonable and most certainly correct and holds for both freshwater and saltwater invertebrate species.

Kirk et al. (1996) conducted a chronic daphnia study with fluroxypyr-MHE. This study, however, involved flow-through exposures in which the concentration of fluroxypyr-MHE was maintained in the test system for the 21-day duration of the study. As would be expected, the toxicity of fluroxypyr-MHE is greater than that of fluroxypyr acid by a factor of nearly 1000—i.e., an LOEC of 0.109 for the ester versus a LOEC of 100 mg/L

for the acid. While the ester study by Kirk et al. (1996) appears to have been properly conducted, the DER classifies the study as Supplemental, based on evidence of undissolved test material floating on the surface of the water in the test system. More importantly, however, the study is not directly relevant to the current Forest Service risk assessment because the type of exposure used in the Kirk et al. (1996) study will not occur in the environment. As discussed above, fluroxypyr-MHE will hydrolyze rapidly to fluroxypyr acid after application. Consequently, the chronic toxicity values for fluroxypyr used in the current Forest Service risk assessment are based on fluroxypyr acid rather than fluroxypyr-MHE, as discussed further in Section 4.3.3.3 (Dose-Response Assessment for Aquatic Invertebrates).

4.1.3.4. Aquatic Plants

4.1.3.4.1. Fluroxypyr

Studies on the toxicity of fluroxypyr acid and fluroxypyr-MHE to aquatic plants are summarized in Table 16, and additional details are provided in Appendix 8. Except for the studies by Ma (Ma 2002; Ma et al. 2001; Ma et al. 2002), all of the studies summarized in Table 16 were submitted to the EPA in support of the registration of fluroxypyr and report measured rather than nominal concentrations. With the exception of one bioassay on fluroxypyr acid (Jones 1984c), all of the available aquatic plant studies were conducted with fluroxypyr-MHE (the end use product).

The publications by Ma (Ma 2002; Ma et al. 2001; Ma et al. 2002) report EC₅₀ values for fluroxypyr-MHE that are much higher than the comparable values reported in the studies submitted to and reviewed by U.S. EPA/OPP (1998b). The publications by Ma and coworkers are essentially survey studies involving the effects of numerous pesticides on algae and provide relatively few experimental details. Specifically, the Ma studies do not specify the formulation of fluroxypyr or even the form of fluroxypyr tested. The formulations are characterized only as 11% EC (Ma 2002, Ma et al. 2001) or 22% EC (Ma et al. 2002). Because the formulations are specified as EC (i.e., emulsifiable concentrates), it is virtually certain that the fluroxypyr used in the Ma studies consisted of an ester of fluroxypyr. It is not clear, however, that the ester was fluroxypyr-MHE. As noted in Table 1 of the current Forest Service risk assessment, the formulations considered in this risk assessment contain 26.2% (Vista Specialty Herbicide) or 45.52 % (Vista XRT), neither of which correspond to the percentages specified in the Ma papers. Furthermore, the Ma studies do not report whether the concentrations are expressed in units of mg formulation, mg a.i., or mg a.e. What is more, there is no indication that the fluroxypyr or other pesticide concentrations were measured. The high EC₅₀ values reported in the studies (i.e., 3 mg/L to 37.5 mg/L) far exceed the water solubility of fluroxypyr-MHE. Thus, it is likely that the concentrations reported in the Ma publications are nominal rather than measured. For the sake of completeness, this risk assessment cites the Ma studies; however, they are not given further consideration due to the uncertainties associated with their reporting.

Fluroxypyr-MHE is much more toxic to aquatic plants than to aquatic animals, as is true for most herbicides. The toxicity studies conducted with fish (Table 14) and aquatic invertebrates (Table 15) report both nominal and measured concentrations of fluroxypyr.

Because fluroxypyr-MHE is much more toxic to aquatic plants than to aquatic animals, the aquatic plant studies (other than the Ma studies) report measured concentrations, and only the measured concentrations are given in Table 15. Most of the toxicity values given in Table 15 exceed the concentration of fluroxypyr-MHE in water—i.e., 0.09 mg/L in pure water and 0.136 mg/L in water buffered at pH 7. As with the toxicity studies conducted with fish and aquatic invertebrates, the measured concentrations that exceed the water solubility of fluroxypyr reflect the hydrolysis of the fluroxypyr-MHE to fluroxypyr acid. For example, the DER for the study by Milazzo et al. (1996c) specifically notes that about 75% of the fluroxypyr-MHE was probably degraded to fluroxypyr acid over the course of the study. Thus, the NOEC of 0.199 reported in Milazzo et al. (1996c) probably consisted of about 0.05 mg/L fluroxypyr-MHE and 0.15 mg/L fluroxypyr acid by the end of the study.

The full study by Kirk et al. (1998) conducted with duckweed provides much more detailed data on the concentrations of fluroxypyr-MHE and fluroxypyr acid over the 7-day course of the study. As summarized in Appendix D4 of Kirk et al. (1998, p. 62), an inverse relationship is apparent in the nominal concentration of fluroxypyr-MHE and the proportion of fluroxypyr-MHE hydrolyzed to the acid form over the 7-day course of the study. At nominal concentrations of 0.451 and 0.9 mg/L, virtually all of the ester was hydrolyzed. At a nominal concentration of 1.8 mg/L, about 80% of the ester was hydrolyzed. At concentrations from 3.6 to 14.4 mg/L, between 54% and 69% of the ester was hydrolyzed. Over this range, however, the proportion of the ester converted to the acid evidences scatter, and the inverse relationship is not apparent. By Day 14 of the study, 100% of the ester was converted to acid at concentrations of 3.6 mg/L, 78.4-88.2% was converted at 7.2 mg/L, and 47.1-52.7% was converted to acid at 14.4 mg/L. This pattern of conversion is consistent with first-order hydrolysis. In water that did not contain duckweed, the proportion of fluroxypyr-MHE converted to fluroxypyr acid was much less, indicating that the rapid hydrolysis of fluroxypyr-MHE to fluroxypyr acid primarily involved biological/enzymatic hydrolysis.

In terms of practical significance to the current risk assessment, the conversion of fluroxypyr-MHE to fluroxypyr acid is clearly a process that will occur in the environment and will be mediated by nontarget organisms like aquatic plants and soil microbes. For exposures associated with runoff or percolation—i.e., the non-accidental exposure scenarios summarized in Section 4.2.5 (Exposure Assessment for Aquatic Organisms)—it is likely that most if not all fluroxypyr-MHE will be hydrolyzed to fluroxypyr acid by the time that the compound reaches water. For the accidental spill scenario, however, this will not be the case, and initial peak exposures will be predominantly to fluroxypyr-MHE. This circumstance is considered further in the dose-response assessment for aquatic plants (Section 4.3.3.4.).

4.1.3.4.2. Metabolites

Toxicity studies in aquatic plants have been conducted on the pyridinol metabolite of fluroxypyr (i.e., 4-amino-3,5-dichloro-6-fluoro-2-pyridinol) and the pyridine metabolite of fluroxypyr (i.e., 4-amino-3,5-dichloro-6-fluoro-2-methoxy-pyridine). This

information is summarized in Table 16, and additional details of the available studies are provided in Appendix 8.

Table 16 gives the toxicity value for each metabolite in the various species on which assays were conducted as well as the corresponding toxicity value for fluroxypyr-MHE. As noted in the previous subsection, very little information is available on the toxicity of fluroxypyr acid to algae, and the acid appears to have a very low order of toxicity (i.e., a NOEC of 100 mg/L). The last column in Table 16 gives the relative potency of the metabolite as the ratio of the toxicity value for fluroxypyr-MHE divided by the toxicity value for the metabolite. Thus, values of less than 1 indicate that the metabolite is less toxic than fluroxypyr-MHE.

As summarized in Table 16, all of the available studies indicate that the toxicity of the fluroxypyr metabolites to aquatic plants is substantially less than the toxicity of fluroxypyr-MHE. For the pyridinol metabolite, the relative potencies range from 0.036 to 0.14, indicating that the metabolite is less toxic by factors from about 7 to more than 27. For the pyridine metabolite, the relative potencies range from 0.037 to 0.33, indicating that the metabolite is less toxic by factors from about 3 to 27.

Notice that all of the estimates of relative potency for the pyridinol metabolite and several of the estimates for the pyridine metabolite are based on NOEC values rather than EC_{50} values—i.e., concentrations associated with a 50% inhibition of growth. While the Forest Service prefers to use NOEC values rather than EC_{50} or LC_{50} values for generating hazard quotients, as discussed further in Section 4.4 (Risk Characterization), the use of NOEC values for assessing relative potency is not desirable because NOEC values are artifacts of study design. The use of EC_{50} or LC_{50} values for estimating relative potency is much more desirable because these types of values incorporate information on the dose-response curve and can be conceptually related to a meaningful definition of relative potency in statistical and conceptual terms (e.g., Finney 1971). Expressions of relative potency can be based on both NOEC and EC_{50} values for three species: *Anabaena flos-aquae*, *Selenastrum capricornutum*, and *Skeletonema costatum*. As indicated in Table 16, the relative potency values for the latter two species are virtually identical based on either measure of relative potency. For *Anabaena flos-aquae*, however, the relative potency based on the EC_{50} values is 0.33; whereas, the relative potency based on the NOEC values is only 0.026. While the difference in the two measures of relative potency for *Anabaena flos-aquae* are substantial, the overall weight of evidence does consistently indicate that the metabolites of fluroxypyr are less toxic than fluroxypyr-MHE. Moreover, the majority of the studies indicate that the differences in toxicity are substantial.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview

Terrestrial animals might be exposed to any applied herbicide from direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. For the maximum application rate of 0.5 lb a.e./acre the exposure scenarios for terrestrial species are summarized in Worksheet G01 of the EXCEL workbook that accompanies this risk assessment. The use of lower applications rates is discussed in the risk characterization. In the ecological risk assessment, as in the human health risk assessment, three general types of exposure scenarios are considered: accidental, acute non-accidental, and longer-term.

Accidental exposure scenarios lead to upper bound estimates of exposure ranging from about 2 mg/kg bw (the consumption of contaminated water by a small mammal) to about 380 mg/kg bw (the consumption of contaminated fish by a fish-eating bird). Central and lower bound estimates of exposure are also derived but are inconsequential to the current risk assessment because the upper bound estimates of accidental exposure do not reach the level of concern—i.e., all HQ values are less than 1, as discussed in the Risk Characterization (Section 4.4.2). As would be expected, the acute non-accidental exposure scenarios lead to low estimates of exposure with upper bound dose estimates ranging from about 0.006 mg/kg bw (consumption of surface water by a small mammal) to about 56 mg/kg bw (the consumption of contaminated insects by a small bird). The lowest estimates of exposure levels are associated with longer-term scenarios with upper bound estimates ranging from about 0.0008 mg/kg bw/day (the consumption of contaminated water by a small mammal) to about 2.3 mg/kg bw/day (the consumption of contaminated vegetation by a large mammal). As with the accidental exposure scenarios, all of the non-accidental acute and longer-term exposures are below the level of concern.

For terrestrial plants, five exposure scenarios are considered quantitatively: direct spray, spray drift, runoff, wind erosion, and the use of contaminated irrigation water. Unintended direct spray is expressed simply as the application rate—i.e., 0.5 lb a.e./acre at the maximum application rate. For directed foliar applications, this scenario should be regarded as an extreme/accidental form of exposure which is not likely to occur in most applications. For broadcast applications, the direct spray scenario is much more plausible. Spray drift is based on estimates from AGDRIFT. The proportion of the applied amount transported off-site from runoff is based on standard GLEAMS modeling of clay, loam, and sand. The amount of fluroxypyr that might be transported off-site from wind erosion is based on estimates of annual soil loss associated with wind erosion and the assumption that the herbicide is incorporated into the top 1 cm of soil. Exposure from the use of contaminated irrigation water is based on the same data used to estimate human exposure from the consumption of contaminated ambient water. All of these exposure scenarios are dominated by situational variability because the levels of exposure are highly dependent on site-specific conditions. Thus, the exposure estimates are intended to represent conservative but plausible ranges of exposure; however, these ranges may over-estimate or under-estimate actual exposures in some cases.

Non-accidental exposures of aquatic plants and animals to fluroxypyr are based on essentially the same information used to assess the exposure to terrestrial species from contaminated water. The accidental spill scenario, however, is problematic because the nominal concentrations of fluroxypyr-MHE in water after an accidental spill are far higher than the water solubility of fluroxypyr-MHE. Estimates of water solubility cannot be used to set an upper bound value for plausible fluroxypyr concentrations in water because data from acute toxicity bioassays indicate that solvents and perhaps some inerts used in fluroxypyr formulations may result in water concentrations of fluroxypyr-MHE that exceed the water solubility. Consequently, the accidental spill scenario is not used explicitly to develop water concentrations of fluroxypyr-MHE, and the potential risks to aquatic organisms after an accidental spill are addressed qualitatively in the risk characterization.

4.2.2. Mammals and Birds

Mammals and birds might be exposed to any applied pesticide from direct spray, the ingestion of contaminated media (e.g., vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. In the exposure assessments for the ecological risk assessment, estimates of oral exposure to mammals and birds are expressed in the same units as the available toxicity data. As in the human health risk assessment, these units are usually expressed as mg of agent per kg of body weight and abbreviated as mg/kg for terrestrial animals. Unless otherwise specified, all exposure estimates for fluroxypyr-MHE are expressed as mg a.e. (acid equivalents).

For dermal exposure of mammals and birds to an applied pesticide, the units of exposure are expressed in mg of agent per cm² of surface area of the organism and abbreviated as mg/cm². In estimating dose, however, a distinction is made between the exposure dose and the absorbed dose. The *exposure dose* is the amount of material on the organism (i.e., the product of the residue level in mg/cm² and the amount of surface area exposed), which can be expressed either as mg/organism or mg/kg body weight. The *absorbed dose* is the proportion of the exposure dose that is actually taken in or absorbed by the animal.

Because of the relationship of body weight to surface area as well as to the consumption of food and water, small animals will generally receive a higher dose, in terms of mg/kg body weight, relative to large animals, for a given type of exposure. Consequently, most general exposure scenarios for mammals and birds are based on a small mammal or a small bird. For small mammals, exposure assessments are conducted for direct spray (F01 and F02a), consumption of contaminated fruit (F03a, F04a, F04b), and contaminated water (F05, F06, F07). Generally, herbicide concentrations on grasses will be higher than concentrations on fruits and other types of vegetation (Fletcher et al. 1994). Although small mammals do not typically consume large amounts of grass over prolonged periods of time, small mammals, like the meadow vole (*Microtus pennsylvanicus*), may consume grasses as a substantial proportion of their diet at certain times of the year. Consequently, the acute consumption of contaminated grass by a small mammal is considered in this risk assessment (F03b). Large mammals may consume grasses over a long period of time, and these scenarios are included both for acute

exposures (Worksheet F10) and longer-term exposures (Worksheets F11a and F11b). Other exposure scenarios for mammals involve the consumption of contaminated insects by a small mammal (Worksheet F14a) and consumption by a large mammalian carnivore of small mammals contaminated by direct spray (Worksheet F16a). Exposure scenarios for birds involve the consumption of contaminated insects by a small bird (Worksheet F14b), the consumption of contaminated fish by a predatory bird (Worksheets F08 and F09), the consumption by a predatory bird of small mammals contaminated by direct spray (F16b), and the consumption of contaminated grasses by a large bird (F12, F13a, and F13b).

4.2.2.1. Direct Spray

The unintentional direct spray of wildlife during broadcast applications of a pesticide is a plausible exposure scenario similar to the accidental exposure scenarios for the general public discussed in Section 3.2.3.2. In a scenario involving exposure to direct spray, the amount of pesticide absorbed depends on the application rate, the surface area of the organism, and the rate of absorption.

For this risk assessment, two direct spray or broadcast exposure assessments are conducted (Worksheets F01, F02). The first spray scenario (detailed in Worksheet F01) concerns the direct spray of half of the body surface of a 20 g mammal as the chemical is being applied. This exposure assessment assumes first-order dermal absorption. The second exposure assessment (detailed in Worksheet F02) assumes complete absorption over day 1 of exposure. This assessment is included in an effort to encompass the increased exposure due to grooming.

There are no exposure assessments for the direct spray of large mammals, principally because allometric relationships dictate that according to body weight, the amount of a compound to which large mammals will be exposed as a result of direct spray is less than the amount to which smaller mammals will be exposed.

4.2.2.2. Dermal Contact with Contaminated Vegetation

As discussed in the human health risk assessment (Section 3.2.3.3), the only approach for estimating the potential significance of dermal contact with contaminated vegetation is to assume a relationship between the application rate and dislodgeable foliar residue. Unlike the human health risk assessment, in which estimates of transfer rates are available, there are no transfer rates available for wildlife species. Wildlife species are more likely than humans to spend long periods of time in contact with contaminated vegetation. It is reasonable to assume that for prolonged exposures, equilibrium may be reached between pesticide levels on the skin, rates of dermal absorption, and pesticide levels on contaminated vegetation. Since data regarding the kinetics of this process are not available, a quantitative assessment for this exposure scenario cannot be made in the ecological risk assessment.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey

Fluroxypyr will typically be used in broadcast foliar applications; therefore, the consumption of contaminated vegetation is an obvious concern. Separate exposure

assessments are developed for acute and chronic exposure scenarios involving a small mammal (Worksheets F03a, F03b, F04a and F04b), a large mammal (Worksheets F10, F11a, and F11b), and large birds (Worksheets F12, F13a, and F13b). Similarly, the consumption of contaminated insects is modeled for a small bird (Worksheet 14a) and a small mammal (Worksheet 14b). As detailed in the exposure assessment for human health (Section 3.2.3.3), the empirical relationships based on those recommended by Fletcher et al. (1994) are used to estimate residues in contaminated insects (Worksheets F14a and F14b). For all exposure scenarios involving contaminated vegetation or insects, residues rates for broadcast foliar liquid applications are higher than those for broadcast granular applications, as indicated in Table 12.

A similar set of scenarios is provided for the consumption of small mammals by either a predatory mammal (Worksheet 16a) or a predatory bird (Worksheet 16a). In addition to the consumption of contaminated vegetation, insects, and other terrestrial prey, exposure pathways for fluroxypyr may be associated with ambient water and fish. Thus, a separate scenario is developed for the consumption of contaminated fish by a predatory bird involving acute (Worksheet F08) and chronic (Worksheet F09) exposure, as detailed in the cited worksheets.

4.2.2.4. Ingestion of Contaminated Water

The methods for estimating fluroxypyr concentrations in water are identical to those used in the human health risk assessment (Section 3.2.3.4). The only major differences in the estimates of exposure involve the weight of the animal and the amount of water consumed. These differences are detailed and documented in the worksheets regarding the consumption of contaminated water for small mammals (Worksheets F05a, F06a, and F07a) and birds (Worksheets F05b, F06b, and F07b).

Unlike the human health risk assessment, estimates of the variability of water consumption are not available. Thus, for the acute scenario, the only factors affecting the estimate of the ingested dose include the field dilution rates (i.e., the concentration of the chemical in the solution that is spilled) and the amount of solution that is spilled. As in the acute exposure scenario for the human health risk assessment, the central estimate of the amount of the spilled solution is taken as 100 gallons of a field solution with a range of 20-200 gallons (Worksheets F05a and F05b).

In the exposure scenario involving ponds or streams contaminated by runoff or percolation, the only variable factors are the water contamination rates (Section 3.2.3.4.2) and the application rates (Worksheets F06a through F07b).

As discussed in Section 3.1.4 (Acute Toxicity) and Section 3.1.5 (Subchronic or Chronic Systemic Toxic Effects), the toxicity of fluroxypyr acid and fluroxypyr-MHE appear to be equivalent in mammals. Consequently, the environmental metabolism of fluroxypyr-MHE to fluroxypyr acid does not have a direct impact on the risk assessment for terrestrial mammals and birds, which is not true for all aquatics species, as discussed further in Section 4.2.5 (Exposure Assessment for Aquatic Organisms).

4.2.3. Terrestrial Invertebrates

4.2.3.1. Direct Spray and Drift

For honeybees, estimated levels of exposure associated with broadcast applications of fluroxypyr are detailed in Worksheet G02b. In all Forest Service risk assessments, honeybee exposure levels associated with broadcast applications are modeled as a simple physical process based on the application rate and surface area of the bee. The surface area of the honeybee (1.42 cm²) is based on the algorithms suggested by Humphrey and Dykes (2008) for a bee with a body length of 1.44 cm. The broadcast application rate is taken as 0.5 lb a.i./acre, the maximum application rate for fluroxypyr.

The amount of fluroxypyr deposited on a bee during or shortly after application depends on how close the bee is to the application site as well as foliar interception of the spray prior to deposition on the bee. Since aerial broadcast foliar applications are considered in this risk assessment (Section 2.3.2), the estimated proportions of the nominal application rate at various distances downwind given in G02b are based on Tier 1 aerial estimates from AgDrift Version 2.0.05 (Teske et al. 2002) for distances of 0 (direct spray) to 900 feet downwind of the treated site.

In addition to drift, foliar interception of a pesticide is a concern in the exposure assessment for honeybees. The impact of foliar interception would vary depending on the nature of the canopy above the bee. For example, in studies investigating the deposition rate of diflubenzuron in various forest canopies, Wimmer et al. (1993) noted 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). In Worksheet G02b, foliar interception rates of 0% (no interception), 50%, and 90% are used.

During broadcast applications of a pesticide, it is likely that terrestrial invertebrates other than bees will be subject to direct spray. As discussed in further detail in Section 4.3.2.3 (dose-response assessment for terrestrial invertebrates), the available toxicity data on terrestrial invertebrates do not support the derivation of separate toxicity values for different groups of terrestrial insects. Thus, the honeybee is used as a surrogate for other insect species, precluding the necessity of developing additional exposure scenarios for other insects.

4.2.3.2. Other Routes of Exposure

In addition to direct spray, terrestrial invertebrates might be exposed to any pesticide applied by broadcast foliar methods through exposure pathways similar to those considered for other terrestrial animals—i.e., contaminated vegetation, prey, soil, or water. Honeybees as well as some other terrestrial insects may also be exposed to pesticides while foraging for nectar or pollen.

Exposure estimates for some of these pathways can be easily developed for fluroxypyr. For example, estimates of fluroxypyr concentrations on contaminated vegetation (Table 10) can be combined with estimates of the amount of vegetation consumed per day by

herbivorous insects (e.g., Reichle et al. 1973; Waldbauer 1968) to calculate daily consumption rates for fluroxypyr, using essentially the same algorithms used in the corresponding exposure assessments for birds and mammals (Section 4.2.2.3). Similarly, the Gleams-Driver modeling discussed in Section 3.2.3.4.2 provides estimates of fluroxypyr concentrations in soil (Appendix 9, Tables 2 and 3). These estimates can be used with toxicity data on soil invertebrates, like earthworms, to assess potential risks to fossorial invertebrates.

As discussed in Section 4.1.2.4 (Hazard Identification for Terrestrial Invertebrates) the available data on the toxicity of fluroxypyr to terrestrial invertebrates are sparse. Moreover, as discussed further in Section 4.3.2.3 (Dose-Response Assessment for Terrestrial Invertebrates), toxicity values for insects can be developed only for the honeybee. Thus, in the absence of adequate toxicity data for terrestrial invertebrates other than the honeybee, exposure assessments for other groups of terrestrial invertebrates are not developed.

4.2.4. Terrestrial Plants

Generally, the primary hazard to nontarget terrestrial plants associated with the application of most herbicides is unintended direct deposition or spray drift. In addition, herbicides may be transported off-site by percolation or runoff or by wind erosion of soil. As noted in Section 4.1.2.5 (Hazard Identification for Terrestrial Plants) and discussed further in Section 4.3.2.5 (Dose-Response Assessment for Terrestrial Plants), the toxicity data on fluroxypyr are sufficient to interpret risks associated with these exposure scenarios. Consequently, exposure assessments are developed for each of these exposure scenarios, as detailed in the following subsections.

4.2.4.1. Direct Spray

Unintended direct spray will result in an exposure level equivalent to the application rate. For many types of herbicide applications, it is plausible that some nontarget plants immediately adjacent to the application site could be sprayed directly. This type of scenario is modeled in the worksheets that assess off-site drift, as discussed in the following subsection.

4.2.4.2. Off-Site Drift

Because off-site drift is more or less a physical process that depends primarily on droplet size and meteorological conditions rather than specific properties of the compound being sprayed, estimates of off-site drift can be modeled using AgDrift. The estimates of drift used for terrestrial plants are identical to those used for the exposure assessment of the honeybee (Section 4.2.3.1.).

The estimates of drift should be regarded as little more than generic estimates similar to the water concentrations modeled using GLEAMS (Section 3.2.3.4). Actual drift will vary according to a number of conditions—e.g., the topography, soils, weather, and the pesticide formulation. All of these factors cannot be considered in this general risk assessment.

The drift estimates used in the current Forest Service risk assessment are based on the most recent release—i.e., AgDRIFT Version 2.0.05 (Teske et al. 2002) using Tier 1 analyses for aerial and ground broadcast applications. The term *Tier 1* is used to designate relatively generic and simple assessments that may be viewed as plausible upper limits of drift. Aerial drift estimates are based on Tier 1 using 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.

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. For the current Forest Service risk assessment, 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).

4.2.4.3. Runoff and Soil Mobility

Any pesticide can be transported from the soil at the application site by runoff, sediment loss, or percolation. Runoff, sediment loss, and percolation are considered in estimating contamination of ambient water. Only runoff and sediment loss are considered in assessing off-site soil contamination. This approach is reasonable because off-site runoff and sediment transport will contaminate the off-site soil surface and could impact nontarget plants. Percolation, on the other hand, represents the amount of the herbicide that is transported below the root zone and thus may impact water quality but should not affect off-site vegetation. The GLEAMS modeling used to estimate concentrations in water provides data on loss by runoff. As with the estimates of fluroxypyr in surface water, runoff estimates are modeled for clay, loam, and sand at nine sites which are representative of different temperatures and rainfall patterns.

For fluroxypyr, the results of the standard GLEAMS modeling of runoff and sediment losses are summarized in Table 1 of Appendix 9. These values are used in Worksheets G04a through G04c to estimate exposures to nontarget vegetation over the range of application rates considered in this risk assessment. As indicated in Appendix 9, Table 1, runoff of up to about 10% of applied fluroxypyr may occur in predominantly clay soils with high rates of rainfall. The upper range of 10% runoff used in the current Forest Service risk assessment is higher than the 5% upper bound estimate used by U.S. EPA/OPP (1998b, p. 33). The 5% estimate from EPA, however, appears to be a largely judgmental rather than an estimate based on monitoring data or environmental fate modeling with PRZM/EXAMS. As indicated in Table 1 of Appendix 9, the 5% estimate from the EPA is reasonable and encompasses the upper bound estimates for most soils, except clay (high runoff potential) in areas with high rates of rainfall. Much less runoff is expected from loam soils, and virtually no runoff is expected from predominantly sand soils.

The amount of pesticide not washed off in runoff or sediment will penetrate into the soil column, and the depth of penetration will depend on the properties of the chemical, the properties of the soil, and the amount of rainfall. The GLEAMS model provides estimates of pesticide concentrations in soil layers of varying depths. These concentrations are output by GLEAMS in mg pesticide/kg soil (ppm). The minimum non-zero value that GLEAMS will output is 0.000001 mg/kg, equivalent to 1 nanogram/kg soil or 1 part per trillion (ppt).

The deepest penetration of fluroxypyr in clay, loam, and sand modeled using GLEAMS is summarized in Table 4 of Appendix 9. Based on GLEAMS modeling, the maximum penetration of fluroxypyr into clay soils is estimated as 4-48 inches, with the depth of penetration increasing as rainfall rates increase. In predominantly loam and sand soils, fluroxypyr may penetrate to a depth of 60 inches, depending on rainfall rates.

4.2.4.4. Contaminated Irrigation Water

Unintentional direct exposure of nontarget plants is possible from the use of contaminated ambient water for irrigation, as observed by Bhandary et al. (1991) for certain herbicides.

The levels of exposure associated with this scenario will depend on the pesticide concentration in the ambient water used for irrigation and the amount of irrigation water used. Concentrations in ambient water are generally based on the concentrations modeled in the human health risk assessment (Section 3.2.3.4). The amount of irrigation used will depend on the climate, soil type, topography, and plant species under cultivation. Thus, the selection of an irrigation rate is somewhat arbitrary. Typically, plants require from 0.1 to 0.3 inches of water per day (Delaware Cooperative Extension Service 1999).

In the absence of any general approach for determining and expressing the variability of irrigation rates, the application of 1 inch of irrigation water is used in this risk assessment. This rate is somewhat higher than the maximum daily irrigation rate for sandy soil (0.75 inches/day) and substantially higher than the maximum daily irrigation rate for clay (0.15 inches/day) (Delaware Cooperative Extension Service 1999). Details about the calculation used to estimate the functional application rates based on irrigation using contaminated surface water are provided in Worksheet F15.

4.2.4.5. Wind Erosion

Wind erosion is a major transport mechanism for soil (e.g., Winegardner 1996). Although in the fluroxypyr literature there are no reports of specific incidents of nontarget damage from wind erosion, this mechanism is associated with the environmental transport of other herbicides (Buser 1990).

Wind erosion leading to off-site contamination of pesticides is likely to be highly site-specific. The amount of fluroxypyr that might be transported by wind erosion depends on several factors, including application, depth of incorporation into the soil, persistence

in the soil, wind speed, and topographical and surface conditions of the soil. Under desirable conditions—e.g., relatively deep (10 cm) soil incorporation, low wind speed, and surface conditions which inhibit wind erosion—it is likely that the amount of fluroxypyr transported by the wind would be neither substantial nor significant.

For this risk assessment, the potential effects of wind erosion are estimated in Worksheet G06. In this worksheet, it is assumed that fluroxypyr is incorporated into the top 1 cm of soil, which is identical to the depth of incorporation used in GLEAMS modeling. Average soil losses are estimated to range from 1 to 10 tons/ha/year with a typical value of 5 tons/ha/year. These estimates are based on field studies conducted on agricultural sites that found that wind erosion may account for annual soil losses ranging from 2 to 6.5 metric tons/ha (Allen and Fryrear 1977).

As noted in Worksheet G06, the offsite losses are estimated to reach up to about 0.014% of the application rate. Larney et al. (1999), however, report 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. This difference appears to be at least partially due to the much higher soil losses noted by Larney et al. (1999)—i.e., up to 56.6 metric tons/ha from a fallow field. The losses reflected in Worksheet G06 may be somewhat more realistic for forest or rangeland applications, because usually they are not made to fallow areas. In any event, the higher offsite losses reported by Larney et al. (1999) are comparable to exposures associated with offsite drift at distances of 100-300 feet from the application site (G05). All of these estimates for wind erosion and offsite drift are likely to vary dramatically according to site conditions and weather conditions.

4.2.5. Aquatic Organisms

For applications of fluroxypyr to vegetation, the plausibility of effects on aquatic species is based on estimated concentrations of fluroxypyr in surface water identical to those used in the human health risk assessment. These values are summarized in Table 11 and discussed in Section 3.2.3.4.6.

This approach, however, cannot be applied to the accidental spill scenario. As detailed in Worksheet D03, the accidental spill scenario involves the spill of 100 (20-200) gallons of a field solution of fluroxypyr-MHE into a small pond. The resulting concentrations of fluroxypyr-MHE are modeled by simple dilution at about 4.5 (0.45-15) mg/L. The water solubility of fluroxypyr-MHE, however, is only about 0.09 mg/L in pure water and about 0.136 mg/L in water buffered at pH 7. Thus, immediately after an accidental spill, most of the fluroxypyr-MHE will remain undissolved in water.

Based on observations made during the course of acute toxicity studies (e.g., Rick et al. 1996a), excess fluroxypyr-MHE was clearly evident floating on the top of the test water. In addition, as discussed in Section 4.1.3.1, solvents used in aquatic bioassays of fluroxypyr-MHE appear to have enhanced the solubility of fluroxypyr-MHE in test water. Accordingly, it is possible that the inerts used in fluroxypyr-MHE formulations may also enhance the solubility of fluroxypyr-MHE in water. In addition, organic compounds in

natural surface water may also tend to enhance the solubility of fluroxypyr-MHE in water. Thus, the reported water solubility values for fluroxypyr-MHE cannot be used to set an upper limit on plausible concentrations of fluroxypyr-MHE in water after an accidental spill.

A further complication in assessing the spill scenario involves the conversion of fluroxypyr-MHE to fluroxypyr acid. As noted by Rick et al. (1996a, p. 11), it appears that about half of the fluroxypyr-MHE was converted to fluroxypyr acid over the 96-hour course of the study. The biologically mediated hydrolysis of fluroxypyr-MHE will also occur after an accidental spill; consequently, exposure to fluroxypyr will entail a mixture of the fluroxypyr-MHE and fluroxypyr acid. The formation of fluroxypyr acid from fluroxypyr-MHE, however, does not seriously limit the risk assessment because fluroxypyr acid is clearly much less toxic than fluroxypyr-MHE to aquatic organisms (Section 4.3.3).

While the formation of fluroxypyr acid during a spill of fluroxypyr-MHE is not a serious limitation, uncertainties in meaningfully assessing exposures of aquatic organisms to fluroxypyr-MHE after an accidental spill are difficult to address quantitatively. In addition and as discussed further in Section 4.3.3 (Dose-Response Assessment for Aquatic Organisms), the toxicity data on fluroxypyr-MHE are also somewhat difficult to address in terms of an accidental spill owing to the large differences in reported nominal and measured concentrations in most bioassays (i.e., Tables 14 and 15). Consequently, the accidental spill scenario is not used to develop HQ values, and the likely consequences of an accidental spill are addressed qualitatively in Section 4.4.3 (Risk Characterization for Aquatic Organisms).

Based on the study by Rick et al. (1996a), discussed above as well as other studies on the environmental fate of fluroxypyr-MHE (Section 3.2.3.4), longer-term exposures to fluroxypyr-MHE will not occur because of its biologically mediated hydrolysis to fluroxypyr acid. Consequently, all longer-term exposures to fluroxypyr are assumed to involve only fluroxypyr acid. This approach has a practical impact only on the assessment of the longer-term effects of fluroxypyr to aquatic invertebrates, as discussed further in Section 4.3.3.3.2.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

The specific toxicity values used in this risk assessment are summarized in Table 18, and the derivation of each of these values is discussed in the various subsections of this dose-response assessment. The available toxicity data support separate dose-response assessments in eight classes of organisms: terrestrial mammals, birds, terrestrial invertebrates, terrestrial plants, fish, aquatic invertebrates, aquatic algae, and aquatic macrophytes. Different units of exposure are used for different groups of organisms, depending on how exposures are likely to occur and how the available toxicity data are expressed. When possible, a range of toxicity values based on the most sensitive and most tolerant species within a given group of organisms is provided. This risk assessment encompasses applications of fluroxypyr-MHE, the active ingredient (a.i.) in formulations considered in this risk assessment. All exposure assessments, however, are given in units of acid equivalents (a.e.). To maintain consistency with the exposure assessment, which is necessary for the development of hazard quotients in the risk characterization, all toxicity values given in Table 18 are expressed as acid equivalents. Where necessary, experimental exposures in units of a.i. are converted to units of a.e. using the conversion factor of 0.694 a.e./a.i. derived in Table 3 and based on the ratio of the molecular weight of fluroxypyr acid to fluroxypyr-MHE.

The dose-response assessments for terrestrial animals are relatively standard. The dose-response assessment for terrestrial mammals is based on the same toxicity data used to derive the RfD in the human health risk assessment, a chronic NOEC of 100 mg/kg bw/day. The available data do not suggest a substantial dose-duration relationship or systematic differences among species. Thus, the chronic NOEC is applied to all exposure scenarios and all groups of mammals: small, large, and canid. The toxicity database in birds is much more limited than that for mammals. Based on acute toxicity data, the NOEC for birds is estimated at 750 mg/kg bw. Based on a reproduction study in birds, the NOEC is estimated at 21 mg/kg bw/day and is used for all longer-term exposures. The lower chronic value for birds clearly indicates that birds are more sensitive than mammals under conditions of repeated dosing. The data on insects are very limited. A NOEC of 165 mg/kg bw in the honeybee is used to characterize risks associated with the direct spray of a bee. No other toxicity values for insects or other terrestrial invertebrates can be derived.

The toxicity of fluroxypyr to terrestrial plants is characterized relatively well. Fluroxypyr is more toxic to dicots than to monocots. The most sensitive plant species have a NOEC value of 0.0006 lbs a.e./acre based on vegetative vigor (direct spray) and a NOEC value of 0.02 lb a.e./acre based on soil exposure. Tolerant species have NOEC values of 0.15 lb a.e./acre for both soil and foliar exposures.

The dose-response assessment for aquatic organisms is complicated by the low water solubility of fluroxypyr-MHE. For acute exposures, fluroxypyr-MHE will be the predominant form of fluroxypyr. For fish and crustaceans, fluroxypyr-MHE appears to be nontoxic at the water solubility limit for fluroxypyr-MHE. Toxicity values are derived

for fish and crustaceans. One study indicates that fluroxypyr-MHE is highly toxic to saltwater oysters, with an estimated NOEC of 0.002 mg/L. A longer-term toxicity value of 56 mg/L is derived for daphnids, based on fluroxypyr acid rather than fluroxypyr-MHE because fluroxypyr-MHE will not persist in the environment.

Aquatic plants are much more sensitive than either fish or crustaceans to fluroxypyr-MHE. For algae, NOECs values range from 0.018 to 0.12 mg a.e./L. For aquatic macrophytes, data are available only for duckweed, with NOEC of 0.086 mg a.e./L.

4.3.2. Terrestrial Organisms

4.3.2.1. Mammals

As summarized in the human health dose-response assessment (Section 3.3), the U.S. EPA Office of Pesticide Programs did not derive an acute RfD and uses a NOAEL of 100 mg a.e./kg bw/day from a chronic feeding study in rats by Quast and McGuirk (1995) to characterize risk. In the current risk assessment, this NOAEL is adopted as the toxicity value for mammalian wildlife and is used to characterize risks associated with both acute and longer-term exposures.

The approach taken in the current Forest Service risk assessment is modestly different from and somewhat more conservative than the approach taken by U.S. EPA/OPP in the ecological risk assessment of fluroxypyr (U.S. EPA/OPP 1998b, p. 16). For acute exposures, the ecological risk assessment uses an acute LD₅₀ value of 880 mg/kg bw from the Cosse et al. (1992a) acute toxicity study in rats. For chronic toxicity, U.S. EPA/OPP (1998b) uses a dietary concentration of 2000 ppm from the Vedula et al. (1996) reproduction study in rats. The source of the dietary value of 2000 ppm is not specified in U.S. EPA/OPP (1998b). The DER for the study by Vedula et al. (1996) does not specify the dietary concentration of 2000 ppm but notes that the dietary exposures were equivalent to doses of 100 mg/kg bw/day in male rats and 500 mg/kg bw/day in female rats. A factor of 0.05 is often used in converting dietary exposures to oral exposures under the assumption that rats eat a daily amount of food equivalent to 5% of their body weight. Speculatively, the dietary concentration of 2000 ppm may be based on such an assumption [$100 \text{ mg/kg bw} \div (0.05 \text{ kg food/kg bw}) = 2000 \text{ mg/kg food} = 2000 \text{ ppm}$].

Forest Service risk assessments do not use LD₅₀ values or any other estimates of lethal doses or concentrations to characterize risk, preferring instead to use NOEC values. As discussed in Section 3.3.2 (Acute RfD), there is no remarkable difference in short-term NOEC values and chronic NOEC values for fluroxypyr; accordingly, there is no basis for deriving a short-term NOEC for mammalian wildlife.

The selection of a reproductive NOAEL rather than a chronic NOAEL in the ecological risk assessment conducted by the EPA (U.S. EPA/OPP 1998b) reflects the major concern in ecological risk assessment with populations rather than individuals. In the case of fluroxypyr, however, the conceptual difference between EPA risk assessments (i.e., selecting the reproductive NOAEL) and Forest Service risk assessments (i.e., selecting

the lowest multiple-dose NOAEL) is inconsequential, since the two NOAEL values are identical (i.e., 100 mg/kg bw/day).

In addition to a lack of a significant dose-duration relationship, there are no apparent systematic differences in sensitivity and body size among mammals; furthermore, there is no indication that canid species are remarkably more sensitive than other groups of mammals to the effects of fluroxypyr (Section 4.1.2.1). Thus, the NOAEL of 100 mg/kg bw/day is used to characterize risks associated with both acute and longer-term exposures, and separate NOAEL values are not derived for canids or mammals of differing body sizes.

4.3.2.2. Birds

As discussed in Section 4.1.2.2, toxicity studies in birds are much less detailed and are fewer in number than toxicity studies in mammals. Some studies report effects in birds—i.e., discolored livers in the acute gavage study by Roberts and Phillips (1984a) and sporadic mortality in the acute dietary study by Roberts and Phillips (1983c). These effects, however, are not dose-related and cannot be clearly attributed to fluroxypyr exposure. Based on the acute gavage doses of 2000 mg/kg bw, the EPA classifies fluroxypyr acid and fluroxypyr-MHE as practically nontoxic to birds, and this classification appears to be justified in that the gavage dose of 2000 mg/kg bw was not associated with signs of toxicity or a significant increase in mortality.

While a dose of 2000 mg/kg bw could be used as an acute NOEC, the current risk assessment takes a somewhat more conservative approach. As detailed in Appendix 3, two acute dietary studies in quail (Roberts and Phillips 1983b,c) note dietary NOEC values of 5000 ppm. Full copies of both of these studies were available during the preparation of the current Forest Service risk assessment and both of these studies are classified as Core in U.S. EPA/OPP (1998b). Neither study noted any signs of toxicity and no mortality in the 5000 ppm groups. The only substantial difference between the two studies involves food consumption. While food consumption was highly variable in both studies, birds in the Roberts and Phillips (1983b) study consumed less food than in the Roberts and Phillips (1983c) study. The differences in food consumption are apparent in both control and treated groups and do not appear to be related to fluroxypyr exposure. Using the study by Roberts and Phillips (1983b), the dietary NOEC corresponds to a dose of 750 mg/kg bw. This NOEC is used in the current risk assessment to characterize risks associated with acute exposure scenarios.

The long-term toxicity studies in birds consist of only two reproduction studies, one in quail (Beavers et al. 1989a) the other in mallards (Beavers et al. 1989b). Mallards are clearly more sensitive than quail. The NOEC for mallards is 250 ppm with a corresponding LOEC of 500 ppm; the NOEC in quail is 1000 ppm. The DERs for the Beavers et al. (1989a,b) studies do not specify food consumption rates or body weights. During the review of the current Forest Service risk assessment, Dow AgroSciences (2009) provided food consumption and body weight data for this study. The average food consumption by birds in the 250 ppm group was 0.12 g food/g bw. Thus, the dose to birds in this group was about 30 mg ester/kg bw [250 mg/kg bw x 0.12]. Because the

application rate and hence the estimated residues in food are expressed in units of acid equivalents, the dose of 30 mg ester/kg bw is converted to 21 mg a.e./kg bw using the ester-to-acid conversion factor of 0.694 from Table 3 [30 mg ester/kg bw x 0.694 a.i./a.e. = 20.82 mg a.e./kg bw].

4.3.2.3. Terrestrial Invertebrates

As discussed in Section 4.1.2.3, very little information is available on the toxicity of fluroxypyr to terrestrial invertebrates, and the dose-response assessment for this group is uncomplicated.

As discussed in Section 4.1.2.4, the studies by Lynn and Hoxter (1991a,b) can be used to identify a honeybee NOEC of 25 µg/bee for both fluroxypyr acid and fluroxypyr-MHE. Since the formulations covered in this risk assessment all contain fluroxypyr-MHE as the active ingredient (a.i.) but the application rate used in all exposure assessments is expressed as acid equivalents (a.e.), the NOEC of 25 µg a.i./bee is converted to 17.3 µg a.e./bee using the conversion factor derived in Table 3 [25 µg a.i./bee × 0.694 a.e./a.i.].

The DERs for the Lynn and Hoxter (1991a,b) studies do not specify the body weights of the bees used in the bioassays. Based on a body weight of 0.093 g (0.000093 kg) for the honeybee (USDA/APHIS 1993), a dose of 17.3 µg a.e./bee corresponds to a mg/kg bw dose of about 186 mg a.e./kg bw [0.0173 mg/0.000093 kg = 186.022 mg a.e./kg], which is comparable to the subacute NOAEL values (i.e., 100-300 mg/kg bw/day) in mammals (Section 4.1.2.1). This dose should be regarded as a free-standing NOEC in that the dose at which toxic effects might be seen is not known.

4.3.2.4. Terrestrial Plants (Macrophytes)

Fluroxypyr is an herbicide, which by definition, is designed to adversely affect plants, particularly dicots or broadleaf weeds. As with most herbicides, there are adequate data from which to derive toxicity values for both sensitive and tolerant plant species involving soil exposures (i.e., herbicide runoff to an untreated field) and foliar exposures (direct spray, wind erosion, or drift). The available studies are discussed in Section 3.1.2.5 and summarized in Appendix 5.

For soil exposures involving assays of fluroxypyr-MHE for seedling emergence, the most sensitive species is the cucumber (dicot) with a NOEC of 0.031 lb a.i./acre and an EC₂₅ of 0.075 a.i./acre (Schwab 1996). The endpoint for both of these effects is gross signs of phytotoxicity—i.e., visible signs of injury to the plant. As with other toxicity values, the NOEC and EC₂₅ values are converted from a.i. to a.e. using the factor of 0.694 derived in Table 3. Thus, for the current Forest Service risk assessment, the NOEC for soil exposures in sensitive species of terrestrial plants is taken as 0.022 lb a.e./acre [0.031 lb a.i./acre x 0.694 = 0.021514 lb a.e./acre]. Based on the ratio of the EC₂₅ to the NOEC, an HQ of about 2.4 would be associated with visible signs of toxicity. The most tolerant species in seedling emergence assays are corn and onions (both monocots) with a NOEC of 0.25 lb a.i./acre. Because of the tolerance of these species to fluroxypyr, an EC₂₅ was not determined. When converted to acid equivalents, the NOEC for tolerant species is 0.17 lb a.e./acre [0.25 lb a.i./acre x 0.694 = 0.1735 lb a.e./acre].

Fluroxypyr is much more toxic in vegetative vigor assays involving direct foliar spray. Based on a combination of NOEC and EC₂₅ values, the most sensitive species are tomatoes and sunflowers (both dicots) with NOEC values of 0.001 lb a.i./acre and EC₂₅ values of 0.004 lb a.i./acre (Schwab 1996). When converted to units of acid equivalents, the NOEC for sensitive species involved in direct spray or drift exposure scenarios is 0.0007 lb a.e./acre [0.001 lb a.i./acre x 0.694 = 0.000694 lb a.e./acre]. For sensitive species, an HQ of 4—i.e., the ratio of the EC₂₅ to the NOEC—would be associated with signs of phytotoxicity. The most tolerant species in vegetation vigor assays is ryegrass (a monocot) with a NOEC of 0.25 lb a.i./acre. As with tolerant species in the seedling emergence studies, an EC₂₅ could not be determined in ryegrass. When converted from units of a.i. to a.e., the NOEC for tolerant species involved in spray or drift exposure scenarios is 0.17 lb a.e./acre [0.25 lb a.i./acre x 0.694 = 0.1735 lb a.e./acre].

4.3.3. Aquatic Organisms

4.3.3.1. Fish

As discussed in Section 4.1.3.1. (Hazard Identification for Fish), fluroxypyr acid and fluroxypyr-MHE are classified as slightly toxic to practically nontoxic to fish. Acute exposure of fish and other aquatic organisms to fluroxypyr is likely to involve fluroxypyr-MHE rather than fluroxypyr acid. Both fluroxypyr formulations covered in the current risk assessment contain fluroxypyr-MHE. While fluroxypyr-MHE will be hydrolyzed rapidly to fluroxypyr acid, detailed bioassays of fluroxypyr-MHE suggest that initial exposures will be predominantly to the ester (e.g., Rick et al. 1996a).

The dose-response assessment for fluroxypyr-MHE in fish is somewhat atypical because of the limited water solubility of fluroxypyr-MHE. As summarized in Table 14, the available NOEC values for fish based on nominal concentrations range from 5 to 100 mg/L. Based on measured concentrations, NOEC values range from 0.087 to 0.7 mg/L. Thus, there is no correlation between nominal concentrations and measured concentrations. For example, both the lower and upper bounds of the range of concentrations based on measured NOEC values are associated with the same nominal concentration—i.e., 100 mg/L from the studies by Boeri et al. (1996) and Willis (1984c and 1984d).

Another issue with the dose-response assessment for fish is that the upper bound of the range of measured concentrations, 0.7 mg/L, exceeds the water solubility of fluroxypyr-MHE, which suggests that solvents used in the toxicity studies may influence the solubility of fluroxypyr-MHE in the test water (Section 4.1.3.1). It is possible, although not certain, that the inerts used in the fluroxypyr-MHE formulations may also influence the water solubility of fluroxypyr-MHE. Thus, the range of measured NOEC values (i.e., 0.087-0.7 mg/L) may have nothing to do with the ranges of sensitivity and may simply reflect differences in solvents or other factors in the different bioassays.

Finally, it is not clear that fluroxypyr-MHE would cause adverse effects under any plausible set of conditions. The only LC₅₀ values available are those reported for fluroxypyr-MHE by Wan et al. (1992) (i.e., 8 and 19 mg/L). These toxicity values,

however, are for unidentified formulations that do not correspond to the formulations covered in the current risk assessment.

In some respects, a formal dose-response assessment is not warranted for fluroxypyr-MHE, and this is particularly true for the accidental spill scenario. As noted in Section 4.2.5 (Exposure Assessment for Aquatic Organisms), the accidental spill scenario involves nominal concentrations of up to 15 mg/L but actual concentrations of fluroxypyr-MHE in the water will be much lower. All that can be said about this exposure is that the available fish bioassays submitted to the EPA suggest the unlikelihood of adverse effects resulting from fluroxypyr exposure, and the development of a hazard quotient is unwarranted.

Estimated peak exposure levels in ambient surface water are 0.011 (0.00025 to 0.04) mg a.e./L (Section 4.2.5 and Worksheet G03). These concentrations are below the water solubility of fluroxypyr-MHE and would be associated with runoff or percolation of fluroxypyr-MHE to water. Furthermore, it is likely that some and perhaps a large proportion of the fluroxypyr-MHE would be hydrolyzed to fluroxypyr acid. For these exposure scenarios, conservative but reasonably plausible HQ values can be based on the assumption that all of the fluroxypyr remains in the ester form. The toxicity values can be taken as the measured NOEC values ranging from 0.087 mg/L (sheepshead minnow from Boeri et al. 1996a) to 0.7 mg/L (rainbow trout and golden orfe from the studies by Willis 1984c,d).

Adjusting for ester to acid with the 0.694 factor (Table 3) in order to maintain consistency with the exposure estimates, the NOEC values for fish used in this risk assessment are taken as 0.060 mg a.e./L for sensitive species [$0.087 \text{ mg a.i./L} \times 0.694 \text{ a.e./a.i.} = 0.060378 \text{ mg a.e./L}$] and 0.49 mg a.e./L for tolerant species [$0.7 \text{ mg a.i./L} \times 0.694 \text{ a.e./a.i.} = 0.4858 \text{ mg a.e./L}$]. The lower value is applied to sensitive species of fish and the higher value to tolerant species of fish. As noted above, however, it is not clear that the range of NOEC values reflects differences in sensitivity or other differences (e.g., solvents) used in the various bioassays.

The fluroxypyr literature does not include chronic fish bioassays. As noted in Section 4.1.3.1, U.S. EPA/OPP waived the requirement for chronic testing because of the low acute toxicity of both fluroxypyr acid and fluroxypyr-MHE to fish.

4.3.3.2. Amphibians

As discussed in Section 4.1.3.2, there are no data regarding the effects of fluroxypyr, acid or ester, to amphibians; accordingly there is no dose-response assessment for amphibians.

4.3.3.3. Aquatic Invertebrates

4.3.3.3.1. Acute Toxicity

The dose-response assessment for aquatic invertebrates is similar in some respects to the dose-response assessment for fish in that solubility issues need to be addressed, including

substantial differences between the nominal and measured NOEC values for fluroxypyr-MHE (Table 15). As with fish, the agent of concern is taken as fluroxypyr-MHE.

One significant difference between the dose-response assessments for fish and aquatic invertebrates is that a sensitive subgroup of aquatic invertebrates can be identified. As summarized in Table 15, aquatic arthropods are relatively insensitive to fluroxypyr-MHE, and the only available toxicity values are NOECs. The aquatic arthropod NOECs in three species range from 56 to 100 mg/L, based on nominal concentrations, and from 0.128 to 0.56 mg/L, based on measured concentrations. As with fish, there is no correlation between reported nominal concentrations and reported measured concentrations. For the current risk assessment, the highest NOEC of 0.56 mg/L (measured) is used for tolerant species of aquatic invertebrates. Adjusted for acid equivalents, this concentration is taken as 0.39 mg a.e./L [$0.56 \text{ mg a.i./L} \times 0.694 \text{ a.e./a.i.} = 0.38864 \text{ mg a.e./L}$].

Based on the study by Boeri et al. (1996b), the Eastern oyster appears to be much more sensitive to fluroxypyr-MHE. The EC_{50} for an inhibition of shell deposition is 0.068 mg/L (measured). An inhibition of shell deposition was observed at the lowest concentration tested (i.e., a nominal concentration of 12 mg/L and a measured concentration of 0.05 mg/L). Thus, a NOEC for shell deposition was not defined. As discussed in Section 4.1.3.3, the study by Boeri et al. (1996b) has several limitations, all of which suggest that the concentrations in the Boeri study may overestimate the toxicity of fluroxypyr-MHE. While the use of the Boeri study is likely to overestimate risk, this study is used by the U.S. EPA and, in the absence of any more relevant studies, the Boeri et al. (1996b) study is used in the current Forest Service risk assessment.

The Forest Service has elected not to base toxicity values on estimates of an EC_{50} or LOEC. U.S. EPA/OPPTS (2004), on the other hand, uses EC_{50} values, but interprets risk with levels of concern of 0.5 for acute risk and 0.05 for endangered species. To maintain compatibility with the EPA, the Forest Service has elected to divide an EC_{50} by a factor of 20 to approximate a NOEC. Using this approach, the EC_{50} of 0.068 mg/L is used to estimate a NOEC of 0.0034 mg/L. This concentration is below the reported LOEC by a factor of about 15 [$0.05 \text{ mg/L} \div 0.0034 \text{ mg/L} \approx 14.71$]. When the NOEC of 0.0034 mg/L is converted to acid equivalents, the acute toxicity value used for sensitive species of aquatic invertebrates is about 0.002 mg a.e./L [$0.0034 \text{ mg a.i./L} \times 0.694 \text{ a.e./a.i.} = 0.00236$].

4.3.3.3.2. Chronic Toxicity

Two sets of chronic toxicity values are available for daphnids: the NOEC/LOEC of 56/100 mg a.e./L for fluroxypyr acid (Jones 1984a) and the NOEC/LOEC of 0.0605/0.109 mg a.i./L for fluroxypyr-MHE (Kirk et al. 1996a).

Generally, Forest Service risk assessments use the most conservative or protective approach. As discussed in Sections 4.1.3.3 and 4.2.5, longer-term exposures to fluroxypyr-MHE will not occur because the ester will be rapidly hydrolyzed to fluroxypyr acid. Consequently, the very low toxicity values obtained by Kirk et al. (1996a) by artificially maintaining constant fluroxypyr-MHE concentrations over the

duration of the study appear to be experimentally correct but are not relevant to the risk assessment. The NOEC of 56 mg a.e./L based on the study by Jones (1984a) using fluroxypyr acid is selected as the chronic toxicity value for tolerant species of aquatic invertebrates.

As discussed in the previous section, bivalves may be much more sensitive than crustaceans to fluroxypyr-MHE. It is possible that bivalves are also more sensitive to fluroxypyr acid. There are no experimental data (i.e., either longer-term studies or field studies) to support this supposition. While acute-to-chronic ratios could be used to estimate a longer-term NOEC for sensitive species of aquatic invertebrates, this would involve both acute-to-chronic extrapolation as well as extrapolation from fluroxypyr-MHE to fluroxypyr acid. It does not appear that this type of extrapolation would be useful. In the absence of any additional information, no dose-response assessment for sensitive species of aquatic invertebrates is proposed.

4.3.3.4. Aquatic Plants

Compared to the dose-response assessments for fish and aquatic invertebrates, the dose-response assessment for aquatic plants is relatively simple and standard. All of the toxicity studies on fluroxypyr-MHE submitted to the EPA in support of the registration of fluroxypyr report concentrations as measured rather than nominal values (Table 16). Fluroxypyr-MHE is much more toxic to aquatic plants than to aquatic animals, and testing at very high concentrations is unnecessary. The studies by Ma (Ma 2002; Ma et al. 2001, 2002) do report what appear to be very high nominal concentrations. As noted previously, however, the studies by Ma involve unidentified formulations that are not considered in the current risk assessment. While the Ma studies are included for the sake of completeness, they are not used quantitatively in the current Forest Service risk assessment.

For algae, the available NOEC values range from 0.03 mg a.i./L (*Anabaena flos-aquae* from the study by Milazzo et al. 1996a) to 0.199 mg a.i./L (*Selenastrum capricornutum* from the study by Milazzo et al. 1996c). When converted to acid equivalents (0.694 a.e./a.i.), these concentrations correspond to about 0.021-0.14 mg a.e./L and are used for sensitive and tolerant species, respectively. As summarized in Table 16, the EC₅₀ for *Anabaena flos-aquae* is about 20 times greater than the NOEC, and the EC₅₀ for *Selenastrum capricornutum* is more than 7 times greater than the NOEC. These ratios are discussed further in the risk characterization.

For macrophytes, only two studies are available, and both were conducted using *Lemna gibba*, duckweed (Kirk et al. 1996b; Kirk et al. 1998). The 7-day NOECs from these studies are 0.412 mg/L (Kirk et al. 1998) and 1.22 mg/L (Kirk et al. 1996b). Kirk et al. (1998) also report a 14-day NOEC of 0.437 mg/L. The study by Kirk et al. (1996b) is classified as Core by U.S. EPA/OPP (1998b). The later study by Kirk et al. (1998) is not cited in U.S. EPA/OPP (1998b) and may not have been available at the time the risk assessment was prepared.

Variability in two studies on the same species is clearly not a measure of differences in sensitive and tolerant species. For the current risk assessment, the lowest NOEC, 0.412 mg/L reported by Kirk et al. (1998) is used for tolerant species. When adjusted for acid equivalents, the toxicity value is about 0.29 mg a.e./L [$0.412 \text{ mg a.i./L} \times 0.694 \text{ a.e./a.e.} = 0.285928 \text{ mg a.e./L}$]. No dose-response assessment is proposed for sensitive species of aquatic macrophytes.

4.4. RISK CHARACTERIZATION

4.4.1. Overview

Like any effective herbicide, fluroxypyr is designed to kill vegetation. As with most auxin mimicking herbicides, fluroxypyr is more toxic to dicots (broadleaf plants) than to monocots (e.g. grasses). Direct spray and spray drift appear to be the modes of exposure most hazardous to terrestrial vegetation. Any dicot, target or nontarget, sprayed directly with fluroxypyr at an effective application rate is likely to die. The hazards associated with drift will depend on the application method. Aerial applications are likely to be most hazardous, followed by high boom ground broadcast, low boom ground broadcast, and backpack directed foliar applications (Table 19). The estimates of risk from drift given in the current risk assessment are conservative—i.e., the estimates of drift are intended to be plausible but are likely to overestimate risk relative to well planned and carefully conducted applications. Runoff from a fluroxypyr site to an untreated site might pose a risk to nontarget vegetation, under worst-case conditions. The transport of fluroxypyr adhering to soil by wind erosion appears to be the least hazardous route of exposure; however, estimates of soil erosion by wind are likely to be highly variable.

Even at the highest proposed application rate in Forest Service programs (i.e., 0.5 lb a.e./acre), fluroxypyr exposure levels are not likely to cause adverse effects in terrestrial animals. The upper bounds of highest acute HQ values are associated with the consumption of fish by a predatory bird after an accidental spill (HQ=0.5), the consumption of contaminated insects by a small mammal (HQ=0.3), the consumption of contaminated grasses by mammals (HQ=0.2), and the direct spray of a small mammal under the assumption of 100% absorption (HQ=0.1). The upper bound of the highest chronic HQ is associated with the consumption of contaminated grasses by a large bird feeding exclusively in the treated area (HQ=0.2). All other HQ values for terrestrial organisms are below the level of concern by factors of greater than 10 to greater than 100,000.

The risk characterization for aquatic species is somewhat more complicated than that for terrestrial species owing to differences in the toxicity and persistence of fluroxypyr-MHE and fluroxypyr acid. Initially, the exposure of aquatic organisms will involve exposure to fluroxypyr-MHE, the active ingredient in the fluroxypyr formulations considered in this risk assessment. Fluroxypyr-MHE is also more toxic than fluroxypyr acid to aquatic species. Fluroxypyr-MHE, however, will be hydrolyzed rather rapidly to fluroxypyr acid, precluding the possibility of long-term exposure. Further complicating the aquatic exposure assessments for fluroxypyr-MHE is its relative insolubility in water, which has a considerable impact on the available concentration in water and therefore on its toxicity.

Despite these different and sometimes offsetting considerations, there does not appear to be any basis for asserting that applications of the fluroxypyr formulations considered in this risk assessment are likely to harm tolerant or sensitive species of fish, tolerant species of aquatic invertebrates (crustaceans), or some tolerant species of algae and aquatic macrophytes. The risk characterization for sensitive species of aquatic

invertebrates is based on only one study which reports adverse effects in Eastern oysters exposed to fluroxypyr-MHE. Based on an inhibition of shell deposition, the HQ is about 6 (0.1-20), based on expected peak concentrations. In other words, both the central estimate and the upper bound of the HQ are above the level of concern. It is not clear that the one Eastern oyster bioassay indicates that all aquatic mollusks or even all aquatic bivalves would be adversely affected by fluroxypyr applications. In the absence of other relevant toxicity studies or any field studies, it is prudent to assume that aquatic mollusks may be at risk from the use of fluroxypyr-MHE. With an upper bound HQ of 20, differences in application rates would not have an impact on this risk characterization, unless site-specific modeling supported the use of lower estimated concentrations of fluroxypyr-MHE in water. Sensitive species of aquatic algae have HQ values of 0.5 (0.01 to 1.9)—i.e., only the upper bound of the HQ is above the level of concern. It is not clear that the modest excursion above the level of concern would result in detectable adverse effects in aquatic algae.

4.4.2. Terrestrial Organisms

4.4.2.1. Mammals

The risk characterization for mammals is simple and unambiguous: there is no basis for asserting that exposure to fluroxypyr will cause adverse effects in mammals. At the maximum application rate of 0.5 lb a.e./acre and over the range of the estimated exposures, the upper bounds of the hazard quotients for mammals range from 0.000008 (the longer-term consumption of surface water by a small mammal) to 0.3 (the consumption of contaminated insects by a small mammal). This range is below the level of concern (1.0) by factors of 10-125,000.

This risk characterization for mammals is qualitatively consistent with the EPA risk characterization, which finds no basis for asserting that adverse effects in mammals are based on both acute risk quotients (U.S. EPA/OPP 1998b, Table 16) or chronic risk quotients (U.S. EPA/OPP 1998b, Table 17). Note that *risk quotient*, a term used by the EPA, is essentially the same as a hazard quotient in that the risk quotient is the ratio of the estimated exposure to the toxicity value. The EPA risk quotients for acute and chronic exposure are all below 0.01. These values are much lower than the maximum risk quotient of 0.3 in the current Forest Service risk assessment. The difference is due primarily to the selection of toxicity values—i.e., the EPA uses an LD₅₀ of 880 mg/kg bw, while this Forest Service risk assessment uses the oral NOAEL of 100 mg/kg bw/day.

Since all HQ values are based on the maximum application rate and are all below the level of concern, the use of lower application rates does not qualitatively affect the risk characterization—i.e., there is no basis for asserting that adverse toxic effects are plausible.

The application of any effective herbicide, including fluroxypyr, is likely to alter terrestrial vegetation. This alteration is likely to lead to some secondary changes that could affect mammals—e.g., changes in food availability and habitat quality. These

secondary effects are likely to vary over time and among species. The changes in vegetation could be beneficial to some mammals and detrimental to others.

4.4.2.2. Birds

The risk characterization for birds is qualitatively identical to that for mammals: At the maximum application rate of 0.5 lb a.e./acre, there is no basis for asserting that adverse toxic effects in birds are plausible. The upper bounds of the hazard quotients for birds, however, are somewhat higher than those for mammals, ranging from 0.00007 (the longer-term consumption of surface water by a small bird) to 0.5 (the consumption of contaminated fish by a predatory bird). This range of HQ values is below the level of concern (1.0) by factors of 2 to somewhat over 14,000.

Qualitatively, the risk characterization for birds presented in this risk assessment is similar to the EPA's (U.S. EPA/OPP 1998b) in that none of the hazard quotients (referred to as *risk quotients* by EPA) exceed a level of concern. The risk quotients developed by the EPA are not directly comparable to those in Forest Service risk assessments because of differences in the toxicity values as well as differences in the exposure assessments. For acute toxicity, U.S. EPA/OPP (1998b) does not present formal risk quotients but notes that the highest expected concentration in the food of wildlife would be 60 ppm, compared with a dietary toxicity value of 5000 ppm, which corresponds to a risk quotient of 0.012. The highest longer-term risk quotient given by U.S. EPA/OPP (1998b, Table 15) is 0.24, virtually identical to the chronic HQ value in the current Forest Service risk assessment for the longer-term consumption of contaminated vegetation by a large bird feeding exclusively on the treated site.

As with mammals, secondary effects on some species of birds may occur through changes in vegetation that might affect food availability and habitat. These effects may be beneficial to some birds and detrimental to others. The magnitude of secondary effects is likely to vary over time. Again, there are no field studies on fluroxypyr that could be used to further characterize potential secondary effects.

4.4.2.3. Terrestrial Invertebrates

The only available toxicity value for terrestrial invertebrates is an estimated acute NOEC of approximately 165 mg a.e./kg bw for honeybees. As indicated in Worksheet G02b, the highest hazard quotient for the honeybee is 0.2, below the level of concern by a factor of 5. This hazard quotient is associated with the direct spray of a honeybee at the maximum application rate of 0.5 lb a.e./acre. Hazard quotients based on drift and hazard quotients considering foliar interception are lower, and, often much lower.

As with most pesticide risk assessments and virtually all herbicide risk assessments, there is a great difference between the number nontarget species, in this case the number terrestrial invertebrate species, and the number of species on which data are available. This is true even for very well-studied herbicides like 2,4-D (SERA 2006a). This circumstance places obvious limitations on the risk characterization for this group of organisms. Nonetheless, based on the available information, there is no basis for

asserting that toxic effects in terrestrial invertebrates are likely given plausible exposures to fluroxypyr.

As with birds and mammals, secondary effects on terrestrial invertebrates are plausible. Applications of fluroxypyr will affect vegetation, target species and possibly nontarget species (Section 4.4.2.4), which may lead to secondary effects on terrestrial invertebrates. The extent to which secondary effects would be regarded as beneficial or detrimental is speculative and likely to vary among different groups and species of terrestrial invertebrates.

4.4.2.4. Terrestrial Plants

A quantitative summary of the risk characterization for terrestrial plants is presented in Worksheets G04 for runoff, Worksheets G05a-d for drift, and Worksheet G07a for off-site contamination due to wind erosion. The G05a-d designation reflects the use of four sets of values for drift: aerial application (G05a), ground high-boom broadcast application (G05b), ground low-boom broadcast application (G05c), and ground backpack application (G05d). For convenience, the HQ values for drift based on all four application methods are summarized in Table 19.

The toxicity values for fluroxypyr are all NOEL values for both sensitive and tolerant species. These values are summarized in Table 18 and discussed in Section 4.3.2.4. Fluroxypyr is much more toxic to dicots (e.g., broadleaf plants) than to monocots (e.g., grasses), and these differences are reflected in the risk quotients for sensitive and tolerant plant species.

For tolerant species such as grasses, no adverse effects would be anticipated from either runoff (Worksheet G04 with an upper bound HQ of 0.3) or the erosion of contaminated soil by wind (Worksheet G06 with an upper bound HQ of 0.004). In the event of a direct spray (a downwind distance of 0 in Table 19), the HQ for tolerant species is only 3. As discussed in Section 4.3.2.4, the toxicity value for tolerant species is based on a free standing NOEC (i.e., the LOEC could not be determined). Thus, it is not clear that exposure to fluroxypyr would cause adverse effects in tolerant species of terrestrial plants, even in the event of a direct spray. At distances of 25 downwind of the application site, HQ values for all application methods are below the level of concern.

The risk characterization for sensitive species of terrestrial vegetation is much more severe. Fluroxypyr is an effective herbicide for broadleaf weeds, and it is likely that fluroxypyr will also be highly toxic to nontarget broadleaf vegetation. The greatest risks to sensitive species of terrestrial vegetation are clearly associated with direct spray and drift. As summarized in Table 19, the hazard quotient associated with direct spray (i.e., a drift distance of 0 feet) is 714. This HQ needs little interpretation. If a sensitive species of terrestrial vegetation is directly sprayed with fluroxypyr at any effective application rate, the plant is likely to die. This can be said of any effective herbicide.

The impact of drift will be highly dependent on the application rate. As detailed in Section 4.2.4.2 and detailed further in SERA (2009), the drift values used in this risk

assessment are based on Tier 1 AgDrift estimates. These drift estimates are intended to be conservative (i.e., drift is likely to be overestimated). In any site-specific application of fluroxypyr, the use of the site-specific capabilities of drift models such as AgDrift or AgDisp is recommended (SERA 2009, Section 3.3.3.3). Notwithstanding these limitations, the generic estimates of drift used in the current risk assessment for different application methods are likely to reflect a reasonable approximation of relative risks among the different application methods. The greatest risks would be associated with aerial or high boom ground broadcast applications. For these application methods, the HQ values exceed the level of concern (HQ=1) for distances up to 900 feet downwind of the application site. Low boom application would be associated with HQ values of concern at distances of up to 500 feet. Even at 900 feet, the HQ of 0.8 approaches a level of concern. Backpack applications (i.e., directed foliar) are likely to present the lowest risk. As discussed in Section 4.2.4.2, however, the estimates used in the current risk assessment are based simply on a modification of the drift that might be associated with low-boom applications using large rather than small droplets. Based on these drift estimates, the HQ values are below the level of concern at a distance of 300 feet downwind.

The hazard quotients for sensitive species associated with exposure to runoff are 0.09 (0.002-2). In other words, risks to sensitive species of terrestrial vegetation may range from below the level of concern by a factor of 500 to above the level of concern by a factor of 2. As discussed in Section 4.3.2.4, an HQ of 2 is very close to the EC₂₅ for visible signs of toxicity. More importantly, however, the high variability in the HQ values for this scenario is based on the nature of GLEAMS modeling (Section 3.2.3.4.3), which encompasses a wide range of site specific factors, including rainfall, temperature, and soil type.

The only scenario that does not reach a level of concern (HQ=1) for sensitive species of terrestrial plants involves exposures associated with contaminated soil transported by wind (Worksheet G06). As discussed in Section 4.2.4.5, the exposure estimates for this scenario are tenuous.

4.4.3. Aquatic Organisms

4.4.3.1. Fish

The risk characterization for fish, which is based on expected peak concentrations of fluroxypyr-MHE in surface water, is relatively simple: There is no basis for asserting that adverse effects on tolerant or sensitive species of fish are plausible. As discussed in Section 4.3.3.1, fluroxypyr-MHE, and fluroxypyr acid are classified as practically nontoxic to fish, and there is no defined adverse effect level for fish. More importantly, acute toxicity studies in fish indicate that nominal exposure levels of up to 100 mg/L to fluroxypyr-MHE do not cause detectable adverse effects. As discussed in the exposure assessment for aquatic organisms (Section 4.2.5), this apparent lack of toxicity is likely to be at least partially attributable to the low water solubility of fluroxypyr-MHE—i.e., about 0.09-0.136 mg/L. Thus, the maximum HQ of 0.7, upper bound of the HQ for sensitive species of fish, should not be interpreted as meaning that twice the estimated level of exposure would exceed a level of concern. For fluroxypyr-MHE, it does not

appear that fluroxypyr-MHE could reach a level of concern. This conclusion is consistent with the assessment by the U.S. EPA:

Since fluroxypyr MHE is not acutely toxic at its solubility limit, it is also considered practically nontoxic to freshwater fish on an acute basis.

-U.S. EPA/OPP (1998b, p. 18)

In some respects, the development of an HQ for fish is only marginally useful. As discussed in Section 4.2.5, the low water solubility of fluroxypyr-MHE is the basis for not considering the standard accidental spill scenario.

The risks to fish from longer-term exposures cannot be evaluated. As discussed in Section 4.1.3.1, the U.S. EPA/OPP (1998b) waived the requirement for a chronic study in fish because of the low acute toxicity of fluroxypyr-MHE and fluroxypyr acid. There is little concern for longer-term exposures to fluroxypyr-MHE. As discussed in some detail in Section 4.3.3.3.2 (Dose-Response Assessment for Aquatic Invertebrates), chronic toxicity data on aquatic species for fluroxypyr-MHE are not relevant to the ecological risk assessment because of the rapid hydrolysis of fluroxypyr-MHE to fluroxypyr acid.

The assumption that fluroxypyr acid will not pose a risk to fish in longer-term exposures, however, is somewhat more tenuous, but seems reasonable. While longer-term exposures to fluroxypyr acid will be very low (Table 11), the assertion that these concentrations will not adversely affect fish is not supported by any experimental data in fish. Nonetheless, the available acute and chronic data on aquatic invertebrates clearly indicate that fluroxypyr acid is much less toxic in longer-term exposures than is fluroxypyr-MHE. The waiver of chronic testing in fish as well as the presumption that adverse chronic effects are unlikely is consistent with the data on aquatic invertebrates.

4.4.3.3. Aquatic Invertebrates

The risk characterization for tolerant species of aquatic invertebrates—i.e., crustaceans—is essentially identical to the risk characterization for fish. At the maximum application rate and at the upper bounds of the HQ values, risks are below the level of concern by a factor of 10 for acute exposures (HQ = 0.1) and a factor of 100 for longer-term exposures (HQ = 0.01).

As discussed in Section 4.3.3.3.1, there is one available acute aquatic toxicity study involving exposure effects in one species of mollusk, the Eastern oyster, which appears to be much more sensitive than other crustaceans to fluroxypyr-MHE. Based on this one bioassay, risks to sensitive species of aquatic invertebrates exceed the level of concern, according to both the central estimate and upper bound of the HQ. As summarized in Worksheet G03, the acute HQ values for sensitive species of aquatic invertebrates are 6 (0.1-20). The HQ values of 6-20 would be associated with decreased shell deposition. The possibility of more severe effects, particularly at the upper range of the HQ values, cannot be disregarded.

The lack of a chronic study in sensitive species of aquatic invertebrates does raise concern. However, as noted in the previous subsection on fish, chronic exposures of fluroxypyr-MHE will not occur. In addition, based on the comparable studies in aquatic species as summarized in Table 15, it is likely that fluroxypyr acid will be much less toxic than fluroxypyr-MHE.

4.4.3.4. Aquatic Plants

The risk characterization for aquatic algae is similar, although somewhat less severe, than that for aquatic invertebrates. For tolerant species of aquatic algae, the upper bound of the acute hazard quotient is 0.3, below the level of concern by a factor of about 3. For sensitive species of algae, the HQ values are 0.5 (0.01-1.9)—i.e., at the upper bound of the acute HQ, the level of concern is exceeded by a factor of about 2. As discussed in Section 4.3.3.4, the EC₅₀ for sensitive species of aquatic algae is a factor of 20 above the NOEC. It is not clear that a relatively modest excursion above the NOEC—i.e., an HQ of 2—would lead to observable adverse effects.

There is no basis for asserting that exposure to fluroxypyr is likely to cause longer-term effects in algae, in that the upper bound of the chronic HQ value for sensitive species of algae is 0.3, below the level of concern by a factor of 3. Note that the same toxicity values used for characterizing risk associated with longer-term exposures to aquatic algae are identical to those used for acute exposures—i.e., the toxicity values are for fluroxypyr-MHE and not fluroxypyr acid. As indicated in Table 16, only one toxicity value is available for fluroxypyr acid, a NOEC of 100 mg/L in *Chlorella vulgaris* from the study by Jones (1984c). As discussed in previous subsections, fluroxypyr-MHE will hydrolyze rapidly to fluroxypyr acid, and longer-term exposures to fluroxypyr-MHE are not plausible. The life cycle of algae, however, is very short. Thus, the toxicity value for fluroxypyr-MHE is used for both acute and longer-term exposures. This approach may be viewed as overly conservative, but, as noted above, the longer-term HQ values are below the level of concern, and the qualitative risk characterization is not affected by the use of the conservative assumption.

For aquatic macrophytes, data are available only on one species of duckweed, *Lemna gibba* (Table 16). Whether this species is representative of aquatic macrophytes that are tolerant or sensitive to fluroxypyr is not known. The current risk assessment makes the conservative assumption that *Lemna gibba* is a tolerant species. No assumptions are made concerning sensitive species of aquatic macrophytes—i.e., risks to sensitive species of aquatic macrophytes are not characterized. For tolerant species of aquatic macrophytes, the upper bound of the acute HQ is 0.1, below the level of concern by a factor of 10, and the upper bound of the longer-term HQ is 0.02, below the level of concern by a factor of 50. As with aquatic algae, the toxicity value for fluroxypyr-MHE is used to characterize risks for both acute and longer-term exposures. The rationale for doing so with aquatic macrophytes is different—i.e., no longer-term toxicity data are available regarding the effects of fluroxypyr acid on aquatic macrophytes. Thus, the upper bound HQ of 0.02 for longer-term exposures may overestimate risk to aquatic macrophytes. As with algae, this overestimate does not affect the qualitative characterization of risk—i.e., there are no apparent risks.

5. REFERENCES

NOTE: The initial entry for each reference in braces {} simply specifies how the reference are cited in the text. The final entry for each reference in brackets [] indicates the source for identifying the reference.

SET00	Papers from previous risk assessments and risk assessments of related compounds.
SET01	Paper from initial TOXLINE search, Jan '08.
Aminop	Studies from aminopyralid risk assessment.
Internet	Various reports on fluroxypyr.
Std	Standard references used in most Forest Service risk assessments.
Dow	Copes of Labels, MSDSs, DERs, and related material from DOW AgroSciences.
ECOTOX	References identified through a search of EPA's ECOTOX database: http://cfpub.epa.gov/ecotox/ .
CR-FOIA01	Cleared reviews obtained via FOIA HQ-RIN-00463-08 [n=9]. Received January 16, 2008.
E-Docket01	These are from the following E-Docket EPA-HQ-OPP-2005-00536. To get the complete listing of items available, go to http://www.regulations.gov/search/index.jsp and enter the docket number in the Search box.
E-Docket02	These are from the following E-Docket EPA-HQ-OPP-2007-0114. See note on E-Docket02 for directions on access this docket.
MRID	A registrant submitted study cited in an EPA risk assessment.
MRID-DER	A registrant submitted study for which the DER is available.
MRID-FULL	A registrant submitted study for which the registrant supplied a copy of the full study.
PR	Studies added during peer review.
Sundry	Studies/publications requested at various times after Set01.

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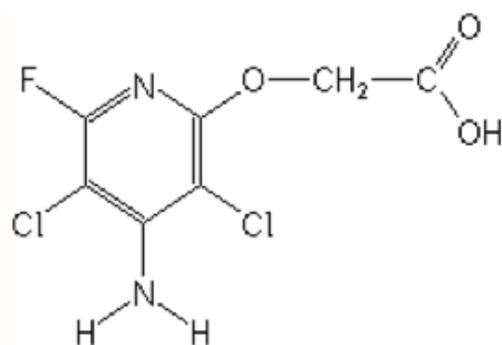
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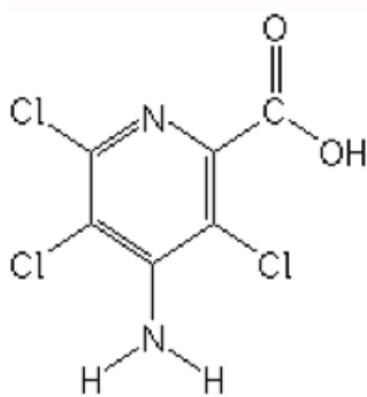
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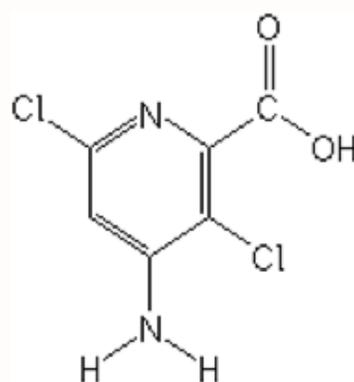
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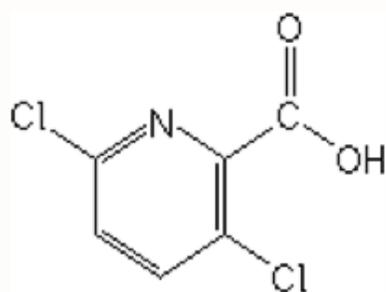
Fluroxypyr



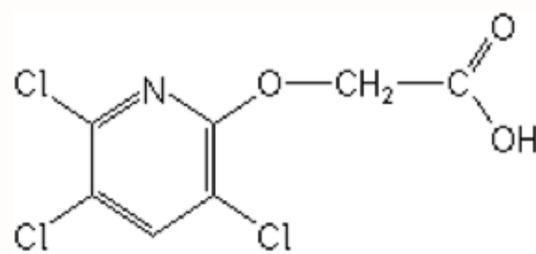
Picloram



Aminopyralid



Clopyralid



Triclopyr

Figure 1: Chemical Structure of Fluroxypyr and Structurally Related Herbicides

FLUROXYPYR - herbicide
 2002 estimated annual agricultural use

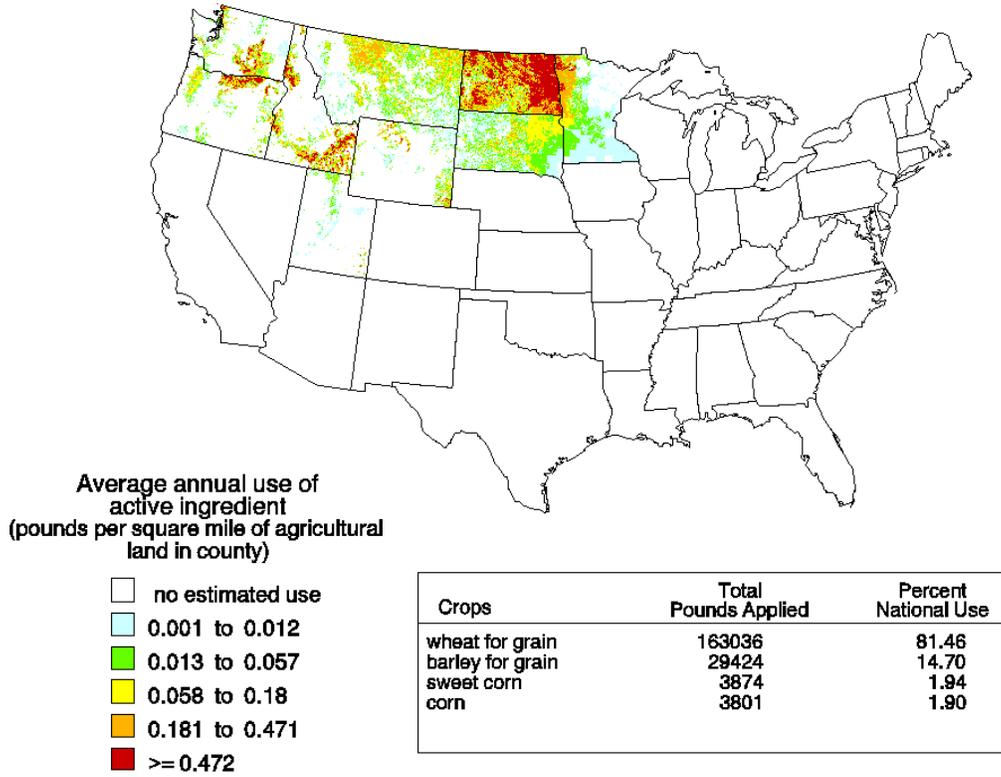


Figure 2: Estimated Agricultural Use of Fluroxypyr in the United States for 2002
 Source: USGS(2003a)

Fluroxypyr - MHE

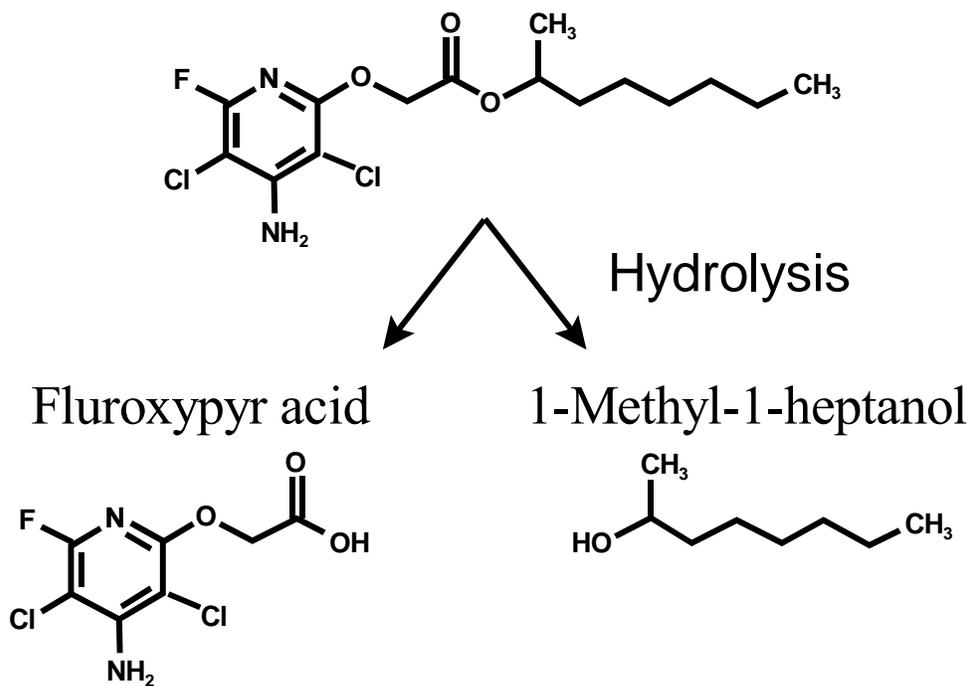


Figure 3: Hydrolysis of Fluroxypyr-MHE

Table 1: Commercial formulations of fluroxypyr-MHE

Property ^a	Vista Specialty Herbicide	Vista XRT (Ultra)
EPA Registration No	62719-308	62719-586
Manufacturer	Dow AgroSciences	Dow AgroSciences
Active Ingredient	Fluroxypyr 1-methylheptyl ester	Fluroxypyr 1-methylheptyl ester
Percent Ester (a.i. w/w)	26.2%	45.52%
Lbs a.e./gallons	1.5 lb a.e./gallon	2.8 lb a.e./gallon
Application Timing	Postemergence	Postemergence
Application Methods		
Ground	Backpack, hydraulic spray, or spot treatments	Backpack, hydraulic spray, or spot treatments
Aerial	Helicopter only to non-cropland areas except pine plantations (both helicopter and fixed wing aircraft).	Helicopter only to non-cropland areas except pine plantations (both helicopter and fixed wing aircraft).
Application Rates		
Minimum	0.12 lb a.e./acre	
Maximum Annual	2 ² / ₃ pints (42.66 oz or 0.5 lb a.e./acre)	22 fl. oz/acre (0.48 lb a.e./acre)
Application Volume		
Ground	At least 5 gallons/acre	At least 5 gallons/acre
Aerial	At least 3 gallons/acre	At least 3 gallons/acre
Other Ingredients		
1-methyl-2-pyrrolidinone, CAS No. 872-50-4)	5.1% (w/w)	0.1%
Naphthalene, CAS No. 91-20-3	<5.4% (w/w)	0.5%
Other (NOS)	63.5%	53.9%

^a All information taken from product labels and material safety data sheets. The most recent labels for Vista and Vista Ultra on the U.S. EPA label system (<http://oaspub.epa.gov/pestlabl/ppls.home>) is August 18, 2006 and December 10, 2007, respectively.

Table 2: Physical and chemical properties of fluroxypyr acid

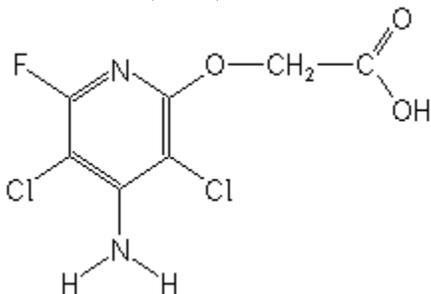
Property	Value ¹	Reference
Nomenclature		
Common Name	Fluroxypyr	Tomlin 2004
IUPAC Name	4-amino-3,5-dichloro-6-fluoro-2-pyridyloxyacetic acid	Tomlin 2004
CAS Name	[(4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy]acetic acid	Tomlin 2004
CAS No.	69377-81-7	Tomlin 2004
Development Codes	Dowco 433 (Dow)	Tomlin 2004
Structure		Tomlin 2004
Smiles Notation:	<chem>Nc1c(Cl)c(F)nc(OCC(=O)O)c1Cl</chem> <chem>n1c(F)c(Cl)c(N)c(Cl)c1OCC(=O)O</chem>	Tomlin 2004 Meylan and Howard 2007
Appearance/state, ambient	White, crystalline solid.	Tomlin 2004
Bioconcentration	3.16 [QSAR]	Meylan and Howard 2007
Density	1.09 (24 °C)	Tomlin 2004
Henry's law constant	1.06×10^{-8} Pa m ³ mol ⁻¹ (calc.)	Tomlin 2004
Henry's law constant	0.0005 atm/mol.m ³	U.S. EPA/OPP 2007c
K _{oc}	68 (average of 4 soils)	U.S. EPA/OPP 2007c, MRID 42137319
K _d and K _{oc}	See Table 2 for ester values.	Table 2
log K _{ow}	-1.24 (pH not specified) [K _{ow} = 0.0575]	Tomlin 2004
log K _{ow}	1.16 (QSAR) [K _{ow} = 14.5]	Howard and Meylan 2007
Melting point	232-233 °C	Tomlin 2004
Molecular formula	C ₇ H ₅ Cl ₂ FN ₂ O ₃	Tomlin 2004
Molecular weight (g/mole)	255.0	Tomlin 2004
pK _a	2.94	Tomlin 2004
pK _a	2.98	Kah and Brown 2007
Soil half-lives (aerobic)	14 days (median value from 4 soils)	U.S. EPA/OPP 2007c, MRID 42137317

Table 2: Physical and chemical properties of fluroxypyr acid

Property	Value ¹	Reference
U.S. EPA Docket Number	HQ-OPP-2005-00536 and HQ-OPP-2007-0114 at http://www.regulations.gov/search/index.jsp	
Vapor pressure	3.784 × 10 ⁻⁶ mPa (20 °C) 5 × 10 ⁻² mPa (25 °C) 9.4 × 10 ⁻⁷ mm Hg	Tomlin 2004 U.S. EPA/OPP 2007c
Water half-life (field dissipation)	24.8, 36.3, and 13.2 days	U.S. EPA/OPP 1998b
Water hydrolysis half-life	185 d (pH 9, 20 °C)	Tomlin 2004
Water, aerobic aquatic metabolism	14 days (silt loam) 42 days (selected EFED value, 3x single soil value)	U.S. EPA/OPP 2007c, MRID 44080345
Water, anaerobic aquatic metabolism	8 days (silt loam sediment) 24 days (selected EFED value, 3x single soil value)	U.S. EPA/OPP 2007c, MRID 44080344
Water photolysis half-life	stable	Tomlin 2004; U.S. EPA/OPP 2007c, MRID 44080342
Water solubility (mg/L)	5700 mg/L (pH 5.0, 20 °C) 7300 mg/L (pH 9.2, 20 °C). 7950 mg/L (pH and temperature not specified)	Tomlin 2004 U.S. EPA/OPP 2007c

¹ Specific environmental fate parameters used in modeling are discussed in Section 3.2.

Table 3: Physical and chemical properties of Fluroxypyr-MHE

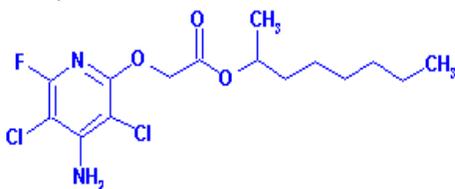
Property	Value ¹	Reference															
Nomenclature		Tomlin 2004															
Common Name	Fluroxypyr 1-methylheptyl ester																
IUPAC Name	4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy) acetic acid, 1-methylheptyl ester	Vista Label															
CAS Name	1-methylheptyl [4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy]acetate	Tomlin 2004															
CAS No.	81406-37-3	Tomlin 2004															
Development Codes	Dowco 433 MHE; XRD-433 1MHE; DOW-43300-H (All Dow)																
Structure		Tomlin 2004															
Smiles Notation:	<chem>CCCCOC(C)OC(=O)COc1nc(F)c(Cl)c(N)c1Cl</chem> <chem>n1c(F)c(Cl)c(N)c(Cl)c1OCC(=O)OC(C)CCCCC</chem>	Tomlin 2004 Meylan and Howard 2007															
Appearance/state, ambient	Off-white solid	Tomlin 2004															
Bioconcentration (L/kg)	613.9 [QSAR] 167 (whole fish) 21 (muscle)	Meylan and Howard 2007 Rick et al. 1996b															
Density	1.322 g/mL 1.3 g/mL	Tomlin 2004 U.S. EPA/OPP 2007b, MRID 44080303															
Ester-to-acid conversion factor	0.694	[255.0 g/mole ÷ 367.2 g/mole]															
Henry's law constant	$5.5 \times 10^{-3} \text{ Pa m}^3 \text{ mol}^{-1}$	Tomlin 2004															
K_{ads} and K_{oc}	<table border="1"> <thead> <tr> <th>Texture</th> <th>K_{ads}</th> <th>K_{oc}</th> </tr> </thead> <tbody> <tr> <td>Loam</td> <td>1.9</td> <td>62</td> </tr> <tr> <td>Sandy loam</td> <td>0.11</td> <td>51</td> </tr> <tr> <td>Silt loam</td> <td>1.7</td> <td>78</td> </tr> <tr> <td>Silty clay loam</td> <td>1.0</td> <td>81</td> </tr> </tbody> </table>	Texture	K_{ads}	K_{oc}	Loam	1.9	62	Sandy loam	0.11	51	Silt loam	1.7	78	Silty clay loam	1.0	81	U.S. EPA/OPP 2007c, MRID 42137319
Texture	K_{ads}	K_{oc}															
Loam	1.9	62															
Sandy loam	0.11	51															
Silt loam	1.7	78															
Silty clay loam	1.0	81															

Table 3: Physical and chemical properties of Fluroxypyr-MHE

Property	Value ¹	Reference
K _{oc}	39-84	Kah and Brown 2007
log K _{ow}	4.53 (pH 5) [K _{ow} = 33,884]	Tomlin 2004
	5.04 (pH 7) [K _{ow} = 109,648]	
log K _{ow}	4.57 (pH 5) [K _{ow} = 37,154]	U.S. EPA/OPP 2007b, MRID 44080303
	5.04 (pH 7) [K _{ow} = 109,648]	
	5.31 (pH 9) [K _{ow} = 204,174]	
log K _{ow}	3.9	Baker et al. 1992
Melting point	58.2-60 °C	Tomlin 2004
Melting point	57.5 °C	U.S. EPA/OPP 2007b, MRID 44080303
Molecular formula	C ₁₅ H ₂₁ C ₁₂ FN ₂ O ₃	Tomlin 2004
Molecular weight (g/mole)	367.2	Tomlin 2004
pH	6.81 in solution containing 90.1 µg/L	U.S. EPA/OPP 2007b, MRID 44080303
pK _a	N/A	
Soil half-lives (NOS)	2 to 168 days	Kah and Brown 2007
Soil half-lives (aerobic)	12 days (silt loam)	U.S. EPA/OPP 2007c, MRID 42137317
	23 days (sandy loam)	
	13 days (loam)	
	7 days (clay)	
Soil photolysis	152.7 days	U.S. EPA/OPP 2007c, MRID 44080343
U.S. EPA Docket Number	HQ-OPP-2005-00536 and HQ-OPP- 2007-0114 at http://www.regulations.gov/search/index.jsp	
Vapor pressure	1.349 × 10 ⁻³ mPa (20 °C)	Tomlin 2004
	2 × 10 ⁻² mPa (20 °C)	
	2.0 × 10 ⁻⁵ kPa at 25 °C	U.S. EPA/OPP 2007b, MRID 44080303
	1.0 × 10 ⁻⁵ kPa at 20 °C	
Water half-life (NOS)	1-3 days (natural water)	Tomlin 2004
Water hydrolysis half- life	stable (pH 5)	Tomlin 2004
	454 days (pH 7)	
	3.2 days (pH 9)	
	stable (pH 5)	U.S. EPA/OPP 2007c, MRID 40244539
	stable (pH 7)	
	3.2 days (pH 9)	
Water, aquatic metabolism (aerobic)	5.1 days (silt loam)	U.S. EPA/OPP 2007c, MRID 44080345
Water, aquatic metabolism (anaerobic)	8 days (silt loam)	U.S. EPA/OPP 2007c, MRID 44080344

Table 3: Physical and chemical properties of Fluroxypyr-MHE

Property	Value ¹	Reference
Water photolysis half-life	Stable	Tomlin 2004
	Stable	U.S. EPA/OPP 2007c, MRID 44080342
Water solubility (mg/L)	0.09 mg/L	Tomlin 2004
	90.1 µg/L in purified water	U.S. EPA/OPP 2007b, MRID 44080303
	294 µg/L in pH 5 buffer	
	136 µg/L in pH 7 buffer	
	57.2 g/L in pH 9 buffer	

Table 4: Summary of metabolism studies of fluroxypyr and fluroxypyr-MHE

Species/Route ^a	Metabolism	Reference
ACID		
Rats, oral (20 and 200 mg/kg) and iv (20 mg/kg)	Rapid absorption (90%) with rapid urinary excretion (90% within 12 hours), mostly as parent compound.	Veenstra and Herman 1983
Cow, oral (20 g)	Predominantly urinary excretion. Detectable concentrations in the kidney at 48 hours. Metabolites not characterized.	Hawkins et al. 1985
Cow, oral (0.4, 4, and 20 g/day for 28 days)	Residues in milk plateaued at 12-15 days. Highest concentration in kidney. No indication of saturation at higher doses. [20g:4g ratio in kidney = 3.4]	Roberts et al. 1986
Goat (0.6 g/day – approx 20 mg/kg bw – for 3 days)	Rapid excretion with about 75% in urine and remainder in feces. No significant metabolism. Highest tissue concentrations in kidney.	Huskin 1996
Goat (200 mg/day – approx 4 mg/kg bw – for 4 days)	Approximately 90% in urine and 10% in feces. Highest tissue concentration in kidney (0.21 ppm).	Yackovich et al. 1990
Goat (600 mg/day – approx 12 mg/kg bw – for 4 days)	Dose-related increased in tissue concentrations. No indication of saturation based on kidney residue (0.68 ppm). Excretion pattern similar to low dose group above.	Yackovich et al. 1990
ESTER		
Rats, Oral (50 mg/kg)	Rapid absorption (90%) with extensive metabolism (20-22 metabolites). Rapidly excreted as CO ₂ in expired air and metabolites. Minor fecal excretion. Kinetics essentially identical to methylhepanol.	Domoradzke and Brzak 1996
Rats, Oral (50 mg/kg for 7 days)	Rapid absorption and rapid urinary excretion (≈92%) with minor fecal excretion (≈5.6%). Some accumulation of ¹⁴ C in thyroid.	Hawkins et al. 1981a

^a Single doses unless otherwise specified. See Section 3.1.3 for discussion.

Table 5: Relative toxicity of acid and esters of fluroxypyr and related herbicides

Chemical	Form	Rat LD₅₀ mg/kg bw	Reference	Relative Toxicity (ester/acid)
Fluroxypyr	Acid	2405 ^a	Lockwood et al. 1975	
	MHE	3450	Cosse et al. 1992	1.43
2,4-D	Acid	639	SERA 2006, Table 3-2	
	BEE	866		1.35
	EHE	896		1.4
Triclopyr	Acid	680 ^b	SERA 2003b, Appendix 4	
	BEE	803		1.2

^a Average of values for male and female rats.

^b Average of two studies reporting LD₅₀ values of 630 and 729 mg/kg.

Table 6: Summary of subchronic and chronic oral toxicity studies in mammals

Studies with fluroxypyr-MHE are shaded. Doses in a.e give in braces[]. Study details are included in Appendix 2.

Species, Sex	Duration (Days)	Endpoint ^a	Dose (mg a.e./kg bw/d) ^b		Reference
			NOAEL	LOAEL	
Mice	91 d	Increased testes and spleen weights and ovarian lesions	N/A	2.7	Perry et al. 1984
Mice	91 d	No effects at highest dose.	1342	N/A	Shirasu et al. 1988
Mice	78 w	No effect	320	N/A	Perry et al. 1985
Mice	18 m	BW decrease and kidney damage	300	1000	Cosse et al. 1993
Rats, F ^d	10 d	Mortality and decreased BW.	500 [306]	750 [459]	Schroeder 1994a
Rats, F ^d	10 d	Mortality and decreased BW.	300 [184]	600 [367]	Schroeder 1994b
Rats, F	14 d	Salivation	125	250	Bottomley et al. 1983
Rats, offspring	Multigen	Marginal reduction in fertility.	150	500	Koeter et al. 1984
Rats, M	Multigen	No signs of toxicity	750	N/A	Koeter et al. 1984
Rats, F	Multigen	No signs of toxicity	1000	N/A	Koeter et al. 1984
Rats, offspring	Multigen	Decreased body weight	500	1000	Vedula et al. 1996
Rats, F	Multigen	Kidney damage, mortality	500	1000	Vedula et al. 1996
Rats, M	Multigen	Decreased BW. Kidney pathology.	100	500	Vedula et al. 1996
Rats, M	91 d	Kidney toxicity with many other secondary effects.	80	750	Jonker et al. 1987
Rats, F	91 d		750	1000	Jonker et al. 1987
Rats	91 d	Decrease BW, increased kidney weight.	700	1000	Grandjean et al. 1992
Rats	91 d	No effect	1000	N/A	Cosse et al. 1991b
Rats	106 w	No effect	320	N/A	Til et al. 1985
Rats	24 m	Increased kidney weight	100 ^c	500	Quast and McGuirk 1995
Rabbits, F ^d	13 d	Increased incidence of abortions.	346 [212]	693 [424]	Liberacki et al. 1996a
Rabbits, F ^d	13 d	No effect	693 [424]	N/A	Liberacki et al. 1996b
Rabbits, F	14 d	Increased post-implantation losses.	100	250	Tesh et al. 1984
Dogs	28 d	Kidney damage	50	150	Ehard et al. 1983
Dogs	365 d	No effects	150	N/A	Kinkel et al. 1984

^a BW = body weight, d = days, w = weeks; m = months; M = males; F = females, Multigen = multigeneration reproduction study.

^b For dietary exposures in which no differences were noted between males and females in the NOAEL, doses for NOAELs and LOAELs are based on the lowest dose for either males or females. For fluroxypyr-MHE, doses expressed as acid equivalents are give in braces [].

^c Basis of chronic RfD.

^d All studies in shade rows involved fluroxypyr-MHE. All other studies involved fluroxypyr acid.

Table 7: Chemical and site parameters used in GLEAMS modeling for fluroxypyr

Parameter	Clay	Loam	Sand	Note/ Reference
Half-Lives (days)				
Aquatic Sediment		8		Note 1
Foliar	2	3	6	Note 2
Soil	7	13	23	Note 3
Water		42		Note 4
Soil K_{oc} , mL/g	81	62	51	Note 5
Sediment K_d , mL/g	1.0	1.9	0.11	Note 5
Water Solubility, mg/L		7950		Note 6
Foliar wash-off fraction		0.95		Note 7
Fraction applied to foliage		0.5		Note 7

Note 1 Value used by U.S. EPA/OPP 2007c, anaerobic, MRID 44080344, 8 days. Aerobic half-time is 5.1 days.

Note 2 Based on publication by Juraske et al. 2008, half-lives on vegetation are taken as $\frac{1}{4}$ of the half-lives in soil rounded to the nearest day. The lower end of the range is very similar to turf half-lives for dislodgeable residues of 1.4 to 2.5 days from the study by Robert and Foster (2000). See Section 3.2.3.6 for discussion.

Note 3 U.S. EPA/OPP 2007c, MRID 42137317: silty clay, loam, and sandy loam soils. Same values used for ester and acid.

Note 4 Value used by U.S. EPA/OPP (2007c) for aerobic aquatic metabolism in PRZM/EXAMS modeling. The estimated anaerobic aquatic metabolism half-life is 24 days. The 42 day half-life is very close to the values (41 to 53 days) calculated by U.S. EPA/OPP in the DER for Lehmann and Miller (1989).

Note 5 U.S. EPA/OPP 2007c, MRID 42137319, p. 6: silty clay loam, loam, and sandy loam soils. These values are for the acid but are use here for ester because of the rapid conversion of fluroxypyr-MHE to fluroxypyr acid.

Note 6 Value used by U.S. EPA/OPP (2007c) in PRZM/EXAMS modeling for drinking water assessment. This applied to fluroxypyr acid and is used because fluroxypyr-MHE will rapidly be converted to fluroxypyr acid in surface water. See Section 3.2.3.4.3 for discussion.

Note 7 The foliar washoff fraction not available for fluridone. Two closely related herbicides (triclopyr and clopyralid) have reported foliar washoff fractions of 0.95 (Knisel and Davis 2000). The fractional application to foliage is a default for liquid formulations.

Table 8: 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. See SERA (2006c) for details.

Table 9: General site conditions used in Gleams-Driver runs

Field Characteristics		Description		
Type of site	Mixed pine-hardwood			
Treated and total field areas	10 acres			
Field width	660 feet			
Slope	0.1			
Depth of root zone	60 inches			
Cover factor	0.15			
Type of clay	Mixed			
Surface cover	No surface depressions			
Pond Characteristics		Description		
Surface area	1 acre			
Drainage area:	10 acres			
Initial Depth	2 meters			
Minimum Depth	1 meter			
Maximum Depth	3 meters			
Sediment Depth	2 centimeters			
Stream Characteristics		Description		
Width	2 meters			
Flow Velocity	6900 meters/day			
Flow Rate	710,000 liters/day			
Soil Specific Factors ^a		Clay	Loam	Sand
Runoff potential	High	Moderate	Low	
Surface type	Meadow	Meadow	Meadow	

^a Detailed input values for the soil types are given in SERA (2007b, Tables 2 and 3) .

Table 10: Summary of modeled and monitored concentrations in surface water

Scenario	Concentrations (ppb or µg/L)	
	Peak	Long-Term Average
MODELING FOR THIS RISK ASSESSMENT (1 lb a.i./acre)		
Direct Spray and Spray Drift		
Pond, Direct Spray (Section 3.2.3.4.2) ^a	112	N/A
Pond, drift at 25 feet (Section 3.2.3.4.2) ^a	4	N/A
Stream, Direct Spray (Section 3.2.3.4.2) ^a	100	N/A
Stream, drift at 25 feet (Section 3.2.3.4.2) ^a	3.2	N/A
Gleams-Driver		
Broadcast Foliar, Single Application		
Pond (Section 3.2.3.4.4) ^b	3.18 (0 to 52)	0.52 (0 -10.9)
Stream (Section 3.2.3.4.4) ^c	6.33 (0 - 79)	0.068 (0 - 1.76)
Other Modeling		
U.S. EPA		
PRZM-EXAMS, Index Reservoir ^d	18.7 (15.42 – 32.9)	0.25 (0.21 – 3.28)
GENEEC ^e	44.8	15.36 [56 day ave.]
SCIGROW (Ground water) ^f	0.025	N/A
Monitoring		
Krueger 1998: Streams in agricultural region of Sweden, maximum weekly concentrations	6 (1.8 – 7)	N/A

^a Section 3.2.3.4.2 discusses expected concentrations in terms of the maximum application rate of 0.5 lb a.i./acre. The values for direct spray and drift are taken from Worksheet 10a (direct spray and drift as 25 feet for a pond) and Worksheet 10b (direct spray and drift as 25 feet for a stream) adjusted to WRC values based on the application rate of 0.5 lbs/acre.

^b See Appendix 9, Tables 5 and 6, for more detailed site-specific summary of pond modeling.

^c See Appendix 9, Tables 7 and 8, for more detailed site-specific summary of stream modeling.

^d U.S. EPA/OPP 2007c, p. 3 for a cumulative application rate of 1 lb/acre.

^e U.S. EPA/OPP 1998b, p. 11, normalized based on modeled rate of 0.125 to 0.25 lb/acre

^f U.S. EPA/OPP 1998b, p. 12.

Table 11: Surface water concentrations used in this risk assessment

(see Section 3.2.3.4.6 for discussion)

Water contamination rate in mg/L per lb/acre applied ^a

	Peak	Longer-term
Central	0.022	0.001
Lower	0.0005	0.0001
Upper	0.08	0.011

^a 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.

Table 12: Estimated residues in food items per lb a.i. applied

Food Item	Concentration in Food Item (ppm per lb a.i./acre)		
	Central ^a	Lower ^b	Upper ^a
Broadcast Foliar Applications			
Short grass	85	30	240
Tall grass	36	12	110
Broadleaf/forage plants and small insects	45	15	135
Fruits, pods, seeds, and large insects	7	3.2	15
Broadcast Granular Applications ^c			
Short grass	3.4	1.2	9.6
Tall grass	1.44	0.48	4.4
Broadleaf/forage plants and small insects	1.8	0.6	5.4
Fruits, pods, seeds, and large insects	0.28	0.13	0.6

^a From Fletcher et al. (1997) and U.S. EPA/EFED 2001, p. 44.

^b Central values \times (Central Value \div Upper Value).

^c Based on estimates from Michael (1992). See Section 3.2.3.6 for discussion.

Table 13: Summary of toxicity values used in human health risk assessment			
Duration	Derivation of RfD	Reference	Comment
Acute – single exposure			
NOAEL Dose			The U.S. EPA did not derive an acute RfD because of the lack of toxicity data from a single exposure and lack of developmental toxicity (U.S. EPA/OPP 2007f).
LOAEL Dose			
LOAEL Endpoint(s)			
Species, sex			
Uncertainty Factor			
RfD	N/A		
Chronic – lifetime exposure			
NOAEL Dose	100 mg a.e./kg bw/day	Quast and McGuirk 1995 MRID 44080322	
LOAEL Dose	500 mg a.e./kg bw/day		
LOAEL Endpoint(s)	Kidney toxicity		
Species, sex	Rat, both		
Uncertainty Factor	100	U.S. EPA/OPP 2007f	
RfD	1 mg a.e./kg bw/day		
Occupational – 1 to 6 month exposure periods			
NOAEL Dose	100 mg a.e./kg bw/day	Quast and McGuirk 1995 MRID 44080322	U.S. EPA/OPP (2007f, p. 22 ff) uses the chronic toxicity value with an MOE of 100 and considers only inhalation exposure. No specific shorter-term occupational RfD.
LOAEL Dose	500 mg a.e./kg bw/day		
LOAEL Endpoint	Kidney toxicity		
Species, sex	Rat, both	U.S. EPA/OPP 2007f	
Uncertainty Factor/MOE	100		
Equivalent RfD	1 mg a.e./kg bw/day		

Table 14: Summary of Toxicity to Fish*(Only acute studies available. See Appendix 6 for additional details.)*

Species	Endpoint	Value	Units	Reference
ACID				
Freshwater				
Bluegill sunfish	96 h LC ₅₀	14.3	mg/L	Weinberg et al. 1991b
Bluegill sunfish	NOEC	7.28	mg/L	
Rainbow trout	NOEC	100	mg/L	Willis 1984a
Golden orfe	NOEC	100	mg/L	Willis 1984b
Saltwater				
Silverside	96-h LC ₅₀	40	mg/L	Boeri et al. 1994a
Silverside	LOEC, equilibrium	18	mg/L	
ESTER^b				
Freshwater				
Salmon, several species	96-h LC ₅₀ , lowest	8	mg/L	Wan et al. 1992 ^a
	96-h LC ₅₀ , highest	19	mg/L	
Bluegill sunfish	NOEC	100 [0.629]	mg/L	Rick et al. 1996a
Rainbow trout	NOEC	100 [0.225]	mg/L	Weinberg et al. 1991c
Rainbow trout	NOEC	5.0 [0.7]	mg/L	Willis 1984c
Golden orfe	NOEC	5.0 [0.7]	mg/L	Willis 1984d
Saltwater				
Silverside	NOEC	0.188	mg/L	Manning 1998a
Sheepshead minnow	NOEC	100 [0.087]	mg/L	Boeri et al. 1996a

^a It is not clear whether the concentrations given in the study reflect a composite of ester and acid or only the ester. The latter seems unlikely because of the low solubility of the ester. These toxicity values are not cited or used quantitatively by U.S. EPA/OPP (1998b). See text for discussion.

^b Nominal concentrations followed by measured concentrations in brackets [].

Table 15: Summary of Toxicity to Aquatic Invertebrates

See Appendix 7 for additional details.

Species, Sex	Endpoint	Value	Units	Reference
ACUTE				
Acid				
Freshwater				
<i>Daphnia magna</i>	NOEC	100	mg/L	Jones and Willis 1984
Saltwater				
Eastern oyster	LC ₅₀	51	mg/L	Boeri et al. 1994b
Eastern oyster	NOEC	16	mg/L	Boeri et al. 1994b
Glass shrimp	NOEC	120	mg/L	Boeri et al. 1994c
Ester^a				
Freshwater				
<i>Daphnia magna</i>	NOEC	100 [0.11]	mg/L	Weinberg et al. 1991a
<i>Daphnia magna</i>	NOEC	56 [0.56]	mg/L	Jones 1984b
Saltwater				
Eastern oyster	EC ₅₀ , shell deposition	≈22 [0.068]	mg/L	Boeri et al. 1996b
	LOEC, shell deposition	12 [0.050]	mg/L	Boeri et al. 1996b
Glass shrimp	NOEC	100 [0.135]	mg/L	Boeri et al. 1995
Pink Shrimp	NOEC	0.128	mg/L	Manning 1988b
CHRONIC				
Acid				
<i>Daphnia magna</i>	NOEC	56	mg/L	Jones 1984a
<i>Daphnia magna</i>	LOEC, immobility	100	mg/L	Jones 1984a
Ester^a				
<i>Daphnia magna</i>	NOEC	0.0605	mg/L	Kirk et al. 1996a
<i>Daphnia magna</i>	LOEC, # neonates	0.109	mg/L	Kirk et al. 1996a

^a Nominal concentrations followed by measured concentrations in brackets [].

Table 16: Fluroxypyr Toxicity to Aquatic Plants

See Appendix 8 for additional details.

Species, Sex	Endpoint	Value ^a	Units	Reference
ALGAE ^b				
Acid				
Freshwater				
<i>Chlorella vulgaris</i>	NOEC	100	mg/L	Jones 1984c
Ester				
Freshwater				
<i>Chlorella pyrenoidosa</i>	EC ₅₀	3.0	mg/L	Ma et al. 2001 ^c
<i>Chlorella vulgaris</i>	EC ₅₀	37.5	mg/L	Ma et al. 2002 ^c
<i>Scenedesmus obliquus</i>	EC ₅₀	26.5	mg/L	Ma 2002 ^c
<i>Selenastrum capricornutum</i>	>EC ₅₀	1.41	mg/L	Milazzo et al. 1996c
<i>Selenastrum capricornutum</i>	NOEC	0.199	mg/L	Milazzo et al. 1996c
<i>Selenastrum capricornutum</i>	LOEC	0.336	mg/L	Hughes and Alexander 1991
<i>Selenastrum capricornutum</i>	NOEC	0.121	mg/L	Hughes and Alexander 1991
<i>Anabaena flos-aquae</i>	EC ₅₀	0.602	mg/L	Milazzo et al. 1996a
<i>Anabaena flos-aquae</i>	NOEC	0.030	mg/L	Milazzo et al. 1996a
Saltwater				
<i>Skeletonema costatum</i>	5-d EC ₅₀	0.292	mg/L	Hughes et al. 1996
<i>Skeletonema costatum</i>	5-d NOEC	0.179	mg/L	Hughes et al. 1996
MACROPHYTES				
Ester				
<i>Lemna gibba</i>	7-d NOEC	1.22	mg/L	Kirk et al. 1996b
<i>Lemna gibba</i>	7-d NOEC	0.412	mg/L	Kirk et al. 1998
<i>Lemna gibba</i>	14-d NOEC	0.437	mg/L	Kirk et al. 1998

^a The studies by Ma report only nominal concentrations. All other studies report measured concentrations. See Section 4.1.3.4.1 for a discussion of solubility issues.

^b The studies by Cowgill et al. (1988) and Milazzo et al. 1996b are classified by the U.S. EPA/OPP as *Invalid* and these studies not included in the above summary. See Appendix 8 for summarizes of these studies.

^c In all of the Ma studies, fluroxypyr is specified only as an 11% or 20% EC formulation. Presumably, this refers to an ester formulation but the percent a.i. does not correspond to the formulations considered in this risk assessment (Table 1).

Table 17: Toxicity of Fluroxypyr Metabolites to Aquatic Plants*See Appendix 8(latter half) for additional details.***4-Amino-3,5-dichloro-6-fluoro-2-pyridinol**

Species	Endpoint ^a	Metabolite Reference	Fluroxypyr Ester Value	Fluroxypyr Ester Reference	Relative Potency ^b
<i>Navicula pelliculosa</i>	NOEC: 3 mg/L	Ward et al. 1999a	N/A		
<i>Anabaena flos-aquae</i>	NOEC: 2.9 mg/L	Ward et al. 1999c	0.030	Milazzo et al. 1996a	0.010
<i>Selenastrum capricornutum</i>	NOEC: 3.3 mg/L	Ward et al. 1999d	0.12	Hughes and Alexander 1991	0.036
<i>Skeletonema costatum</i>	5-d NOEC: 3 mg/L	Ward et al. 1999e	0.18	Hughes et al. 1996	0.06
<i>Lemna gibba</i>	14-d NOEC: 3.2 mg/L	Ward et al. 1999b	0.44	Kirk et al. 1998	0.14

4-amino-3,5-dichloro-6-fluoro-2-methoxy-pyridine

Species	Endpoint	Metabolite Reference	Fluroxypyr Value	Fluroxypyr Reference	Relative Potency ^a
<i>Navicula pelliculosa</i>	120- h EC ₅₀ : 3.2 mg/L	Ward et al. 1999f	N/A		
<i>Anabaena flos-aquae</i>	120-h EC ₅₀ : 1.8 mg/L	Ward et al. 1999h	0.602 mg/L	Milazzo et al. 1996a	0.33
<i>Anabaena flos-aquae</i>	120-h NOEC: 1.12 mg/L	Ward et al. 1999h	0.03 mg/L	Milazzo et al. 1996a	0.026
<i>Selenastrum capricornutum</i>	5-d EC ₅₀ : 2.8	Kirk and Landre 1995	0.29 mg/L	Hughes et al. 1996	0.10
<i>Selenastrum capricornutum</i>	5 d NOEC: 0.94	Kirk and Landre 1995	0.12 mg/L	Hughes and Alexander 1991	0.13
<i>Skeletonema costatum</i>	5-d NOEC: 2.52 mg/L	Ward et al. 1999i	0.18	Hughes et al. 1996	0.071
<i>Skeletonema costatum</i>	5-d EC ₅₀ : 7.82 mg/L	Ward et al. 1999i	0.29	Hughes et al. 1996	0.037
<i>Lemna gibba</i>	14-d NOEC: 3.52 mg/L	Ward et al. 1999g	0.44	Kirk et al. 1998	0.13

^a When values are available for more than one endpoint and/or from more than one study, the lowest toxicity value is selected. Values for EC₅₀s expressed as greater than are not used. See text for discussion. Toxicity values are rounded to two significant digits.

^b Toxicity value for fluroxypyr divided by toxicity value for metabolite.

Table 18: Summary of toxicity values used in ecological risk assessment

Group/Duration	Organism	Endpoint	Toxicity Value (a.e.)	Reference
Terrestrial Animals				
Acute				
	Non-canine Mammals	NOEL, Kidney toxicity	100 mg/kg bw	Section 4.3.2.1.
	Canine Mammals	Non-canine mammals	100 mg/kg bw	Section 4.3.2.1.
	Birds	NOEL, acute dietary	750 mg/kg bw	Section 4.3.2.2.
	Honey Bee ^a	NOEC, mortality	186 mg/kg bw	Section 4.3.2.3.1.
Longer-term				
	Small Mammal	NOEL, Kidney toxicity	100 mg/kg bw/day	Section 4.3.2.1.
	Large Mammal	NOEL, Kidney toxicity	100 mg/kg bw/day	Section 4.3.2.1.
	Bird	NOEL, reduced egg production	21 mg/kg bw/day	Section 4.3.2.2.
Terrestrial Plants				
Soil	Sensitive	NOEL, seedling emergence	0.022 lb/acre	Section 4.3.2.4.
	Tolerant	NOEL, seedling emergence	0.17 lb/acre	
Foliar	Sensitive	NOEL, vegetative vigor	0.0007 lb/acre	Section 4.3.2.4.
	Tolerant	NOEL, vegetative vigor	0.17 lb/acre	
Aquatic Animals				
Acute				
Amphibians	Sensitive		N/A	
	Tolerant		N/A	
Fish	Sensitive	NOEC, sheepshead minnow	0.060	Section 4.3.3.1.1.
	Tolerant	NOEC, several species	0.49	Section 4.3.3.1.1.
Invertebrates	Sensitive	NOEC (est.), eastern oyster	0.002	Section 4.3.3.3.1.
	Tolerant ^a	NOEC, daphnids	0.39	Section 4.3.3.3.1.
Longer-term				
Amphibians	Sensitive		N/A	
	Tolerant		N/A	
Fish	Sensitive		N/A	Section 4.3.3.1.2.
	Tolerant		N/A	Section 4.3.3.1.2.
Invertebrates	Sensitive		N/A	Section 4.3.3.3.2.
	Tolerant ^a	NOEC, daphnids	56	Section 4.3.3.3.2.
Aquatic Plants				
Algae	Sensitive	NOEC, <i>Anabaena flos-aquae</i>	0.021	Section 4.3.3.4.2.
	Tolerant	NOEC, <i>Selenastrum capricornutum</i>	0.14	Section 4.3.3.4.2.
Macrophytes	Sensitive	NOEC, <i>Lemna gibba</i>	0.29	Section 4.3.3.4.1.
	Tolerant	NOEC, <i>Lemna gibba</i>	N/A	Section 4.3.3.4.1.

^a The acute toxicity values based on fluroxypyr-MHE and the chronic is based on fluroxypyr acid. See text.

Table 19: HQ Values for Drift to Terrestrial Plants

Drift Distance (feet)	HQ Values by Application Method ^a			
	Aerial	High Boom	Low Boom	Backpack
Sensitive Species				
0	714	714	714	714
25	159	74	25	6
50	122	36	13	3
100	70	18	7	1.7
300	22	5	3	0.7
500	14	3	1.5	0.4
900	9	1.2	0.8	0.2
Tolerant Species				
0	3	3	3	3
25	0.7	0.3	0.1	2E-02
50	0.5	0.1	5E-02	1E-02
100	0.3	7E-02	3E-02	7E-03
300	9E-02	2E-02	1E-02	3E-03
500	6E-02	1E-02	6E-03	2E-03
900	4E-02	5E-03	3E-03	9E-04

^a See Worksheets G05a-d in the EXCEL workbook that accompanies this risk assessment for the details of the calculations.

Appendix 1: Chemical Properties and Environmental Fate

Property	Data Summary	Reference, MRID, OPP Classification
Catalyzed hydrolysis of fluroxypyr-methylheptyl ester to fluroxypyr in soil/water suspensions	In distilled, deionized water (pH 7, 25°), the half-life was 454 days; however, in 1:100 soil/water suspensions of Barnes loam, Catlin silt loam, and Mhoon clay, the half-lives were 2, 5, and 5.5 hours, respectively. In soil incubated at <i>field moist conditions</i> , all but 1-2% of the fluroxypyr-MHE hydrolyzed after 3 days.	Lehmann and Miller 1989
Aerobic soil metabolism of fluroxypyr-MHE	<p>Within 1 day of application (approximately 2.0 ppm [¹⁴C] fluroxypyr-MHE – purity 100% in incubation flasks) most of the fluroxypyr-MHE had hydrolyzed to fluroxypyr (herbicide).</p> <p>Registrant calculated degradation half-lives of fluroxypyr in soil: 12 days (silt loam), 23 days (sandy loam), 12 days (loam), and 7 days (silty clay). DER notes that registrant did not use the complete data set to calculate the half-lives and did not explain rationale for not doing so. The degradates were identified as the pyridinol metabolite and the methoxyppyridine metabolite.</p> <p>Using the COMPLETE DATA SET, the EPA calculated half-lives of 46 days (silt loam), 41 days (sandy loam), 46 days (loam), and 53 days (silty clay).</p>	Lehmann and Miller 1989 MRID 42137317 Supplemental
Formation of fluroxypyr from fluroxypyr-MHE by soil catalysis	<p>0.079 ppm [¹⁴C] fluroxypyr-MHE (purity 98.7%) added to silt loam, loam, and silty clay soil).</p> <p>Registrant calculated degradation half-life: approximately 2-2.5 hours. Fluroxypyr-MHE was 76.2-92.2% of recovered radioactivity at 1 hour post treatment, which decreased to 39.6-73.8% at 4 hours. Fluroxypyr (herbicide) was the only degradate, which increased from 7.8-23.8% of recovered radioactivity at 1 hour to 39.6-73.8% at 4 hours post treatment.</p> <p>In soil:distilled water slurries, [¹⁴C] fluroxypyr-MHE was 71.4% at 1 hour post treatment, and 23.1% at 5 hours; fluroxypyr was 28.6% of recovered radioactivity at 1 hour and 76.9% at 5 hours post treatment.</p>	Lehmann 1988 MRID 42137316 Supplemental <i>Voluntary study initiated to provide hydrolysis information for conditions more representative of natural waters.</i>

Appendix 1: Chemical Properties and Environmental Fate (*continued*)

Property	Data Summary	Reference, MRID, OPP Classification
Batch equilibrium studies with fluroxypyr-MHE	<p>At single point concentration of 0.066 mg/L in soil, fluroxypyr to be very mobile in silt loam, sandy loam, loam, and silty clay.</p> <p>The batch equilibrium k_d values for fluroxypyr-MHE were: 260 (silt loam) 95 (sandy loam) 190 (loam) 210 (silty clay)</p> <p><i>Study authors stated that since fluroxypyr-MHE was unstable in the test system, and equilibration period of 10 minutes was arbitrarily chosen for the experiment.</i></p> <p>DER reviewer indicates that <i>since fluroxypyr-MHE degraded in the test system, it is unlikely that an equilibrium was established.</i></p>	Lehmann et al. 1988 MRID 42137319 Acceptable
Soil degradation under laboratory and greenhouse conditions	<p>Following initial rapid hydrolysis of fluroxypyr-MHE to fluroxypyr, the compound degraded with the following first order half-lives:</p> <p>Barnes loam: 12 days Catlin silt loam: 12 days Hanford sandy loam: 23 days Mhoon clay: 7 days</p> <p>Metabolites identified: 4-amino-3,5-dichloro-6-fluoro-pyridin-2-ol and 4-amino-3,5-dichloro-6-fluoro-2-methoxypyridine. The pyridinol reached maximum concentration of 5-20% applied after 2-4 weeks of incubation; whereas the methoxypyridine reached maximum concentration (ranging from 10-40% applied) after 8 weeks.</p> <p>Degradation of fluroxypyr and its pyridinol were not significantly altered by diurnal variations in soil temperature (from 21 to 32°C), moisture, or the presence of growing grass.</p> <p>The further dissipation of methoxypyridine (by both microbial degradation and volatilization) was more rapid with half-life estimates of 3-5 months under greenhouse conditions, compared with an estimated half-life of 19 months in laboratory flasks, leading the investigators to suggest that the laboratory studies underestimated the dissipation rate of the metabolite.</p>	Lehmann et al. 1990a Note: This is similar to but not identical to Lehmann and Miller 1989b, MRID 42137317.

Appendix 1: Chemical Properties and Environmental Fate (*continued*)

Property	Data Summary	Reference, MRID, OPP Classification
Soil mobility of fluroxypyr determined by adsorption and desorption K_{oc} values	<p>Adsorption K_{oc} values = 20,000/kg for fluroxypyr-MHE and 74/kg for fluroxypyr, indicating increased mobility following hydrolysis of the ester.</p> <p>Desorption K_{oc} values (after 1-2 weeks of incubation) = 100-200/kg for fluroxypyr, which increased to 400-700/kg after 8 weeks of incubation. The increase was related to incubation time and not to concentration, and was attributed to entrapment of the fluroxypyr in the soil organic matter. Furthermore, similar increases in desorption K_{oc} values were observed for the pyridinol and methoxy pyridine metabolites.</p> <p>The investigators conclude from the results of the study that <i>mobility of the fluroxypyr aromatic ring strongly decreases with increased residence time in the soil.</i></p>	Lehmann et al. 1990b
Fate and effects of ^{14}C -labelled fluroxypyr-MHE in a small field plot in Midland, MI.	<p><u>Plot:</u> DowElanco experimental farm in Midland, MI characterized by Londo sandy loam (68% sand, 20% silt, 12% clay, and 2-4% organic matter). Rainfall was unusually low during the 1987 and 1988 growing season, so irrigation water was used to offset the dry conditions.</p> <p><u>Test chemical:</u> Radiolabelled 2,6-^{14}C- fluroxypyr-MHE (99+% pure).</p> <p><u>Application:</u> 600 g/ha or 0.32 mg/kg fluroxypyr equivalents to the top 15 cm of soil on May 4, 1987, following fertilization with 168 kg N/ha on May 1, 1987. At 30, 120, and 366 days, the plot was planted with lettuce, turnips, bush green beans, soybeans and wheat.</p> <p><u>Results:</u> 30 days after treatment, fluroxypyr degraded to about 60% of the initial concentration, but still the major compound in the soil; however, after 120 and 366 days, the major compound in the soil was methoxy pyridine. Fluroxypyr caused no apparent injury to the lettuce, turnips, green beans, soybeans, or wheat planted at 30, 120, and 366 days after the plot was treated. Furthermore, ^{14}C-residues in the edible crops were indistinguishable from the ^{14}C in control plants exposed to $^{14}\text{CO}_2$. There was no evidence of metabolite uptake by the plants.</p>	Lehmann et al. 1991

Appendix 1: Chemical Properties and Environmental Fate (*continued*)

Property	Data Summary	Reference, MRID, OPP Classification
<p>Dissipation (photolysis, aerobic metabolism, and anaerobic metabolism) of fluroxypyr in laboratory studies with water from Brewer lake in North Dakota</p>	<p><u>Photolysis</u>: negligible in sterilized water with and without natural photosensitizers. Recovery of radioactivity in buffered water was 97.4% for fluroxypyr-MHE and 101.3% for fluroxypyr. Photodegradation half-lives were 7 months for fluroxypyr-MHE and 1 year for fluroxypyr (extrapolated from 35 days of data). In Brewer lake water, recovery of radioactivity was 102.3%. The hydrolysis of fluroxypyr-MHE to fluroxypyr was slow with an extrapolated half-life of 3 weeks (dark) and 9 weeks (light).</p> <p><u>Aerobic aquatic metabolism</u>: Recovery of radioactivity was 93.8% (lighted experiment) and 100.7% (dark experiment); hydrolysis of fluroxypyr-MHE to fluroxypyr was rapid with only trace amounts of the ester ($\leq 1\%$) observed after day 1; degradation of fluroxypyr was rapid with dt_{50} values (time required for disappearance of 50% of the initial concentration) of 2 weeks (lighted experiment) and 1 week (dark experiment). Identified main metabolites included dichloropyridinol and 3-chloropyridinol (these were not observed in soil systems). 3-chloropyridinol formed after (and presumably from) the dichloropyridinol, which appeared at significant levels. The metabolites degraded more rapidly in the lighted experiment.</p> <p><u>Anaerobic aquatic metabolism</u>: The average recovery of radioactivity was 100.1%; $dt_{50} = 0.5$ weeks under anaerobic conditions; however the two major metabolites were not readily degraded.</p> <p><u>Fate of fluroxypyr in water</u>: Fluroxypyr and the pyridinols are expected to disappear from typical pond and lake water by the end of the growing season.</p>	<p>Lehmann et al. 1993</p>

Appendix 1: Chemical Properties and Environmental Fate (*continued*)

Property	Data Summary	Reference, MRID, OPP Classification
Transferable foliar residues of fluroxypyr on turf	<p>Single application of fluroxypyr 1-MHE (Vista Specialty Herbicide; emulsifiable concentrate) to three sites via tractor mounted boom sprayer with flat fan nozzles at a target rate of 560 g a.e./ha (1.33 qt/acre) in April-May 2000. The spray rate at the three sites ranged from 64-71 gallons/acre.</p> <p>The theoretical application rates were 636 g a.e./ha (114% of target) at CA site; 496 g a.e./ha (89% of target) at MS site, and 606 g a.e./ha (109% of target) at PA site.</p> <p>Plots were approximately 5-10 ft wide x 120-189 ft long. Turf varieties included dwarf fescue (CA), dwarf Bermuda (MS), and mixed fescue (PA).</p> <p>From days 0-6 after treatment, transferable fluroxypyr residues ranged from 0.001-0.045 µg a.e./cm² or from 0.03 to 0.74% of applied parent a.e.</p> <p>Transferable fluroxypyr residues from turf were detected for 2 days after application at the PA site and for 6 days after application at the CA and MS sites.</p> <p>First-order field half-lives of transferable fluroxypyr residues on turf ranged from 1.4-2.5 days.</p> <p>The investigators conclude that with a use rate of 560 g a.e./ha under typical post-treatment management practices and typical environmental conditions, fluroxypyr transferable residues are not likely to exceed 0.045 µg a.e./cm² (45 g a.e./ha) or 0.74% of applied a.e.</p>	Robert and Foster 2000 MRID 45361602 (Full study from Dow)

Appendix 1: Chemical Properties and Environmental Fate (*continued*)

FIELD STUDIES		
Application/Field Conditions	Results	Reference
<p><u>Application</u>: 1-methylheptyl ester of fluroxypyr (Starane 250) at 187.5 g a.e./ha to two lysimeters or 375.0 g a.e./ha to two lysimeters in Lanna and Kjettslinge fields (central Sweden). The aqueous dilution was applied using a small plot sprayer (volume = 400 L/ha) on June 2.</p> <p><u>Leachate</u>: collected in lysimeters with undisturbed soil (sand) and in tile-drained plots (clay). Leachate samples at both sites were collected weekly, if drainage occurred for 332 days post application at Kjettslinge and for 168 days post spraying at Lanna.</p> <p><u>Soil samples</u>: collected to a depth of 1 meter to characterized temporal depth distribution of fluroxypyr.</p> <p>Limit of detection (leachate) = 1 µg/L</p> <p>Limit of detection (soil) = 5 µg/kg dry soil</p>	<p><u>Leachate samples</u>: only two samples (one from each soil), which were collected within 2 months after application, had fluroxypyr concentrations greater than the limit of detection: 2 and 5 µg/L (see Table 3; pg 413 of study). Neither sample contained the methylheptyl ester of fluroxypyr.</p> <p><u>Soil samples</u>: No fluroxypyr above the limit of detection was found below the topsoil (0-2 mm) in the clay profile; in the sand profiles, concentrations just above the limit of detection were occasionally found in deeper soil layers.</p> <p>Concentrations in soil were either undetectable or at very low levels within 3 months after the application of fluroxypyr.</p>	<p>Bergstrom et al. 1990</p>

Appendix 2: Toxicity to experimental mammals

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
ORAL – ACUTE			
Rats	Fluroxypyr acid and fluroxypyr MHE	Acid, MRID 40354010, Lockwood et al. 1975 LD ₅₀ = 2405 mg/kg Toxicity Category III Ester, MRID 40354005 LD ₅₀ = >5000 mg/kg Toxicity Category IV	U.S. EPA/OPP 2003a
Rats, Fischer 344, 6 to 7-wks-old, 175-184 g (males), 120-129 g (females), 5/sex/group, fasted	XRM-5316 (fluroxypyr 25.6%) [fluroxypyr-MHE] Gavage dose levels: 500, 2000, or 5000 mg XRM/kg body weight 14-day observation period.	<u>Mortality</u> : 4/5 males and 5/5 females in high-dose group. All of the high dose females and one of the high dose males died on Day 1; remaining males died on Day 2. <u>Signs of toxicity</u> : decreased activity, lacrimation, salivation, incoordination, labored breathing, and closed eyelids. No adverse findings at necropsy. Calculated LD ₅₀ values:: 3738 mg/kg [2288 mg a.e./kg] (males) 3162 mg/kg [1935 mg a.e./kg] (females) Toxicity Category III	Cosse et al. 1992a MRID 44080329 Acceptable

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
ORAL – DEVELOPMENTAL STUDIES			
<p>Rabbits, New Zealand White, 20 time-mated females, 5- to 6-months-old, ≈3250 g on Day 0 of gestation</p>	<p>Fluroxypyr MHE (95.8% a.i.)</p> <p>Dose levels: 0 (vehicle: methocel*A4M), 100, 500, or 1000 mg/kg/day via gavage on days 7-19 of gestation in dosing volume of 4 mL/kg bw/day.</p> <p>These dose levels represented fluroxypyr acid equivalents of: 0, 69, 346, or 693 mg/kg/day.</p>	<p><u>Maternal toxicity</u>: increased incidence of abortion at the high dose.</p> <p>Maternal/developmental LOEL = 1000 mg/kg/day, based of an increased incidence of abortions</p> <p>Maternal NOEL = 500 mg/kg/day</p> <p>No effects on body weight except a non-treatment-related decrease in mid- and high-dose groups, primarily at dosing period which may be attributable to palatability; corrected maternal body was comparable with controls.</p> <p>No treatment-related effects on pregnancy rate, no premature deliveries or does with 100% intrauterine deaths. All does had live fetuses at necropsy, and there were comparable numbers of corpora lutea, implantations, resorptions, live fetuses and pre- and post-implantation losses among groups.</p> <p>Investigators observed a slight decrease (97% of controls) in fetal body weight at the high-dose level, which may have been due to the increased number of fetuses/doe.</p> <p>No treatment-related external, skeletal, or visceral anomalies, no variations, or increases in visceral or skeletal malformations were observed.</p> <p>The incidence of minor anomaly, retrocaval ureter was increased at the mid-and high-dose levels, but its toxicological significance <i>is doubtful</i>.</p>	<p>Liberacki et al. 1996a MRID 44080319 Acceptable</p>

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
<p>Rabbits, New Zealand White, 7 time- mated females, 5- to 6- months-old, ≈2500-3500 g</p>	<p>Fluroxypyr MHE (95.8% a.i.) [an impurity, pyridine, was present at 1.37% by weight.]</p> <p>Dose levels: 0 (vehicle: methocel*A4M), 300, 500, 750, or 1000 (limit dose) mg/kg/day via gavage on days 7-19 of gestation in dosing volume of 4 mL/kg bw/day</p> <p>These dose levels represented fluroxypyr acid equivalents of: 0, 208, 347, 520, or 693 mg/kg/day.</p>	<p>No treatment-related effects on survival, clinical oar gross pathology changes, body weight/gain, food consumption, absolute and relative liver and kidney weights. Pregnancy rates were comparable among the groups, and there were no premature deliveries or dams with 100% intrauterine deaths. All does had live fetuses at necropsy, and there were comparable numbers of corpora lutea, implantations, resorptions, live fetuses and pre- and post-implantation losses among groups. No treatment-related effects on reproductive or developmental parameters up to and including the limit dose (1000 mg/kg/day).</p> <p>Maternal NOEL = 1000 mg/kg/day</p> <p>Developmental NOEL = 1000 mg/kg/day</p>	<p>Liberacki et al. 1996b MRID 44080320 Acceptable</p>

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
<p>Rabbits, New Zealand White, ≈29 females/dose group, 18- to 24-weeks-old, 3.56-4.65 kg</p>	<p>Dowco 433 (fluroxypyr acid), 95.8% a.i.</p> <p><u>Single daily gavage dose levels:</u> 0, (0.5% carboxymethyl cellulose) 25, 100, 400*, or 250 mg/kg/day on days 6-19 of gestation..</p> <p><i>*assay terminated after treatment of one batch of animals on day 9... in view of the unlikely survival of animals until the end of dosing.</i></p>	<p><u>Maternal Toxicity:</u> Clinical signs of toxicity including increased respiration, ataxia, and muscular weakness observed at 400 mg/kg/day (dose level terminated on day 9). No clinical signs of toxicity observed at 250 mg/kg/day (highest dose evaluated completely in the study).</p> <p>No treatment-related effects on body weight gain or kidney weights; no adverse findings in maternal rabbits at necropsy (however individual observations were not provided for independent assessment).</p> <p>No treatment-related increases in the incidence of abortion or total litter loss at any dose level, relative to controls.</p> <p>Post-implantation losses were increased at the 250 mg/kg/day dose.</p> <p>Maternal NOEL = 100 mg/kg/day</p> <p><u>Developmental Toxicity:</u> Necropsy revealed gall bladder alterations/anomalies at the highest dose.</p> <p>Developmental NOEL = 100 mg/kg/day</p> <p>NOTES:</p> <p>(1) DER reviewer indicates <i>the discontinuation of the 400 mg/kg/day dose group appears to have been improper.</i></p> <p>(2) U.S. EPA/OPP 2003a (HHRA) indicates the following: Maternal NOAEL = 250 mg/kg/day LOAEL = 400 mg/kg/day, based on increased maternal deaths. Developmental NOAEL = 250 mg/kg/day (HDT) LOAEL not established.</p>	<p>Tesh et al. 1984 MRID 40345013 Supplemental</p> <p><i>No necropsy data provided for maternal animals.</i></p> <p>Note: U.S. EPA/OPP 2003a (HHRA) classifies the study as Acceptable</p>

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
Rats, CD, pregnant, 8- to 9-weeks-old, 174-210 g, 25/dose group	Dowco 433 (fluroxypyr acid), 99% Doses: 0, 125, 250, or 500 mg /kg/day by gavage suspended in 1% methylcellulose on days 6-19 of gestation.	<p>Parental Animals: Clinical signs of toxicity (salivation and brown facial staining) observed at the two highest doses (250 and 500 mg/kg/day). NOEL = 125 mg/kg/day for clinical signs of toxicity.</p> <p>One animal died in the high-dose group and death may have been treatment related. No effects observed on food consumption, body weight gain, live young embryonic deaths, implants, corpora lutea, pre-implantation loss, post-implantation loss, litter weight, or mean fetal weight.</p> <p>Statistically significant increase in mean kidney weight (10%) observed in high-dose group. NOAEL = 250 mg/kg/day for increased mean kidney weight.</p> <p>Increased incidence of renal pelvic dilatation observed at the highest dose. NOEL = 250 mg/kg/day for increased incidence of renal pelvic dilatation.</p> <p>Fetal Malformations and Anomalies: No increases in fetal malformation at any dose tested. No dose-related fetal visceral anomalies observed. Some evidence in the high-dose group of an increase in the percentage of fetuses with reduced skeletal ossification indicative of maternal and/or developmental toxicity. NOEL = 250 mg/kg/day for reduced skeletal ossification.</p> <p>No evidence of teratogenicity.</p>	Bottomley et al. 1983 MRID 40244509 Core (Acceptable)
<p>Bottomley et al. 1983 (MRID 40244509) continued: U.S. EPA/OPP 2003 a (HHRA): Maternal NOAEL = 250 mg/kg/day LOAEL = 500 mg/kg/day, based on increased kidney weights</p> <p>Developmental NOAEL = 500 mg/kg/day (HDT) LOAEL not established</p>			

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
<p>Rat, Sprague-Dawley, 10 time-mated females, 70-days-old at mating (add on group: 84-days-old at mating), 209-264 g (add on group: 251-199 g) on day 0 of gestation</p>	<p>Fluroxypyr MHE (95.8% a.i.). Vehicle: Mazola corn oil.</p> <p><u>Gavage dose levels:</u> 0, (Mazola corn oil), 100, 500, 750, or 1000 mg/kg/day on days 6 through 15 of gestation under conditions of range finding study.</p>	<p>Maternal NOEL = 500 mg/kg/day Maternal LOEL = 750 mg/kg/day based on deaths and decreased body weight gain.</p> <p><u>Mortality:</u> treatment-related increases in mortality were observed at the two highest dose levels: 40% (750 mg/kg/day) and 70% (1000 mg/kg/day), and termination of the high-dose group on day 11 of gestation.</p> <p><u>Body weight gain:</u> treatment-related decreases in body weight gain (80% of controls overall) was observed at 750 mg/kg/day.</p> <p>There were no premature deliveries or dams with 100% intrauterine deaths. All surviving dams had live fetuses at necropsy, and there were comparable numbers of corpora lutea, implantations, resorptions, and live fetuses among the groups; fetuses were not examined.</p> <p>750 mg/kg/day determined to be an appropriate dose level for a definitive developmental toxicity study based on maternal mortality.</p>	<p>Schroeder 1994a MRID 44080318 Acceptable</p>

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
<p>Rat, Sprague-Dawley, 28 time-mated females, 67-days-old at mating, 186-255 g on day 0 of gestation</p>	<p>Fluroxypyr MHE (95.8% a.i.). Vehicle: Mazola corn oil.</p> <p><u>Gavage dose levels:</u> 0, (Mazola corn oil), 100, 300, or 600 mg/kg/day on days 6 through 15 of gestation</p>	<p>Maternal NOEL = 300 mg/kg/day Maternal LOEL = 600 mg/kg/day based on mortality and decreased body weight gain and food consumption.</p> <p><u>Mortality:</u> 8 deaths in high-dose group (following 4, 6, 7, 7, 8, 8, 10, 10 days of treatment).</p> <p><u>Body weight gain and food consumption:</u> treatment-related decreases in body weight gain (77% of controls overall) and food consumption was observed at 600 mg/kg/day.</p> <p>Clinical signs of toxicity included anogenital skin/fur staining, lethargy, hypothermia, labored breathing, irregular gait, paleness. In treated dams, dose related increase in the incidence of excessive salivation, which may have resulted from residual amounts of the test material in the buccal cavity. There were no treatment-related effects on gross pathology changes or absolute and relative liver or kidney weights at any at dose level.</p> <p>Pregnancy rates were comparable among dose groups and there were no abortions, premature deliveries, or dams with 100% intrauterine deaths (except for one mid-dose dam).</p>	<p>Schroeder 1994b MRID 44094901 Acceptable</p>

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA- HED Classification
<p>Schroeder 1994b (continued): At necropsy, all dams had live fetuses, and among the dose groups, numbers of corpora lutea, implantations, resorptions, and live fetuses were comparable.</p> <p>Developmental NOEL = 300 mg/kg/day Developmental LOEL = 600 mg/kg/day based on increased ossification (incompletely ossified cervical vertebral transverse processes and pubes).</p> <p>Overall incidences of fetuses and litters with fetuses with one or more ossification variation was comparable among the groups; however there was an increase in the incidences of incompletely ossified cervical vertebral transverse processes (mid- and high-dose levels, not dose-related) and incompletely ossified pubes at the high-dose level, relative to the concurrent and historical controls. These increases occurred at a dose level that resulted in severe maternal toxicity (death).</p> <p>There were no dead fetuses, no external malformations, visceral malformations or variations, or skeletal formations related to treatment. Fetal body weights and sex ratios were comparable among the groups.</p>			

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
ORAL – REPRODUCTION STUDY			
<p>Rats, Wistar, 6-wks-old, 67-94 g (males), 58-88 g (females), 24/sex/dose group</p>	<p>Dowco 433 acid (fluroxypyr acid), purity not disclosed.</p> <p>Dietary concentrations: 0, 50, 150, or 500 mg/kg bw/day in multigenerational reproduction study.</p>	<p><u>General Observations:</u> No adverse effects observed at any dose level. No effects on body weight gain or food consumption of F₀ or F₁ parental animals.</p> <p><u>Glutamic-pyruvic transaminase:</u> statistically significant decreases (degree of inhibition 12-13%) observed in females in the mid- and high-dose groups. The EPA Toxicology Branch did not consider the finding to be of toxicological importance.</p> <p><u>Fertility:</u> possible evidence or suggestion of adverse effect on fertility index at the high dose for both matings of F₀ generation; however, the EPA Toxicology Branch did not consider <i>this to constitute a meaningful adverse effect of the test material.</i></p> <p><u>Number of pups/litter:</u> reduced in the high-dose group for both matings of F₀ generation. For the first mating, the reduction was statistically significant; however, since the effect was not observed at the high dose for either of the two matings of the F₁ generation, the EPA Toxicology Branch did not consider the effect in the F₀ generation to be treatment related.</p> <p>No meaningful treatment-related effects on absolute or relative kidney weights for either the F₀ or F₁ parental animals. Furthermore, histopathological examination of selective kidney tissues did not suggest adverse effects in the high-dose group F₀ or F₁ parental animals, relative to controls..</p>	<p>Koeter et al. 1984 MRID 40244510 Supplemental <i>No histopathology provided on reproductive organs for F₀ or F₁ parental animals; no gross pathology provided for all animals; highest dose tested considered inadequately low.</i></p>

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
<p>Rats, Sprague-Dawley, (P1) ≈6-weeks-old, (P2) ≈3-weeks-old, (P1) males: 104.4-132.2 g, females: 100.6-120.7 g, (P2) males: 124.5-195.1 g, females: 107.4-152.2 g [2outliers included (67.1 & 77.2 g)], 30/sex/dose group</p>	<p>Fluroxypyr, 99.0% a.i.</p> <p><u>Dietary target dose levels:</u> 0, 100, 500, or 750 mg/kg bw/day (males) and 0, 100, 500, or 1000 mg/kg/day (females) during the 10-week pre-mating period (F₁ generation) or the 12-week pre-mating period (F₂ generation).r</p>	<p>In this multi-generation reproduction study, there was one litter (F₁) in the first generation and there were two litters (F_{2A} and F_{2B}) in the second generation.</p> <p>Treatment-related mortality due to renal failure was observed in both sexes at the high dose in both generations: (one P₁ male [day 100]; two P₁ females [days 48 & 71]; one P₂ male [day 112], and one P₂ female [day 50]).</p> <p>In males of both generations, body weight [P₁ (91-94% of control); P₂ (89-93% of control)] and body weight gain [P₁ (93% of control); P₂ (91% of control)] were low, compared with controls; body weight and body weight gain were comparable among P₁ females throughout the study, while P₂ females had lower body weight (88.94% of controls) and body weight gain (91% of control) during the study.</p> <p>Food consumption was comparable among P₁ rats (both sexes) but decreased among P₂ rats (both sexes).</p> <p>Adverse effects on body weight were dose-dependent and grew progressively worse with time.</p> <p>Increases in kidney weight corresponded with gross and microscopic findings, including papillary atrophy, edema, necrosis, hyperplasia of the pelvic epithelium, degeneration/regeneration of the tubular epithelium, tubule-interstitial nephritis, and dilation of the tubules in both sexes of both generations exposed to the high-dose level and to a lesser degree in second-generation males exposed to the mid-dose.</p>	<p>Vedula et al. 1996 MRID 44080321 Acceptable</p>

Appendix 2: Toxicity to experimental mammals (*continued*)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA- HED Classification
<p>Vedula et al. 1996 (<i>continued</i>): Absolute liver weight was decreased in high-dose males (both generations) and high-dose females (second generation). The effect was attributed to the nutritional status of these rats.</p> <p>There were no treatment-related effects on reproductive indices (mating performance, fertility, gestation length, time to mating, or pup:sex ration) in both generations up to the limit dose in females and up to 750 mg/kg/day (HDT) in males.</p> <p>Pup survival was decreased during days 1-4 of lactation in the F_{2A} and F_{2B} litters at the high-dose level. (The investigator attributed the decrease in litter size/survival to the compromised health (decreased body fat and moderate to severe renal disease) of a few dams. Note: DER reviewer indicates that this conclusion was "not very apparent from the data as presented".</p> <p>In the high-dose group, decreased pup body weight and body weight gain was observed in both sexes of F_{2A} and F_{2B} litters; the effect was not observed in the mid- or low-dose groups.</p> <p>NOEL (maternal/paternal toxicity) = 500/100 mg/kg/day LOEL (maternal/paternal toxicity) = 1000/500 mg/kg/day based on female mortality and increased kidney weight with corresponding gross and microscopic findings.</p> <p>Reproductive NOEL = 1000/750 mg/kg/day (HDT)</p> <p>Neonatal NOEL = 1000/750 mg/kg/day (HDT) Neonatal LOEL = 1000 mg/kg/day based on decreased pup body weight/body weight gain and slightly lower survival.</p>			

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
ORAL – SUBCHRONIC DIETARY			
Mice, CD-1, 7-weeks-old, 24-30 g, 10 males and 10 females per group	Dowco 433 acid (fluroxypyr acid), purity not given. Exposure period: 13 weeks. Dietary concentrations: 0, 20, 80, or 320 ppm	No gross signs of toxicity. No data on food consumption. Assuming the same rate as low dose group from Shirasu et al. 1988, 20 ppm = 2.7 mg/kg bw. NOAEL: not defined. LOAEL: 20 ppm based on increased testes weights (absolute), increased spleen weights (absolute) in males. Ovarian lesions in females. Increase in spleen and testes weights attributed by study author to low testes weights in control group. No historical control data provided. Ovarian lesions (<i>p</i> -value using Fisher Exact Test): 2/10 (controls), 3/10 (<i>p</i> =0.5), 5/10 (<i>p</i> =0.17), and 7/10 (<i>p</i> =0.035). See Section 3.1.5 for detailed discussion.	Perry et al. 1984 MRID 40354012 Supplemental
<p>Note on Perry et al. 1984: This study is not discussed in any of the U.S. EPA risk assessments – i.e., U.S. EPA/OPP(1998a,b, 2003a, 2006a,b,c, 2007c,d,e,f).</p>			
Mice, SPF ICR, 6-weeks-old at start, ≈30 g (males), ≈23 g (females), 12/sex/group	Fluroxypyr (99.3% a.i.) Exposure period: 13 weeks Dietary dose levels: 0, 200, 500, 2500, or 1000 ppm Test material intake: Males: 26.7, 67.7, 330, or 1347 mg/kg/day Females: 32.5, 81.7, 418, or 1748 mg/kg/day	No significant adverse effects in treated mice. NOEL = 1000 ppm (HDT) (1342 mg/kg/day –males) (1748 mg/kg/day – females) LOEL not established.	Shirasu et al. 1988 MRID 42137337 Acceptable

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
Rats, Wistar, weanling, 10/sex/dose group	Dowco 433 acid (98.3 – 99.5% a.i.) <u>Intended dietary intake levels:</u> 80, 750, 1000, or 1500 mg/kg bw/day for 90 days <u>Mean dietary intake levels:</u> 79, 721, 924, or 1215 mg/kg bw/day (males) and 81, 755, 969, or 1392 mg/kg bw/day (females)	Bad health condition, mortality, growth depression and decreased food consumption and efficiency at 1000 and 1500 mg/kg bw/day (males and females) and at 750 mg/kg bw/day (males); Decreased prothrombin time at 1500 mg/kg bw/day (males) and increased thrombocyte counts at 1000 and 1500 mg/kg bw/day (females).	Jonker et al. 1987 MRID 42164502
<p>Jonker et al. 1987 (continued): Decreased plasma total protein concentration at ≥ 1000 mg/kg bw/day (females) and at ≥ 750 mg/kg bw/day (males) and decreased albumin concentration at 1500 mg/kg bw/day (females);</p> <p>Increased alkaline phosphatase activity in plasma at 750 mg/kg bw/day (males) and at 1500 mg/kg bw/day (females), and plasma activity of GPT and GOT were increased at 1500 mg/kg bw/day (females) with no histopathological evidence of liver damage;</p> <p>Severe histopathological renal lesions at 1500 mg/kg bw/day (females) and at ≥ 750 mg/kg bw/day (males), with characteristic lesions identified as papillary necrosis, nephrocalcinosis and medullary mineralization, tubular dilatation, cortical tubular regeneration, and epithelial abnormalities of the pelvis and pelvic collecting ducts. Condition was accompanied by increased absolute and relative kidney weights at 1500 mg/kg bw/day (females), increased volume and decreased density of the urine at 1500 mg/kg bw/day (males and females) and decreased urinary pH at ≥ 750 mg/kg bw/day (females).</p> <p>Adrenal lesions: hypertrophy and vacuolation of the zona glomerulosa cells at ≥ 1000 mg/kg bw/day (males and females). Pathological changes in thymus, testes, prostate and seminal vesicles in rats with severe kidney damage.</p> <p>Most of the changes disappeared at the end of the 12-week recovery period. Kidney lesions, however, often progressed to (chronic) interstitial nephritis. In male rats in the high-dose group (1500 mg/kg bw/day), especially those with severely affected kidneys, renal function was still impaired as indicated by edema, increased plasma urea concentration and urinary volume and decreased urinary density. Renal lesions persisted until the end of the 24-week recovery period, although the incidence had decreased. Adrenal changes were also present after the 12-week recovery period (males only), but did not persist through the 24-week recovery period.</p> <p>Conclusions: Dowco 433 acid nephrotoxic, causing lethal renal changes at 1000 and 1500 mg/kg bw/day in males and females and in males at 750 mg/kg bw/day;</p> <p>Males rats were more sensitive than female rats to the toxicity of Dowco 433;</p> <p>NOEC = 80 mg/kg bw/day when fed to rats for 13 weeks.</p>			

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
Rats, Fischer 344, ≈137 g (males), ≈100 g (females), 10/sex/group	Dowco 433 (fluroxypyr acid), 98.9% a.i. Exposure period: 13 weeks with 4-week recovery period on basal diet in control and highest-dose group. Target doses: 0, 320, 700, or 1000 mg/kg/day	<p>No mortality and no effects on ophthalmoscopy, urinalysis, gross or microscopic examinations in either sex of treated rats. No effects on food consumption.</p> <p><u>Body-weight gain</u>: slight decrease observed in both sexes at the high-dose level.</p> <p><u>Kidneys</u>: slight increases in kidney weights were observed in both sexes at terminal sacrifice; however, there were no macroscopic or microscopic lesions.</p> <p><u>Other organ weight differences at the limit dose</u>: decreased brain weight (females), increased liver weight (females), and increased kidney weight (males) following the recovery phase.</p> <p>LOEL =1000 mg/kg/day, based on decreased body weight gain in males, increased kidney weight in both sexes, and an apparent decrease in brain weight in females and testes weight in males.</p> <p>NOEL = 700 mg/kg/day</p>	Grandjean et al. 1992 MRID 44080316 Acceptable

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
Rats, Wistar, 3.5-weeks-old upon arrival, 35-50 g, 10/sex/dose group	<p>Dowco 433 acid (fluroxypyr), purity not reported.</p> <p>Exposure period: 90 days</p> <p>Target doses: 0, 20, 100, or 500 mg/kg/day in diet.</p> <p><u>Mean compound intake:</u></p> <p>Males: 0, 20.8 ± 1.2, 102.0 ± 8.1, 511.0 ± 27.5 mg/kg/day</p> <p>Females: 21.2 ± 1.4, 105.2 ± 7.0, 538.7 ± 44.8 mg/kg/day</p>	<p>No overt signs of toxicity or treatment-related effects on mortality, body weight, food consumption, hematology, urinalyses, or gross pathology.</p> <p>SGPT and alkaline phosphatase levels were increased in mid- and high-dose males; SGOT levels were increased in males in all dose groups. Absolute and relative thyroid and relative adrenal weights were decreased in mid- and high-dose females (no correlating histological changes observed).</p> <p><u>DER reviewer indicates:</u> <i>A histologic reexamination of kidney tissues by the testing laboratory revealed an increased incidence of minimum to slight tubular changes in high-dose males and females. Since the kidneys were not examined histologically in low- and mid-dose males and females, the LOEL and NOEL for this study cannot be established.</i></p>	<p>Til et al. 1980 MRID 40244505 Supplemental</p> <p><i>Kidneys not examined histologically.</i></p>
Rats, Fischer 344, males and females, 4-weeks-old upon arrival, 10/sex/dose level	<p>AGR 248743 (fluroxypyr MHE) 99.1% a.i.)</p> <p><u>Nominal doses levels:</u> 0, 100, 250, 500, or 1000 mg/kg/bw for 13 weeks.</p> <p><u>Acid equivalent dose levels:</u> 0, 69, 174, 347, or 694 mg fluroxypyr/kg bw.</p>	<p>NOEC = 1000 mg/kg/day (HDT)</p> <p>No adverse treatment-related effects on body weights, clinical chemistry, hematology, urinalysis, organ weights, or gross and histopathological evaluations.</p>	<p>Cosse et al. 1991b MRID 42137336</p>

Appendix 2: Toxicity to experimental mammals (*continued*)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
Dogs, Beagle (NOS), 2/sex/dose group	Dowco 433 (NOS) Dietary dose levels: 0, 20, 50, 150, or 500 mg/kg/day for 4 weeks (range-finding study).	<p>NOEC = 50 mg/kg/day</p> <p>At high dose level, within the first 2 weeks food consumption was reduced from 500 mg/kg/day to 342 and 376 (males) and to 265 and 318 (females). Consequently, test substance was administered by capsule in week 3. Dogs were sacrificed on days 16 and 17 due to severe body weight reduction, ataxia, and weakness of the hind legs. Clinical lab results indicated marked treatment-related high levels of BUN, creatinine, and glucose, and slightly increased levels of uric acid in females, and decreased potassium levels in both sexes, and decreased serum calcium in females and one male. At post-mortem, exams revealed increased kidney weights and moderate acute tubular nephrosis and slight to moderate superacute gastroenteritis in all dogs. Hematology parameters were slightly altered, but there were no significant treatment-related effects observed in urinalysis.</p> <p>Gross treatment-related lesions were not observed in any of the other treatment groups, compared with controls. Kidney lesions were limited to the proximal tubules, and early tubular regeneration was observed.</p> <p>At 150 mg/kg/day, histopathological observations included early signs of superacute tubular nephrosis).</p>	Ehard et al. 1983 MRID 42137340

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
ORAL – CHRONIC			
Dogs, Beagle, 7- to 8-months-old, 13.9 kg (males), 12.9 kg (females), 4/sex/dose group	Dowco 433 (Fluroxypyr acide), 98% a.i. Exposure period: 12 months Dosage: 0, 20, 50, or 150 mg/kg/day	No signs of toxicity under the conditions of the experiment. Effects levels could not be established; dogs could have tolerated a higher dose. NOAEL = 150 mg/kg/day (HDT) LOAEL not established.	Kinkel et al. 1984 MRID 40244507 Acceptable
<p>Kinkel et al. 1984 (MRID 40244507) continued: U.S. EPA/OPP 2003a (HHRA) cites the date as 1988, which is the year that the DER was prepared and approved. The study itself seems to have been done in 1984.</p>			
Mice, CD-1, 5-weeks-old, 18-20 g on day of receipt, 50 males and 50 females/dose group	Dowco 433 acid (fluroxypyr, 98% or 99.4% a.i., depending on batch) <u>Dosage:</u> 0, 20, 80, or 320 mg/kg/day in the diet for 78 weeks. <u>Mean compound intake:</u> Males: 19.3 ± 1.4, 78.5 ± 5.0, or 312.7 ± 16.5 mg/kg/day, which represents 97, 98, or 98% of nominal dose. Females: 20.0 ± 2.0, 79.9 ± 7.9, or 316.5 ± 31.2 mg/kg/day, which represents 100, 100, or 99% of nominal dose.	Maximum tolerated dose was not achieved. No adverse effects of dosing on clinical signs, survival, body weights, food consumption, hematology, clinical chemistry, or urinary parameters. Organ weights in treated groups did not differ from control group at 39 weeks. No toxicologically significant gross or histopathological findings in treated mice, and no increases in neoplastic lesions at any site. Doses ≤ 320 mg/kg/day Dowco 433 fed in the diet to male and female CD-1mice for 78 weeks were not carcinogenic. NOAEL based on food consumption: 312.7 mg/kg bw/day (males) and 316.5 mg/kg bw/day (females)	Perry et al. 1985 MRID 40244508 Core Supplemental <i>Dosing was not adequate, and histological examinations of gross lesions, lung, liver, and kidney were not performed in the mid- and low-dose groups. Furthermore, organ weights were not recorded at study termination and dietary analysis data were not provided.</i>

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
<p>Mice, CD-1, ≈5-wks-old at start, ≈28 g (males), ≈23 g (females) at start, 60/sex/group</p>	<p>Fluroxypyr (98.9% a.i.) Exposure Period: 18 months Target dietary dose levels: 0, 100, 300, or 1000 mg/kg/day Measured concentration range: 88-102% Average concentration range: 93-98% of targeted concentrations</p>	<p>No evidence of carcinogenicity.</p> <p>No adverse effects on survival or clinical signs of toxicity in either sex. No adverse effects on food consumption or any of the monitored hematology ophthalmoscopy parameters in either sex.</p> <p>Body weight was slightly decreased among high-dose males and there was an overall decrease in body weight gains in both sexes in the high-dose group. The effect was not statistically significant.</p> <p>A slight increase in the incidence of distended gall bladder was observed (macroscopically and microscopically) in both sexes in the high-dose group. The number of male or female mice with a unilateral decrease in kidney size was slightly increased in the high-dose group. Also, there was a significant increase in the incidence of renal papillary necrosis and regenerative nephrosis (severe grade only) in the high-dose females.</p> <p>LOEL = 1000 mg/kg/day, based on decreased body weight/gain in males and an increased incidence of kidney lesion in females.</p> <p>NOEL = 300 mg/kg/day.</p>	<p>Cosse et al. 1993 MRID 44080317 Acceptable</p>

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
Rats, Wistar, 21- to 24-days-old, 35-50 g, 50/sex/dose group	<p>Dowco 433 acid (fluroxypyr) 98.1-99.5% a.i.</p> <p>Target dietary dose levels: 0, 20, 80, or 320 mg/kg/day for 106 weeks.</p>	<p>No treatment-related effects on survival, mean body weight, food consumption, or food efficiency. No effects on hematology or clinical chemistry parameters.</p> <p>Water consumption increased in females in the 320 mg/kg/day group at 104 weeks, which resulted in increased urinary volume and decreased density (considered of questionable toxicological significance).</p> <p>No increases in neoplastic or hyper-plastic and pre-neoplastic lesions in any dose group.</p> <p>At 1-year sacrifice, there was an increased incidence of very slight bile duct sclerosis in males in the 320 mg/kg/day group (4/10) compared with controls (0/10). This is marginally significant [p=0.0433] using Fisher Exact test.</p> <p>Neither chronic nor systemic toxicity could be evaluated because non-neoplastic lesions, other than pre-neoplastic, were not evaluated.</p>	<p>Til et al. 1985 MRID 40244506 Invalid/Supplemental</p> <p><i>The study is Core invalid for chronic toxicity because of the limited histopathological evaluation. Study is supplementary for oncogenicity since a maximum tolerated dose was not achieved, and because several tissues could not be properly evaluated because of autolysis.</i></p>

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
<p>Rats, Fischer 344, ≈5-wks-old at purchase, ≈161-165 g (males), ≈107 g (females) at start, 50/sex/dose group for 24 months, 10/sex/dose for 12 months</p>	<p>Fluroxypyr (99.0% a.i.) <u>Target dietary dose levels:</u> 0, 100, 500 or 1000 mg/kg/day for 24 months. (Note: due to increase in mortality in both sexes at the high dose [6 deaths among male rats prior to day 112], the 1000 mg/kg/day dose level was terminated on day 118 for males only.)</p> <p><u>Measured concentrations</u> ranged from 88-102% and averaged from 93-98% of the targeted concentrations.</p>	<p>Kidney found to be the major target organ in both sexes.</p> <p>Male rats appeared to be more sensitive than female rats to treatment. During the first 13 weeks of treatment, males in the high-dose group exhibited erratic body weight gains, effects on clinical chemistry indicative of impaired renal function, increased mortality (6 deaths prior to day 112), and the appearance of thinness; this group was terminated on day 118.</p> <p>Female rats in the high-dose group had a mortality rate of 42%; 48% of the deaths were attributed to renal failure.</p> <p>Body weight gain: decreased to 79% of controls among males in the high-dose group during the first 90-day interval; overall body weight gain decreased to 69% of controls among females in the high-dose group.</p> <p>Food consumption was not adversely affected by treatment; furthermore, there were no adverse effects on hematology, clinical chemistry, or urinalysis.</p> <p>Kidney weight was increased among males in the 500 mg/kg/day group, and in females at all three dose levels; however, the increase in the low-dose group was within that of historical controls.</p> <p>Gross and microscopic lesions characteristic of renal toxicity (i.e., decreased size, papillary necrosis, and roughened surface) were observed in high-dose males sacrificed at day 118.</p>	<p>Quast and McGuirk 1995 MRID 44080322 Acceptable</p> <p>This is the basis of the U.S. EPA/OPP (2007f) chronic RfD.</p>

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
<p>Quast and McGuirk (continued): At study termination, chronic progressive glomerulonephropathy (CPG) of a severe or very severe degree was slightly increased in males in the 500 mg/kg/day group, compared with low-dose males and controls; in females, the severity of renal CPG was increased in the mid- and high-dose groups, compared with low-dose females and controls.</p> <p>Other changes including decreased body fat and erosion/ulcers of the glandular mucosa were considered secondary effects due to nutritional state of the rat.</p> <p>Histological changes included hyperplasia of the pelvic epithelium, papillary necrosis, and tubular nephrosis in males in the 500 mg/kg/day group and females in the 1000 mg/kg/day group.</p> <p>No apparent treatment-related increase in tumor types in either sex.</p> <p>LOEL = 500 mg/kg/day based on increased kidney weight in both sexes, increased incidence of atrophy, adipose tissue (mesenteric tissues) in males, and increased severity renal CPG in both sexes.</p> <p>NOEL = 100 mg/kg/day.</p>			
<p>DERMAL – ACUTE (toxicity, irritation, and sensitization)</p>			
<p>Guinea Pig, Hartley Albino, 10 males, weight not specified</p>	<p>XRM-5316 (25.6% fluroxypyr MHE) Dermal Sensitization Induction Phase Dermal application of 0.4 mL (10% dilution) applied to shaved, intact skin of left side of each guinea pig and covered with a gauze patch. Challenge Phase 2 weeks after the induction phase, similar approach was taken : 0.4mL of 1% test material or 5% positive control were applied to the right side (clipped free of hair) of each guinea pig) for a 6-hour exposure period. Application sites were graded for sensitization 24 and 48 hours after the challenge application.</p>	<p>XRM-5316 was not a dermal sensitizer under the conditions of the study.</p> <p>Edema was not observed in any of the guinea pigs in either group during the induction and challenges phases of the experiment. All of the positive control guinea pigs displayed a positive response, as expected.</p> <p>NOTE: Concentration of the test material was decreased from 10% to 5% due to erythema observed at the application site of two guinea pigs after the first induction application and again reduced from 5% to 1% due to erythema observed in one guinea pig after the second induction application. The concentration of the positive control was decreased from 10% to 7.5% due to erythema observed in one guinea pig after the second induction application</p>	<p>Cosse and Berdasco 1992 MRID 44080334 Acceptable</p>

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
Rabbits, New Zealand White, 5 male and 1 female, 2.5-2.9 kg bw	<p>XRM-5316 (25.6% fluroxypyr MHE) Dermal Irritation Dosing: 0.5 mL aliquot for 4 hours to 6.25 cm² on backs/flanks.</p> <p>Post treatment observations for dermal irritation took place at 15 and 30 minutes, 4, 24, 48, and 72 hours.</p> <p>Irritation scored via Draize method (though not identified as such).</p>	<p>XRM found to be a slight dermal irritant; all observations of erythema and edema resolved within 48 hours.</p> <p>Primary irritation index: 0.75</p> <p>Toxicity Category IV</p>	<p>Cosse et al. 1992d MRID 44080333 Acceptable</p>
Rabbits, New Zealand, 2.3-3.1 kg, 5/sex/group	<p>XRM-5316 (25.6% fluroxypyr MHE)</p> <p>Dermal dose: 2000 mg XRM/kg body weight applied to shaved back; test material held in contact with skin by gauze dressing and non-irritating tape.</p> <p>24-hour exposure period, after which the skin was washed with mild soap and water.</p> <p>2-week observation period; body weights recorded on Days 1, 2, 8, and 15.</p>	<p>LD₅₀ >2000 mg/kg for each sex.</p> <p>No mortality; clinical signs observed at application site included burn, edema, erythema, and scaling in all rabbits of each gender.</p> <p>Toxicity Category III</p>	<p>Cosse et al. 1992b MRID 44080330 Acceptable</p>
DERMAL – SUBCHRONIC			
Rabbits, New Zealand white, ≈5-months-old, ≈3800 g (males), ≈3850 g (females) at start, 5/sex/group	<p>Fluroxypyr MHE (99.1% a.i.) Duration: 6 hours/day for 21 days Dosing: 0, 100, 300, or 1000 mg/kg</p>	<p>No signs of dermal or systemic toxicity.</p> <p>NOEL = 1000 mg/kg/day (HDT)</p>	<p>Cosse et al. 1991a MRID 42137338 Core Minimum</p>

Appendix 2: Toxicity to experimental mammals (continued)

Animal, number, initial body weight or age	Dose/Exposure	Response	Reference, MRID No., U.S. EPA-HED Classification
EYES			
Rabbits, New Zealand White, 2 male and 4 female, 2.1-2.4 kg bw, age not provided	XRM-5316 (25.6% fluroxypyr MHE) Dosing: 0.1 mL aliquot WRM-5315 instilled into conjunctival sac of right eye. Observation period: 21 days Penlight examination at 1, 24, 48, and 72 hours, and 7, 14, and 21 days.	Ocular irritation observed in all rabbits at 1 hour after dosing. Reddening of the iris observed in only one male at 1 hour after dosing; corneal opacity(grade 1) observed in all rabbits at 1, 24, 48, and 72 hours; however, only one female displayed this lesion at day 7. By day 21 after dosing, all signs of ocular irritation had subsided. Toxicity Category II	Cosse et al. 1992c MRID 44080332 Acceptable
INHALATION			
Rats, Fischer 344, 5/sex, 10-weeks-old at start, 195-224 g (males), 141-155 g (females)	XRM-5316 (Fluroxypyr MHE) (25.6% a.i.) Single, nose-only exposure to the limit dose (5 mg/L) for 4 hours	No adverse effects observed. LC ₅₀ >6.2 mg/L aerosolized XRM-5316 Toxicity Category IV for acute inhalation.	Beekman and Yano 1993 MRID 44080331 Acceptable

Appendix 3: Toxicity to birds

Animal	Dose	Response	Reference, EFED Classification
Acute, Gavage			
Northern Bobwhite Quail (<i>Colinus virginianus</i>), >16-wks-old, 5/sex/group	Fluroxypyr acid (98.8% a.i.) Corn oil vehicle	LD ₅₀ >2000 mg a.i./kg One mortality at 2000 mg/kg within 24 hours of dosing and one mortality in control group 7 days after dosing. No signs of toxicity during 14-day observation period; no treatment-related effects on body weight or food consumption. Toxicity category: practically nontoxic	U.S. EPA 1998b MRID 40244515 Supplemental <i>Only three concentrations were tested; five test concentrations are required.</i> Roberts and Phillips 1984 (Cited in Mayes 1996)
Northern Bobwhite Quail (<i>Colinus virginianus</i>)	Fluroxypyr MHE (a.i. not reported)	LD ₅₀ >2000 mg a.i./kg Toxicity category: practically nontoxic	U.S. EPA 1998b 40244546 Core
Mallard Duck (<i>Anas platyrhynchos</i>), >16-wks-old, 5/sex/group	Fluroxypyr acid (Dowco 433 acid): 0, 500, 1000, or 2000 mg/kg bw gavage. Group designations follow the order of doses with controls designated as Group 1. Corn oil vehicle	No mortality attributed to treatment; no dose-related effects on bodyweights, which were considered to be within normal limits; and no dose-related effects on food consumption, which was variable. <i>Upon post-mortem examination, some birds had enlarged and discolored livers</i> (Mayes 1996). Full study indicates that <i>a number of birds in Groups 2, (4/10), 3 (3/10), and 4 (2/4) were found to have enlarged livers which were orange-yellow in color and hard to the touch. In two birds in Group 3 the body cavity was found to be filled with clear fluid.</i> Toxicity category: practically nontoxic	Roberts and Phillips 1984a MRID 40244514 Core (Cited in Mayes 1996; U.S. EPA 1998b)

Appendix 3: Toxicity to birds (*continued*)

Animal	Dose	Response	Reference, EFED Classification
Mallard Duck (<i>Anas platyrhynchos</i>)	Fluroxypyr MHE (98.6% a.i.)	LD ₅₀ >2000 mg a.i./kg Toxicity category: practically nontoxic	U.S. EPA 1998b MRID 40244516 Core
Acute, Dietary			
Northern Bobwhite Quail (<i>Colinus virginianus</i>), 12-days-old at test initiation, 10/dose group. 30 in control group.	Fluroxypyr acid (Dowco 433 acid): <u>Dietary concentrations:</u> Nominal: 0, 658, 988, 1481, 2222, 3333 or 5000 mg/kg of diet for 5 days followed by basal diet only for 5 days followed by a 5-day post-treatment period. <i>Notes from full study:</i> Average body weights: about 24 g/bird. [Study Table 1] Average food consumption: about 8 g/bird [Study Table 2, highly variable] Food consumption factor: about 0.3.	Mortality: 1/10 at concentrations of 658 ppm, 2222 ppm, and 3333 ppm. No mortality in controls or in the 988 ppm, 1481 ppm, and 5000 ppm dose groups. Mortality was not dose-related and none of the control to dose group mortalities are statistically significant. No treatment-related effects were observed on food consumption or body weight. LD ₅₀ >5000 mg a.i./kg No changes in gross tissue examination. Toxicity category: practically nontoxic	Roberts and Phillips 1983c MRID 40244547 Core (Cited in Mayes 1996; U.S. EPA 1998b) Dow AgroSciences provided a full copy of the study.
Northern Bobwhite Quail (<i>Colinus virginianus</i>), 11-days-old at test initiation, 10 birds/dose group	Fluroxypyr MHE (Dowco 433 ester): Dietary levels of 658, 988, 1481, 2222, 3333, or 5000 ppm for 5 days with a 5-day post-treatment period. <i>Notes from full study:</i> Average body weights: about 20 g/bird. [Study Table 2] Average food consumption: about 3 g/bird [Study Table 2, highly variable] Food consumption factor: about 0.15.	One mortality occurred at doses of 988, 1481, and 2222 ppm, and two mortalities occurred at 3333 ppm; No mortality at 5000 ppm. No dose-related effects on general bird health, bodyweight, or food consumption; and no abnormalities were found at post-mortem examination. Toxicity category: practically nontoxic	Roberts and Phillips 1983b MRID 40244517 Core (Cited in U.S. EPA 1998b) Dow AgroSciences provided a full copy of the study.

Appendix 3: Toxicity to birds (*continued*)

Animal	Dose	Response	Reference, EFED Classification
Mallard Duck (<i>Anas platyrhynchos</i>), approximately 10-days-old at start, 10 ducklings/treatment group	Fluroxypyr acid (98.3% a.i.) in the diet for 5 days and observed for 3 days following exposure. <u>Dietary concentrations:</u> Nominal: 0, 562, 1000, 1780, 3160, or 5620 ppm a.i. (i.e., mg test substance/kg of diet) for 5 days followed by basal diet only for 3 days	5-day LC ₅₀ >5620 ppm a.i. No mortality or sublethal effects observed at any dose level. NOEC = 5620 ppm Toxicity category: practically nontoxic.	Grimes et al. 1991 MRID 42137302 Core No full study.
Mallard Duck (<i>Anas platyrhynchos</i>), approximately 10-days-old at start, 10 ducklings/treatment group	Fluroxypyr 1-MHE (99.1% a.i.) in the diet for 5 days and observed for 3 days following exposure. <u>Dietary concentrations:</u> Nominal: 0, 562, 1000, 1780, 3160, or 5620 ppm a.i.	5-day LC ₅₀ >5620 ppm a.i. No mortality or sublethal effects observed at any dose level. Toxicity category: practically nontoxic.	Grimes and Jaber 1988 MRID 42137301 Core No full study.
Reproduction – Dietary			
Bobwhite Quail (<i>Colinus virginianus</i>), Approximately 15-weeks-old at start, 16 males and 16 females/dose group	Fluroxypyr 1-MHE (99.1% a.i.) in one-generation reproduction study (19-week exposure period). Test diets of fluroxypyr premix included acetone and corn oil; dietary concentrations were not adjusted to correct for purity of the test material <u>Dietary concentrations:</u> Nominal: 0, 250, 500, or 1000 ppm Mean measured: N.D. (limit of detection = 5 mg/kg), 232.2, 463.3, or 909.3 ppm	NOEC = 1000 ppm a.i. (highest concentration tested). LOEC not determined LOEC endpoints: none No treatment-related mortality, overt signs of toxicity, or effects on adult body weight or feed consumption; no apparent treatment-related effects on reproductive parameters at any exposure concentration.	Beavers et al. 1989a MRID 42137303 Core

Appendix 3: Toxicity to birds (*continued*)

Animal	Dose	Response	Reference, EFED Classification
<p>Mallard Duck (<i>Anas platyrhynchos</i>), approximately 19-weeks-old at start, 16 males and 16 females/dose group</p>	<p>Fluroxypyr 1-MHE (99.1% a.i.) in diet for 18 weeks; test diets of fluroxypyr premix included acetone and corn oil; dietary concentrations were not adjusted to correct for purity of the test material.</p> <p><u>Dietary concentrations:</u> Nominal: 0, 250, 500, or 1000 ppm</p> <p>Mean measured: N.D. (limit of detection = 5 mg/kg), 232.2, 463.3, or 909.3 ppm</p>	<p>NOEC = 250 ppm a.i. (U.S. EPA/OPP 1998b)</p> <p>LOEC = 500 ppm a.i. (U.S. EPA/OPP 1998b)</p> <p>LOEC endpoint: reduced egg production (U.S. EPA/OPP 1998b).</p> <p>No treatment-related mortality in any of the treatment groups; one incidental mortality occurred in both the control group and the 250 ppm treatment group; no overt signs of toxicity observed at any concentration tested.</p> <p>Gross necropsy revealed an increased incidence of egg yolk peritonitis among hens in the 1000 ppm treatment group; there were no other treatment-related findings.</p> <p>No treatment-related effects on adult body weight or feed consumption were observed; a slight statistically significant ($p < 0.05$) increase in feed consumption among the 1000 treatment group during week 2 of exposure was considered incidental to treatment.</p> <p>There was an apparent reduction in egg production at 500 ppm and a reduction in egg production and hatchability at 1000 ppm, but none of the effects were statistically significant.</p>	<p>Beavers et al. 1989b MRID 42137304 Core</p>

Appendix 4: Toxicity to Terrestrial Invertebrates

Animal	Dose/Exposure	Response	Reference, EFED Classification ¹
Honey Bee – Contact Bioassay			
Honeybee (<i>Apis mellifera</i>)	Fluroxypyr 1-MHE technical (97% a.i.).	LD ₅₀ not determined Toxicity category: not determined	U.S. EPA/OPP 1998b MRID 40244527 Supplemental
Honeybee (<i>Apis mellifera</i>), 1- to 5-days-old at start, mean individual weight = 0.1 g, 2 replicates of 50 bees each/treatment and control groups	Fluroxypyr acid (technical grade) (98.3% a.i.) <u>Doses:</u> 0, solvent control (2µL acetone/bee), 1.6, 3.1, 6.3, 12.5, or 25 µg a.i./bee (doses corrected for purity of test substance)	48-hour LD ₅₀ >25 µg a.i./bee Toxicity category: relatively nontoxic. Mortality in the negative and solvent control groups was 8 and 18%, respectively; furthermore, some of the bees in both control groups appeared to be immobile on Day 0. Mortality in the treatment groups ranged between 6 and 17%, but the pattern did not appear to be dose-dependent and was not considered to be treatment-related.	Lynn and Hoxter 1991a MRID 42137314 Core
Honeybee (<i>Apis mellifera</i>), 1- to 5-days-old at start, mean individual weight = 0.1 g, 2 replicates of 50 bees each/treatment and control groups	Fluroxypyr 1-MHE technical (98.5% a.i.). <u>Doses:</u> 0, solvent control (2µL acetone/bee), 1.6, 3.1, 6.3, 12.5, or 25 µg a.i./bee (doses corrected for purity of test substance)	48-hour LD ₅₀ >25 µg a.i./bee Toxicity category: relatively nontoxic. Mortality in the negative and solvent control groups was 8 and 18%, respectively; furthermore, some of the bees in both control groups appeared to be immobile on Day 0. Mortality in the treatment groups ranged between 1 and 7%, but the pattern did not appear to be dose-dependent and was not considered to be treatment-related.	Lynn and Hoxter 1991b MRID 42137313 Core

Appendix 4: Toxicity to Terrestrial Invertebrates (*continued*)

OTHER INVERTEBRATES			
<p>Potato bug (<i>Calocoris norvegicus</i>), 135 nymphs. Body weights not specified</p>	<p>Fluroxypyr (Starane-2), 0.5 µg a.i./insect for 12, 24, or 48 hours. Applied in aqueous solution by pipette.</p>	<p>12-hour mortality was not significant at $3.7\% \pm 1.6\%$, compared with mortality of $0.7\% \pm 0.7\%$ in controls (water)</p> <p>24-hour mortality was significant ($P < 0.001$) at $14.1\% \pm 3.0\%$, compared with mortality of $1.3\% \pm 0.9\%$ in controls (water)</p> <p>No significant differences in mortality rates were observed between 24 and 48 hours.</p>	<p>Moreby 1991</p>

Appendix 5: Toxicity to Terrestrial Plants

Plant	Response	Reference
Tomato plants (<i>Lycopersicon esculentum</i>), 4-weeks old, shoot dry weights ≈0.5 g, 10 plants/chamber, 5 chambers	<p>Exposure to Starane 2 vapor at concentrations of 0.0, 0.37, 1.1, 2.8, or 5.5 pg/L for 48 hours.</p> <p><u>Effects:</u> signs of phytotoxicity observed on all treated plants 4 weeks after exposure. Shoot dry weight of significantly decreased only at the 5.5 pg/L concentration; however, dry matter content was significantly decreased at exposure concentrations ≥2.8 pg/L, and plant height was increased by exposure (i.e., tallest plants in the 2.8 pg/L group).</p>	Breeze 1988
<p>Leafy spurge (<i>Euphorbia esula</i>), one stem/pot, grown for 30, 60, or 80 days to provide vegetative, flowering, and post flowering growth stages</p> <p><i>This is an efficacy study concerning the absorption and translocation of fluroxypyr.</i></p>	<p><u>Treatment:</u> Entire plant treated with 0.56 kg/ha fluroxypyr-MHE; <i>target leaf</i> (initially under protective envelope) treated subsequently with ¹⁴C-fluroxypyr and enough commercial formulation to obtain final concentration of 0.56 kg/ha.</p> <p><u>Results:</u> Adsorption of ¹⁴C-fluroxypyr: 39% in vegetative plants 25% in flowering or post flowering plants 2% in roots, regardless of growth stage.</p> <p>Exposure to high relative humidity (>90%) for ≥ 6 hours increased ¹⁴C-fluroxypyr absorption and translocation, compared with exposure to low humidity (<30%); absorption and translocation were independent of temperature (18 or 24°C).</p> <p>Note: Investigator concludes from results of study that fluroxypyr would likely be used in a leafy spurge control program only during environmental conditions adverse to control with picloram, such as unseasonably warm or cold temperatures or in areas with a high water table.</p>	Lym 1992
<p>Tier 2 Seedling Emergence and Vegetative Vigor Assays of Fluroxypyr-MHE (26.9% purity). Assays conducted at doses ranging from 0.55 grams a.i./ha to 280 grams a.i./ha (0.0005 – 0.25 lb a.i./acre). Maximum labeled rate: 280 grams a.i./ha (0.25 lb a.i./acre). Toxicity values in the DER are expressed in grams a.i./ha. Toxicity values in U.S. EPA/OPP 1998b are expressed in lb a.i./acre. The values below are expressed in the same units as those in the DER. Necessary conversions are discussed in the body of this Forest Service risk assessment.</p>		<p>Schwab 1996 MRID 44080335 Core</p> <p>Summarized from U.S. EPA/OPP 1998b</p>
<p>Dicots: Vegetative Vigor</p>		
Cotton	<p>Phytotoxicity (most sensitive parameter): EC₂₅ = 2.2 grams a.i./ha NOEL = 1.1 grams a.i./ha</p>	

Appendix 5: Toxicity to Terrestrial Plants (*continued*)

Plant	Response	Reference
Cucumber	Phytotoxicity (most sensitive parameter): EC ₂₅ = 12.8 grams a.i./ha NOEL = 4.4 grams a.i./ha	
Radish	Phytotoxicity (most sensitive parameter): EC ₂₅ = 75 grams a.i./ha NOEL = 35 grams a.i./ha	
Soybean	Phytotoxicity (most sensitive parameter): EC ₂₅ = 13.1 grams a.i./ha NOEL = 4.4 grams a.i./ha	
Sunflower	Phytotoxicity (most sensitive parameter): EC ₂₅ = 3.7 grams a.i./ha NOEL = 1.1 grams a.i./ha	
Tomato	Phytotoxicity (most sensitive parameter): EC ₂₅ = 3.8 grams a.i./ha NOEL = 2.2 grams a.i./ha Note: U.S. EPA/OPP 1998b indicates that the most sensitive parameter is “Shoot fresh weight”	
Monocots: Vegetative Vigor		
Corn	Phytotoxicity (most sensitive parameter): EC ₂₅ = 205 grams a.i./ha NOEL = 35 grams a.i./ha	
Onion	Phytotoxicity (most sensitive parameter): EC ₂₅ = 248 grams a.i./ha NOEL = 35 grams a.i./ha	
Ryegrass	Phytotoxicity (most sensitive parameter): EC ₂₅ = >280 grams a.i./ha NOEL = 280 grams a.i./ha	
Wheat	Phytotoxicity (most sensitive parameter): EC ₂₅ = 112 grams a.i./ha NOEL = 70 grams a.i./ha	
Schwab 1996 (continued): According to DER, <i>in the vegetative vigor tests, symptoms of toxicity were mainly manifest as stunting, lodging, leaf wrinkle/rolling, epinasty, and wilting.</i>		
Tier 2 Seedling Emergence Assays of Fluroxypyr-MHE (26.9% purity). Assays conducted at doses ranging from 0.55 grams a.i./ha to 280 grams a.i./ha (0.0005 – 0.25 lb a.i./acre). Maximum labeled rate: 280 grams a.i./ha (0.25 lb a.i./acre).		U.S. EPA/OPP 1998b MRID 44080335 Core
Dicots: Seedling Emergence		
Cotton	Phytotoxicity (most sensitive parameter): EC ₂₅ = 0.125 lb a.i./acre NOEC = 0.062 lb a.i./acre	

Appendix 5: Toxicity to Terrestrial Plants (*continued*)

Plant	Response	Reference
Cucumber	Phytotoxicity (most sensitive parameter): EC ₂₅ = 0.075 lb a.i./acre NOEC = 0.031 lb a.i./acre	
Radish	All test parameters similarly sensitive EC ₂₅ >0.25 lb a.i./acre NOEC = 0.25 lb a.i./acre	
Soybean	Phytotoxicity (most sensitive parameter): EC ₂₅ = 0.24 lb a.i./acre NOEC = 0.062 lb a.i./acre	
Sunflower	Phytotoxicity (most sensitive parameter): EC ₂₅ = 0.109 lb a.i./acre NOEC = 0.062 lb a.i./acre	
Tomato	Shoot fresh weight (most sensitive parameter): EC ₂₅ = 0.142 lb a.i./acre NOEC = 0.124 lb a.i./acre	
Monocots: Seedling Emergence		
Corn	All test parameters similarly sensitive EC ₂₅ >0.25 lb a.i./acre NOEC = 0.25 lb a.i./acre	
Onion	All test parameters similarly sensitive EC ₂₅ >0.25 lb a.i./acre NOEC = 0.25 lb a.i./acre	
Ryegrass	Phytotoxicity (most sensitive parameter): EC ₂₅ >0.25 lb a.i./acre NOEC = 0.124 lb a.i./acre	
Wheat	All test parameters similarly sensitive EC ₂₅ >0.25 lb a.i./acre NOEC = 0.25 lb a.i./acre	
Phytotoxicity of Fluroxypyr Acid –Tier II Seedling Emergence Tests		U.S. EPA/OPP 1998b MRID 44094902 Supplemental
Dicots:		
Cotton	Fresh weight (most sensitive parameter) EC ₂₅ = 0.025 lb a.i./acre	
Radish	Fresh weight (most sensitive parameter) EC ₂₅ = 0.295 lb a.i./acre	
Soybean	Fresh weight (most sensitive parameter) EC ₂₅ = 0.072 lb a.i./acre	
Sunflower	Plant height (most sensitive parameter) EC ₂₅ = 0.036 lb a.i./acre	
Monocots:		

Appendix 5: Toxicity to Terrestrial Plants (*continued*)

Plant	Response	Reference
Corn	Fresh weight (most sensitive parameter) EC ₂₅ = 0.178 lb a.i./acre	
Wheat	Fresh weight (most sensitive parameter) EC ₂₅ = 0.079 lb a.i./acre	
Metabolite Studies		
<p>Effect of Two Soil Metabolites of Fluroxypyr on the Emergence and Vegetative Vigor of Non-Target Plants (Tier I/II). Tier 1 non-target seedling emergence and vegetative vigor greenhouse studies were conducted on six dicot (cucumber, radish, soybean, sugar beet, sunflower, and tomato) and four monocot (barnyard grass, corn, onion, and wheat) species from April to May 1999 using pyridinol and methoxy pyridine formulated in a 50% acetone 50% water solution to yield an application rate of 560 g/ha. Application was made via overhead track sprayer in approximately 20 gallons/acre spray volume to plant at the 2-leaf growth stage for the vegetative vigor test, and to seeds planted within 24 hours of application in the seedling emergence test. Plants were rated for emergence, visual injury, height, and fresh weight 2 weeks after treatment. Since there were no adverse effects greater than 25% on any species in either test, Tier II testing was not required.</p> <p>Results: No treatment-related visual injury in either seedling emergence or vegetative vigor study.</p> <p>Seedling emergence: No reductions in emergence or plant height greater than 20%; pyridinol treatment caused a 28% reduction in onion fresh weight, which was related to the slightly reduced germination (19%). The effect was considered non-significant (only a 7% reduction in fresh weight) after the fresh weight/plant basis was adjusted to correct for fewer plants.</p> <p>Vegetative vigor: Treatment effects on height and weight were less than 20%.</p>		<p>McCormick 1999 MRID 448796704 (Full study from Dow)</p>

Appendix 6: Toxicity to Fish

Animal	Dose/Exposure	Response	Reference, EFED Classification ¹
FISH			
Freshwater Fish – Acute			
Coho salmon (<i>Onchorhynchus kisutch</i>), juvenile (3.5 ± 0.5 months), length = 4.1 ± 0.1 cm, weight = 0.8 ± 0.1 g, 30 fish	XRM-5084 (34.9% methylheptyl ester of fluroxypyr) under static conditions	<u>Soft water:</u> 96-hour LC ₅₀ = 17 mg formulation/L <u>Intermediate (reconstituted) water:</u> 96-hour LC ₅₀ = 10 mg formulation/L <u>Hard (lake) water:</u> 96-hour LC ₅₀ = 14 mg formulation/L	Wan et al. 1992
Chinook salmon (<i>Onchorhynchus tshawytscha</i>), juvenile, (3.5 ± 0.5 months), length = 4.1 ± 0.1 cm, weight = 0.8 ± 0.1 g, 30 fish	XRM-5084 (34.9% methylheptyl ester of fluroxypyr) under static conditions	<u>Soft water:</u> 96-hour LC ₅₀ = 13 mg formulation/L <u>Intermediate (reconstituted) water:</u> 96-hour LC ₅₀ = 9 mg formulation/L <u>Hard (lake) water:</u> 96-hour LC ₅₀ = 16 mg formulation/L	Wan et al. 1992
Chum salmon (<i>Onchorhynchus keta</i>), juvenile, (3.5 ± 0.5 months), length = 4.1 ± 0.1 cm, weight = 0.8 ± 0.1 g, 30 fish	XRM-5084 (34.9% methylheptyl ester of fluroxypyr) under static conditions	<u>Soft water:</u> 96-hour LC ₅₀ = 19 mg formulation/L <u>Intermediate (reconstituted) water:</u> 96-hour LC ₅₀ = 10 mg formulation/L <u>Hard (lake) water:</u> 96-hour LC ₅₀ = 14 mg formulation/L	Wan et al. 1992

Appendix 6: Toxicity to fish (*continued*)

Animal	Dose/Exposure	Response	Reference, EFED Classification ¹
Pink salmon (<i>Onchorhynchus gorbuscha</i>), juvenile), length = 4.1 ± 0.1 cm, weight = 0.8 ± 0.1 g, 30 fish	XRM-5084 (34.9% methylheptyl ester of fluroxypyr) under static conditions	<p><u>Soft water:</u> 96-hour LC₅₀ = 12 mg formulation/L</p> <p><u>Intermediate (reconstituted) water:</u> 96-hour LC₅₀ = 8 mg formulation/L</p> <p><u>Hard (lake) water:</u> 96-hour LC₅₀ = 11 mg formulation/L</p>	Wan et al. 1992
Sockeye salmon (<i>Onchorhynchus nerka</i>), juvenile), length = 4.1 ± 0.1 cm, weight = 0.8 ± 0.1 g, 30 fish	XRM-5084 (34.9% methylheptyl ester of fluroxypyr) under static conditions	<p><u>Soft water:</u> 96-hour LC₅₀ = 15 mg formulation/L</p> <p><u>Intermediate (reconstituted) water:</u> 96-hour LC₅₀ = 10 mg formulation/L</p> <p><u>Hard (lake) water:</u> 96-hour LC₅₀ = 13 mg formulation/L</p>	Wan et al. 1992
Rainbow trout (<i>Onchorhynchus mykiss</i>), juvenile), length = 4.1 ± 0.1 cm, weight = 0.8 ± 0.1 g, 30 fish	XRM-5084 (34.9% methylheptyl ester of fluroxypyr) under static conditions	<p><u>Soft water:</u> 96-hour LC₅₀ = 17 mg formulation/L</p> <p><u>Intermediate (reconstituted) water:</u> 96-hour LC₅₀ = 12 mg formulation/L</p> <p><u>Hard (lake) water:</u> 96-hour LC₅₀ = 17 mg formulation/L</p>	Wan et al. 1992

Appendix 6: Toxicity to fish (*continued*)

Animal	Dose/Exposure	Response	Reference, EFED Classification ¹
<p>Rainbow trout (<i>Salmo gairdneri</i>), mean weight of 1.63 g, mean length of 48.8 mm, 10 fish/concentration</p>	<p>EF689 (herbicide formulation containing 200 g/L Dowco 433 NOS)</p> <p><u>Nominal concentrations:</u> 1.8, 3.2, 5.6, 10, or 18 mg/L for 96 hours under flow-through conditions.</p>	<p>NOEC = 0.54 mg ester/L LOEC = 0.88 mg ester/L</p> <p>24 to 96-hour LC₅₀ = 3.99 mg ester /L</p> <p>General signs of toxicity included loss of equilibrium, quiescence, darkening in color, rapid respiration rates, coughing, and twitching.</p> <p>No mortality occurred at concentrations from 1.8 to 10 mg/L.</p>	<p>Hill et al. 1984 MRID 40244525</p>
<p>Note on Hill et al. 1984: A full copy of this study was provided by Dow AgroSciences for the conduct of the Forest Service risk assessment. U.S. EPA/OPP 1998b, Table 7, indicates the 96-hour LC₅₀ as 13.4 mg a.i./L and that the test substance is the acid and not the ester. The full study indicates that these values are for a formulation, EF 689 containing 200 g/L fluroxypyr (Dow 433). Dow AgroSciences (2009) indicated that the formulation is 29.7% w/w and contains the ester. The ester, however, is not described in the study. Given the uncertainties in the test material, this study is not used quantitatively in this risk assessment.</p>			
<p>Bluegill sunfish (<i>Lepomis macrochirus</i>), mean weight = 0.59 g, standard length = 3.1 (2.6-3.5) cm.</p>	<p>Fluroxypyr MHE (99.5 mole % a.i.) under static test conditions.</p>	<p>Study not scientifically sound.</p>	<p>Dill and Bartlett 1989 MRID 42137305 Invalid</p>
<p>Bluegill sunfish (<i>Lepomis macrochirus</i>), juvenile, 1-2 inches, mean weight: 0.74 g, 10/test/control group.</p>	<p>Fluroxypyr acid (98.8% a.i.) under static test conditions.</p> <p><u>Concentrations:</u> Nominal: 0, acetone control, 2.3, 3.9, 6.5, 10.8, 18.0, or 30 mg a.i./L Mean measured (mean of 0 and 96-hour values): 2.53, 4.32, 7.28, 11.9, 19.1, or 31.3 mg a.i./L</p>	<p>96-hour LC₅₀ = 14.3 mg/L (mean analyzed concentration) 95% CI = 11.9-19.1 mg/L</p> <p>NOEC = 7.28 mg/L</p> <p>Surviving fish at concentrations ≥11.9 mg/L showed signs of lethargy, loss of equilibrium and/or erratic body movements.</p> <p>Toxicity category: slightly toxic</p>	<p>Weinberg et al. 1991b MRID 42137306 Core</p> <p>Also cited in Mayes 1996</p>

Appendix 6: Toxicity to fish (*continued*)

Animal	Dose/Exposure	Response	Reference, EFED Classification ¹
Bluegill sunfish (<i>Lepomis macrochirus</i>),	<p>Fluroxypyr MHE (AGR283750) (95.8% a.i.)</p> <p><u>Target concentration:</u> 100 mg/L for 96 hours under static renewal (daily renewal) test conditions.</p>	<p>No sublethal effects or mortality during the study.</p> <p>NOEC 629 µg/L (mean measured concentration of fluroxypyr 1-MHE determined in the test solutions after filtration).</p> <p><i>The targeted 100 mg/L dose level greatly exceeded the reported water solubility of fluroxypyr 1-MHE (109 µg/L at pH 7 and 25° C) and undissolved test material was clearly evident in the test vessels.</i></p>	Rick et al. 1996a MRID 44080307
Trout, Rainbow (<i>Oncorhynchus mykiss</i>), eyed embryos, 30 exposed fish, 10 fish/replicate	<p>Fluroxypyr 1-MHE (98.5% a.i.) under static test conditions.</p> <p><u>Concentrations:</u> Nominal: 0, acetone control, or 100 mg/L</p> <p>Overall mean measured: 225 µg/L</p> <p>Reported solubility: 109 ± 5 µg/L at pH 7.</p>	<p>96-hour LC₅₀ greater than the reported water solubility; 96-hour mortality threshold concentration was also greater than the water solubility.</p> <p>Toxicity category: not determined because the test concentration up to the solubility limit caused no mortality.</p>	Weinberg et al. 1991c MRID 42137307 Core
Trout, Rainbow (<i>Salmo gairdneri</i>), ≈ 4-months-old, mean weight of 0.73 g, 10 fish/test/control group	<p>Fluroxypyr acid (a.i. not specified)</p> <p><u>Concentrations:</u> Nominal: 10, 18, 32, 56, or 100 mg/L Measured mean (lowest, middle, and highest at 96-hours): 10.5, 34.0, or 103 mg/L</p>	<p>96-hour LC₅₀ > 100 mg/L</p> <p>No treatment-related mortality or other adverse effects observed.</p>	Willis 1984a MRID 40244518 (Cited in Mayes 1996)
Golden Orfe (<i>Leuciscus idus</i>), 5/test vessel	<p>Dowco 433 acid (99% a.i.)</p> <p><u>Concentrations:</u> Nominal: 10, 18, 32, 56, or 100 mg/L for 96 hours</p>	<p>96-hour LC₅₀ > 100 mg/L</p> <p>No treatment-related mortality or other adverse effects observed</p>	Willis 1984b MRID 40244519 Supplemental

Appendix 6: Toxicity to fish (*continued*)

Animal	Dose/Exposure	Response	Reference, EFED Classification ¹
Trout, Rainbow (<i>Salmo gairdneri</i>), average weight of 0.72 g, average ; average length of 4.2 cm, 10 fish/test vessel	Dowco 433 ester (NOS) Acetone vehicle <u>Nominal concentrations:</u> 0.18, 0.32, 0.56, 1.0, or 5.0 mg/L for 96 hours under static conditions	One mortality observed at the nominal concentration of 0.32 mg/L at 96 hours; no dose-related adverse effects observed. Due to solubility problems, 0.7 mg/L is the highest concentration at which the test substance was presumed to be in solution under test conditions.	Willis 1984c MRID 40244522 Core
Golden Orfe (<i>Leuciscus idus</i>), mean wet weights of 2.03 and 2.09 g (based on sample of 10 fish removed at random from holding tank), 5 fish /test vessel	Dowco 433 ester (a.i. not specified) Acetone vehicle <u>Nominal concentrations:</u> 0.18, 0.32, 0.56, 1.0, or 5.0 mg/L for 96 hours.	No mortality; no dose-related adverse effects observed during the test. Due to solubility problems, 0.7 mg/L is the highest concentration at which the test substance was presumed to be in solution under test conditions.	Willis 1984d MRID 40244523 Supplemental
Saltwater Fish – Acute			
Silverside (<i>Menidia beryllina</i>), 40 mm, 0.39 g, 20/treatment or control group, 10/replicate vessel	Fluroxypyr acid (98.7% a.i.) <u>Concentrations:</u> Nominal: 0, 18, 30, 48, 72, or 120 ppm Mean measured: <1.0, 16, 27, 47, 69, 120 ppm Flow-through study; no solvent	96 hour EC ₅₀ (shell growth) = 40 mg a.i./L (measured) 95% CI = 27-47 ppm NOEC not determined due to treatment-related effects at all concentrations. Signs of toxicity included erratic swimming and loss of equilibrium in all treatment groups containing live fish at 72 and 96 hours after initiation. Toxicity category: slightly toxic	Boeri et al. 1994a MRID 44080309 Core

Appendix 6: Toxicity to fish (*continued*)

Animal	Dose/Exposure	Response	Reference, EFED Classification ¹
<p>Atlantic silverside (<i>Menidia menidia</i>), average length = 18.1 (14-26) mm, average weight = 0.048 (0.013-0.094) g, 20 fish/chamber, 1 chamber/treatment.</p>	<p>Fluroxypyr MHE (99.1% a.i.) under flow-through conditions with solvent (64 µL DMF/L).</p> <p><u>Concentrations:</u> Nominal: 0, solvent control, 0.10, 0.17, 0.29, 0.48, or 0.80 mg a.i./L</p> <p>Mean measured: 0.035, 0.063, 0.084, 0.142, or 0.188 mg/L</p>	<p>96 hour LC₅₀ >0.188 mg a.i./L (measured)</p> <p>No mortality observed during the test.</p> <p>Toxicity category not determined because test concentrations up to the solubility limit did not cause mortality.</p>	<p>Manning 1998a MRID 42137309 Supplemental</p>
<p>Sheepshead minnow, 25 mm, 0.24 g, 30/treatment or control group, 15/replicate vessel</p>	<p>Fluroxypyr MHE (95.8% a.i.)</p> <p><u>Concentrations:</u> Nominal: 0, solvent control, or 100 mg/L (corrected for purity)</p> <p>Mean measured: <0.025, <0.025, or 0.087 ppm</p> <p>Flow-through study with DMF solvent (0.5 mL/L maximum)</p>	<p>96 hour LC₅₀ >0.087 mg a.i./L (measured)</p> <p>Toxicity category not determined because test concentration up to the solubility level did not cause mortality.</p>	<p>Boeri et al. 1996a MRID 44080308 Core</p>

Appendix 7: Toxicity to Aquatic Invertebrates.

Animal	Dose/Exposure	Response	Reference, EFED Classification ¹
Freshwater – Acute			
<p><i>Daphnia magna</i>, juveniles, more than 6- to less than 24-hours-old, 10/test vessel</p>	<p>Dowco 433 acid (technical grade fluroxypyr acid) (99% a.i.).</p> <p><u>Nominal concentrations:</u> 10, 18, 32, 56, or 100 mg/L under static conditions for 48 hours.</p>	<p>No mortality and no adverse effects observed. At highest concentration, 1/10 immobilized (p=0.5 using Fisher Exact test). NOEC= 100 mg/L.</p> <p>48-hour LC₅₀ >100 mg a.i./L</p> <p>Toxicity category: practically nontoxic</p>	<p>Jones and Willis 1984 MRID 40244524 (Full study from Dow not on review CD) Core</p> <p>(Also cited in U.S. EPA/OPP 1998b)</p>
<p><i>Daphnia magna</i>, neonates (<24 hours old), 30 daphnids exposed, 10/replicate</p>	<p>Technical grade fluroxypyr MHE (98.5% a.i.). Static renewal study.</p> <p><u>Concentrations:</u> Nominal: 0, acetone control, or 100 mg/L</p> <p>Mean measured: 183 µg/L</p> <p>Water solubility of test material: 109 ± 5 µg/L at pH 7)</p>	<p>48-hour LC₅₀ > 0.11 mg a.i./L</p> <p>Toxicity category: not determined <i>U.S. EPA 1988b (EFED review) indicates that mortality did not occur when fluroxypyr MHE was tested up to its solubility limit.</i></p>	<p>Weinberg et al. 1991a MRID 42137308 Core</p>
<p><i>Daphnia magna</i>, juveniles, 5/test vessel</p>	<p>Technical grade fluroxypyr MHE (a.i. not reported).</p> <p>Acetone vehicle.</p> <p><u>Nominal Concentrations:</u> 0.10, 0.18, 0.32, or 0.56 mg/L for 48 hours under static conditions</p> <p>According to full study: <i>After 48 hours, the ester concentrations as determined by analysis had dropped remarkably (to as low as 43% of the nominal concentration).</i></p>	<p>48-hour LC₅₀ > 0.6 mg a.i./L</p> <p>No statistical analysis performed; only 1 <i>daphnia</i> (5% of the total exposed) was immobilized at 48 hours in one of the vessels at the nominal concentration of 0.18 mg/L. There were no other adverse effects observed in the remaining treated or control groups. NOEC: 0.56 mg/L.</p> <p>Toxicity category: not determined <i>U.S. EPA 1988b (EFED review) indicates that mortality did not occur when fluroxypyr MHE was tested up to its solubility limit.</i></p>	<p>Jones 1984b MRID 40244520 Core</p> <p>(Cited in U.S. EPA/OPP 1998b)</p>

Appendix 7: Toxicity to Aquatic Invertebrates (*continued*)

Freshwater – Chronic			
<p><i>Daphnia magna</i>, <24 hours old, 5 daphnids /replicate; 4 replicates per treatment and control</p>	<p>Fluroxypyr 1-methylheptyl ester (fluroxypyr 1-MHE) 95.8% pure. 21-day flow-through test.</p> <p><u>Nominal concentrations</u>: 78.0, 130, 216, 360, 600, or 1000 µg/L;</p> <p><u>Mean measured concentrations</u>: 37.7, 60.5, 109, 174, 294, or 499 µg/L</p> <p><u>Solvent</u>: acetone; maximum concentration: 0.1 mL/L</p>	<p>NOEC = 60.5 ppb</p> <p><u>LOECs for specific effects</u>: Neonates produced: 109 ppb Daphnid survival: 499 ppb Growth (length): 174 ppb</p> <p>MATC: 81.2 ppb</p> <p>Toxicity Observations: None</p>	<p>Kirk et al. 1996, MRID 44080314</p> <p>Supplemental: <i>Testing conducted above the solubility limit; likely (but not reported) that there was undissolved material in system; samples placed in acetonitrile, so test concentrations unknown; likely that reported measured concentrations are an overestimate.</i></p>
<p><i>Daphnia magna</i>, between 6- and 24-hours-old, 10/test vessels, four replicates</p>	<p>Dowco 433 acid (a.i. not specified)</p> <p><u>Nominal concentrations</u>: 10, 18, 32, 56, or 100 mg/L for 21 days under semi-static (replacement) conditions in natural groundwater.</p>	<p>At day 21, 15% of parental generation was immobilized in the control group, which was similar in all treated groups except for the highest; at 100 mg/L, 45% of the parental generation was immobilized. <i>This effect was significantly different from the controls (0.001 < p < 0.005).</i></p> <p>NOEC = 56 mg/L for immobilization.</p>	<p>Jones 1984a MRID 40244521</p>
<p>Jones 1984a, MRID 40244521 (<i>continued</i>): The total juvenile production in all treatment groups was lower than that in control group; however, the reductions in the 18, 32, and 56 mg/L groups were minor and not significant. In the lowest (10 mg/L) and highest (100 mg/L) treatment group, the numbers of juveniles produced were significantly lower ($p < 0.01$), compared with controls; however there was no significant systematic trend throughout the dose range.</p> <p><i>For the derived quantity 'juveniles per mobile <u>Daphnia</u>' there was no apparent reduction at the 100 mg/L level.</i></p>			

Appendix 7: Toxicity to Aquatic Invertebrates (*continued*)

Saltwater – Acute			
Eastern Oyster (<i>Crassostrea virginica</i>), juvenile, valve height = 25-33 mm, control shell deposition = 3.0 mm, 20 oysters/treatment group	Fluroxypyr acid (98.7% a.i.) Flow-through shell deposition study <i>DER does not specify whether or not a salt was used.</i> <u>Concentrations:</u> Nominal: 0, 16, 28, 44, 66 or 110 mg/L (corrected for purity) Mean measured: <1.0, 16, 26, 45, 66, 120 mg/L	96-hour LC ₅₀ = 51 mg a.i./L (measured concentration) 95% CI = 42-62 ppm NOEC = 16 ppm No sublethal effects observed in control or treatment groups. Toxicity category: slightly toxic	Boeri et al. 1994b MRID 44080311 Core
Grass Shrimp (<i>Palaemonetes pugio</i>), juvenile, 30 shrimp/control or treatment group, 15/replicate vessel	Fluroxypyr acid (98.7% a.i.) Flow-through study <i>DER does not specify whether or not a salt was used.</i> <u>Concentrations:</u> Nominal: 0, or 120 ppm Mean measured: <1.0, or 120 ppm	96-hour LC ₅₀ >120 mg a.i./L (measured concentration) NOEC = 120 ppm Toxicity category: practically nontoxic	Boeri et al. 1994c MRID 44080312 Core
Eastern Oyster (<i>Crassostrea virginica</i>), juvenile, mean valve height = 26-40 mm, peripheral shell growth prior to testing = 3-5 mm,	Fluroxypyr MHE (95.8% a.i.) Flow-through shell deposition study; solvent = DMF, maximum concentration: 0.5 mL/L <u>Concentrations:</u> Nominal: 0, solvent control, 12, 20, 32, 48, or 80 mg/L (corrected for purity) Mean measured: <0.025, <0.025, 0.050, 0.063, 0.094, 0.127, 0.167 mg/L	96-hour LC ₅₀ = 0.068 mg a.i./L (measured concentration) NOEC could not be determined due to treatment-related reductions in shell deposition at all treatment levels. Toxicity category: very highly toxic	Boeri et al. 1996b MRID 44080310 Core in U.S. EPA/OPP 1998b
Eastern Oyster (<i>Crassostrea virginica</i>), average length = 34.3 (27-45) mm, average wet weight tissue weight = 0.418 g, 20/chamber, 1 chamber/treatment	Fluroxypyr 1-MHE (99.1% a.i.), shell deposition study. <u>Concentrations:</u> Nominal: 0, solvent control (53.8 µL/L DMF), 0.26, 0.43, 0.72, 1.2, or 2.0 mg a.i./L) Mean measured: 0.086, 0.135, 0.171, 0.342, or 0.239 mg/L	EC ₅₀ could not be determined; study is scientifically unsound. Due to poor solubility of the test material, the highest concentration was <100 mg/L and produced <50% mortality.	Manning 1988c MRID 42137310 Invalid This study is not used in body of risk assessment. The above study by Boeri et al. 1996b is used.

Appendix 7: Toxicity to Aquatic Invertebrates (*continued*)

<p>Grass Shrimp (<i>Palaemonetes pugio</i>), juvenile, 30 shrimp/control or treatment group, 15/replicate vessel</p>	<p>Fluroxypyr MHE (95.8% a.i.) Flow-through study; solvent = DMF, maximum concentration: 0.5 mL/L</p> <p><u>Concentrations:</u> Nominal: 0, or 100 mg/L (corrected for purity)</p> <p>Mean measured: <0.063, or 0.135 ppm</p>	<p>96-hour LC₅₀ >0.135 mg a.i./L (measured concentration)</p> <p>96-hour LC₅₀ >0.100 ppm (nominal concentration)</p> <p>NOEC = 0.135 ppm (mean measured concentration) or 100 ppm (nominal concentration)</p> <p>Toxicity category: not determined <i>because concentrations at the solubility limit caused no mortality</i></p>	<p>Boeri et al. 1995 MRID 44080313 Core</p>
<p>Boeri et al. 1995 (cont.): DER reviewer indicates that the test material was supplied at a concentration of 100 ppm; however, investigators reported that the material was soluble in water only to a concentration of 100 ppb (at 25°C). The investigators made every effort (use of DMF solvent and shear pump mixer) to solubilize the test material in saltwater. Consequently, the study is considered scientifically sound and classified as Core.</p>			
<p>Pink Shrimp (<i>Penaeus duorarum</i>), average rostrum-telson length = 46 (38-54) mm, average wet weight = 0.69 (0.37-1.08) g, 20 shrimp/chamber, 1 chamber/treatment</p>	<p>Fluroxypyr MHE (99.1% a.i.) Flow-through study.</p> <p><u>Concentrations:</u> Nominal: 0, solvent control (17 µL/L DMF), 0.052, 0.09, 0.14, 0.24, or 0.40 mg a.i./L</p> <p>Mean measured: 0.029, 0.044, 0.057, 0.104, or 0.128 mg/L</p>	<p>96-hour LC₅₀ >0.128 mg a.i./L (measured concentration)</p> <p>No sublethal effects were observed.</p> <p>NOEC = 0.128 mg/L</p> <p>Toxicity category: not determined <i>because 5% mortality occurred at the solubility limit.</i></p>	<p>Manning 1988b MRID 42137311 Supplemental</p>

¹ U.S. EPA/OPP EFED classifications given only for registrant submitted studies.

Appendix 8: Toxicity to Aquatic Plants

Studies on fluroxypyr followed by studies on fluroxypyr metabolites.

FLUROXYPYR ACID AND ESTER			
Organism	Dose/Exposure	Response	Reference/ Classification ¹
Freshwater – Algae			
Green alga (<i>Scenedesmus obliquus</i>)	Fluroxypyr, 11% EC	EC ₅₀ = 26.5486 mg/L	Ma 2002
Green alga (<i>Chlorella pyrenoidosa</i>)	Fluroxypyr, 11% EC	EC ₅₀ = 3.044 mg/L	Ma 2002, Ma et al. 2001
Green alga (<i>Chlorella vulgaris</i>)	Fluroxypyr, 20% EC	EC ₅₀ = 37.5331 mg/L EC ₅₀ = 1.02x10 ⁻⁴ mol/L	Ma et al. 2002
Green alga (<i>Scenedesmus quadricauda</i>)	Fluroxypyr, 20% EC	No toxicity value specified; investigator reports that compared with <i>C. pyrenoidosa</i> , <i>S. quadricauda</i> was less sensitive to fluroxypyr.	Ma et al. 2003
Green alga (<i>Chlorella vulgaris</i>)	Fluroxypyr acid (99% a.i.)	EC ₅₀ >100 ppm NOEC = 100 ppm	Jones 1984c
Green algae (<i>Selenastrum capricornutum</i>) a.k.a. <i>Kirchneria subcapitata</i>	Fluroxypyr 1-MHE (95.8% a.i.) in Tier 2 test for 96 hours. <u>Concentrations:</u> Nominal: 0, solvent control (acetone), 63, 126, 253, 506, 1010, or 2020 ppb Measured (initial): 0, solvent control, 50, 101, 199, 390, 754, or 1410 µg/L	96-hour EC ₅₀ >1410 ppb NOEC = 199 ppb <i>Note U.S. EPA/OPP 1998b (EFED review) expresses the toxicity values in ppm.</i>	Milazzo et al. 1996c MRID 44080340 Core

Appendix 8: Toxicity to Aquatic Plants (continued)

FLUROXYPYR ACID AND ESTER			
Organism	Dose/Exposure	Response	Reference/Classification ¹
Green algae (<i>Selenastrum capricornutum</i>) a.k.a. <i>Kirchneria subcapitata</i>	Fluroxypyr acid (99.2% a.i.) in Tier 2 5-day growth and reproduction test. <u>Concentrations:</u> Nominal: 0, 4.7, 7.8, 13, 21.6, 36, 60, or 100 mg/L Measured: 4.7-97.7 mg/L <i>pH ranged from 3.7 to 9.0 in all vessels that contained growth (see page 3 of DER)</i>	120-hour EC ₅₀ = 51.3 mg/L (based on cell counts) 95% CI = 12.3-90.2 mg/L 120-hour EC ₅₀ = 49.8 mg/L (based on cell volume) 95% CI = 11.3-88.3 mg/L NOEC = 35.6 mg/L (based on both cell counts and volume) NOEC = 34 mg/L (measured) LOEC = 58 mg/L (measured) EC ₅₀ = 47 mg/L (measured)	Cowgill et al. 1988 MRID 42164501 Invalid
Cowgill et al. 1988 (cont): DER stated rationale for classifying the study as invalid is that the <i>pH level was low enough to confound the effects of the toxicant and the results of the study.</i>			
Green algae (<i>Selenastrum capricornutum</i>) a.k.a. <i>Kirchneria subcapitata</i>	Fluroxypyr 1-MHE (98.5% a.i.) in Tier 2 5-day growth and reproduction test. <u>Concentrations:</u> Nominal: 0, solvent control, 0.125, 0.25, 0.5, 1.0, or 2.0 mg/L Measured (day 0): N.D., N.D., 0.0730, 0.121, 0.336, 0.644, 1.620 mg/L (detection limit = 0.50 mg/L)	120-hour EC ₅₀ >1.62 mg a.i./L (based on initial measured concentrations) 120-hour EC ₅₀ >2 mg a.i./L (based on nominal concentrations) LOEC = 0.336 mg a.i./L (based on initial measured concentrations) LOEC = 0.5 mg a.i./L (based on nominal concentrations) NOEC = 0.121 mg a.i./L (based on initial measured concentrations) DER states <i>Since no test concentration resulted in more than 22.6% inhibition; the EC₂₅ and EC₅₀ were greater than the highest nominal test concentration or water solubility.</i>	Hughes and Alexander 1991 MRID 42137312 Supplemental <i>Due to insolubility, the concentration of the test material in solution was uncertain.</i>

Appendix 8: Toxicity to Aquatic Plants (continued)

FLUROXYPYR ACID AND ESTER			
Organism	Dose/Exposure	Response	Reference/ Classification ¹
Blue-green Alga (<i>Anabaena flos-aquae</i>)	Fluroxypyr 1-MHE (95.8% a.i.) in Tier 2 test for 120 hours. <u>Concentrations:</u> Nominal: 0, solvent control (acetone), 30, 60, 120, 241, 481, or 961 ppb Measured (initial): 0, solvent control, 30, 73, 112, 226, 461, 986 µg/L	120-hour EC ₅₀ = 602 ppb 95% CI = 434-999 ppb NOEC = 30 ppb <i>Note U.S. EPA/OPP 1998b (EFED review) expresses the toxicity values in ppm – i.e., 0.030 ppm. Both forms are correct.</i>	Milazzo et al. 1996a MRID 44080336 Core
Diatom (<i>Navicula pelliculosa</i>)	Fluroxypyr 1-MHE (95.8% a.i.) in Tier 2 test for 120 hours. <u>Concentrations:</u> 0, solvent control (acetone), 16, 31, 63, 125, 250, or 500 ppb Measured (initial): solvent control, 15, 33, 75, 132, 217, or 500 µg/L	120-hour EC ₅₀ = 93 ppb 95% CI = 13-640 ppb NOEC = 132 ppb <i>DER states that the solvent control solutions were contaminated with test material and that the negative control data were not included in the report.</i>	Milazzo et al. 1996b MRID 44080339 Invalid
Freshwater – Macrophytes			
Duckweed (<i>Lemna gibba</i>), 16 fronds/replicate (4 plants with 4 fronds each)	Fluroxypyr 1-MHE (95.8% a.i.) in Tier 2 static renewal test for 14 days. <u>Concentrations:</u> Nominal: 0, solvent control (acetone), 188, 375, 750, 1500, or 3000 ppb Measured (initial): 0, solvent control, 176, 289, 744, 1220, 2310 µg/L	EC ₅₀ >2310 ppb NOEC = 1220 ppb <i>Note U.S. EPA/OPP 1998b (EFED review) expresses the toxicity values in ppm.</i>	Kirk et al. 1996b MRID 44080338 Core

Appendix 8: Toxicity to Aquatic Plants (continued)

FLUROXYPYR ACID AND ESTER			
Organism	Dose/Exposure	Response	Reference/Classification ¹
Duckweed (<i>Lemna gibba</i>), 4 plants (1 fronds, 4 fronds/ plant), 5 replicate vessels/dose level.	<p>Starane 180 (EF-1463) [active ingredient in this emulsifiable concentrate formulation is fluroxypyr MHE with 180 grams a.e./L of formulation] for 7 days.</p> <p><u>Concentrations:</u> Nominal: 0.31, 0.63, 1.3, 2.5, 5.0, or 10 mg fluroxypyr MHE/L</p> <p>Measured: 0.437, 0.865, 1.57, 2.87, 5.30, or 7.98 mg fluroxypyr MHE/L</p>	<p>Results data based on the averaged mean analyzed fluroxypyr MHE concentrations for samples taken on day 0, 7, and 14.</p> <p>7-day EC₂₅ = 1.22 mg fluroxypyr MHE/L (4.73 mg Starane 180/L)</p> <p>7-day EC₅₀ = 6.48 mg fluroxypyr MHE/L (25.1 mg Starane 180/L)</p> <p>7- day NOEC = 0.412 mg fluroxypyr MHE/L (1.59 mg Starane 180/L)</p> <p>14-day EC₂₅ = 0.63 mg fluroxypyr MHE/L (2.44 mg Starane 180/L)</p> <p>14-day EC₅₀ = 1.66 mg fluroxypyr MHE/L (6.44 mg Starane 180/L)</p> <p>14-day NOEC = 0.437 mg fluroxypyr MHE/L (1.70 mg Starane 180/L)</p> <p>On day 14, the effects of exposure on mean frond counts, relative to controls, ranged from 7.2% growth inhibition at 0.437 mg fluroxypyr MHE/L (1.7 mg STARANE 180/L), to 85.7% growth inhibition at 7.98 mg fluroxypyr MHE/L (31.1 mg STARANE 180/L).</p>	<p>Kirk et al. 1998 MRID 44744001 (Full study from Dow)</p>

Appendix 8: Toxicity to Aquatic Plants (continued)

FLUROXYPYR ACID AND ESTER			
Organism	Dose/Exposure	Response	Reference/ Classification ¹
Saltwater – Algae			
Marine diatom (<i>Skeletonema costatum</i>)	Fluroxypyr 1-MHE (95.8% a.i.) in Tier 2 test. <u>Concentrations:</u> Nominal: 0, 0.5 mg/L DMF (solvent control), 63, 126, 252, 503, 1005, or 2010 ppb (corrected for purity) Measured (initial): 0, solvent control, 43, 85, 179, 347, 798, 1722 µg/L	120-hour EC ₅₀ = 292 ppb NOEC = 179 ppb <i>Note U.S. EPA/OPP 1998b (EFED review) expresses the toxicity value as 0.18 ppm, equivalent (after rounding) to those noted above from the DER.</i>	Hughes et al. 1996 MRID 44080337 Core

Appendix 8: Toxicity to Aquatic Plants (*continued*)

FLUROXYPYR METABOLITES			
Organism	Dose/Exposure	Response	Reference/ Classification ¹
Freshwater – Algae			
Diatom (<i>Navicula pelliculosa</i>)	<p>4-amino-3,5-dichloro-6-fluoro-2-pyridinol (99.5% a.i.) for 120 hours under static conditions.</p> <p>Solvent control: acetone</p> <p><u>Concentrations:</u> Nominal: 0, solvent control (0.1 mL/L acetone), 0.19, 0.38, 0.75, 1.5, or 3.0 mg/L</p> <p>Mean measured concentrations (used for all calculations): <0.011, (control and solvent control) 0.19, 0.39, 0.70, 1.5, or 3.0 mg/L. [Mean measured concentrations ranged from 93 to 103% of corresponding nominal concentrations.]</p>	<p>120-hour EC₅₀ >3.0 mg/L calculated from number of cells/mL or average specific growth rate.</p> <p>NOEC = 3.0 mg/L (calculated from number of cell/mL)</p> <p>NOEC = 0.19 (calculated from average specific growth rate).</p>	Ward et al. 1999a MRID 45011601 (Full study from Dow)
Diatom (<i>Navicula pelliculosa</i>)	<p>4-amino-3,5-dichloro-6-fluoro-2-methoxy-pyridine (99.9% a.i.) for 120 hours under static conditions.</p> <p><u>Concentrations:</u> Nominal: 0 (control), 1.5, 3.0, 6.0, 12, or 24 mg/L</p> <p>Initial measured concentrations (used for all calculations): <0.240 (control), 1.09, 3.22, 4.52, 9.50, or 20.0 mg/L.</p>	<p>120-hour EC₅₀ =3.37 mg/L calculated from number of cells/mL</p> <p>120-hour EC₅₀ =3.20 mg/L calculated from the average specific growth rate.</p> <p>120-hour NOEC = 3.22 mg/L calculated from number of cells/mL or average specific growth rate.</p> <p>No insoluble material was observed during the test.</p>	Ward et al. 1999f MRID 45011606 (Full study from Dow)

Appendix 8: Toxicity to Aquatic Plants (continued)

<p>Blue-green Alga (<i>Anabaena flos-aquae</i>)</p>	<p>4-amino-3,5-dichloro-6-fluoro-2-pyridinol (99.5% a.i.) for 120 hours under static conditions.</p> <p>Solvent control: acetone</p> <p><u>Concentrations:</u> Nominal: 0, solvent control (0.1 mL/L acetone), 0.19, 0.38, 0.75, 1.5, or 3.0 mg/L</p> <p>Mean measured concentrations (used for all calculations): <0.035 (control and solvent control), 0.19, 0.35, 0.65, 1.4, or 2.9 mg/L [Mean measured concentrations ranged from 87 to 100% of corresponding nominal concentrations.]</p>	<p>120-hour EC₅₀ >2.9 mg/L calculated from the number of cells/mL or the average specific growth rate.</p> <p>NOEC = 2.9 mg/L calculated from the number of cells/mL or the average specific growth rate.</p>	<p>Ward et al. 1999c MRID 45011604 (Full study from Dow)</p>
<p>Blue-green Alga (<i>Anabaena flos-aquae</i>)</p>	<p>4-amino-3,5-dichloro-6-fluoro-2-methoxy-pyridine (99.9% a.i.) for 120 hours under static conditions.</p> <p><u>Concentrations:</u> Nominal: 0 (control), 1.5, 3.0, 6.0, 12, or 24 mg/L</p> <p>Initial measured concentrations (used for all calculations): <0.0546 (control), 1.12, 2.15, 4.63, 8.94, or 19.9 mg/L</p>	<p>120-hour EC₅₀ = 1.80 mg/L calculated from the number of cells/mL</p> <p>120-hour EC₅₀ = 2.23 mg/L calculated from the specific average growth rate.</p> <p>120-hour NOEC = 1.12 mg/L calculated from the number of cells/mL or the average specific growth rate.</p> <p>No insoluble material was observed during the test.</p>	<p>Ward et al. 1999h MRID 45011608 (Full study from Dow)</p>

Appendix 8: Toxicity to Aquatic Plants (continued)

<p>Green alga (<i>Selenastrum capricornutum</i>)</p>	<p>4-amino-3,5-dichloro-6-fluoro-2-pyridinol (99.5% a.i.) for 120 hours under static conditions.</p> <p>Solvent control: acetone</p> <p><u>Concentrations:</u> Nominal: 0, solvent control (0.1 mL/L acetone), 0.19, 0.38, 0.75, 1.5, or 3.0 mg/L</p> <p>Mean measured concentrations (used for all calculations): <0.054 (control and solvent control), 0.19, 0.38, 0.74, 1.5, or 3.3 mg/L [Mean measured concentrations ranged from 99 to 110% of corresponding nominal concentrations.]</p>	<p>120-hour EC₅₀ >3.3 mg/L calculated from number of cells/mL or average specific growth rate.</p> <p>120-hour NOEC = 3.3 mg/L calculated from number of cells/mL or average specific growth rate.</p> <p>No insoluble material was observed during the test.</p>	<p>Ward et al. 1999d MRID 45011603 (Full study from Dow)</p>
<p>Green alga (<i>Selenastrum capricornutum</i>)</p>	<p>4-amino-3,5-dichloro-6-fluoro-2-methoxy-pyridine (99.9 % a.i.)</p> <p><u>Nominal concentrations:</u> 15 µg/L to 15 mg/L</p>	<p>Results expressed in terms of algal cell growth, relative to controls:</p> <p>3-day EC₅₀ =2794 µg/L 3-day NOEL = 938 µg/L</p> <p>5-day EC₅₀ =2164 µg/L 5-day NOEL = 938 µg/L</p>	<p>Kirk and Landre 1995 MRID 44080341 Supplemental <i>Study did not comply with GLP standards (U.S. EPA/OPP 1998b).</i></p>

Appendix 8: Toxicity to Aquatic Plants (*continued*)

Freshwater – Macrophytes			
Duckweed (<i>Lemna gibba</i>)	<p>4-amino-3,5-dichloro-6-fluoro-2-pyridinol (99.5% a.i.) for 14 days under static conditions.</p> <p>Solvent control: acetone</p> <p><u>Concentrations:</u> Nominal: 0, solvent control (0.1 mL/L acetone), 0.19, 0.38, 0.75, 1.5, or 3.0 mg/L</p> <p>Initial mean measured concentrations (used for all calculations): <0.028, (control and solvent control), 0.15, 0.40, 0.84, 1.5, or 3.2 mg/L. [Measured concentrations ranged from 79 to 112% of corresponding nominal concentrations.]</p>	<p>All observations at 14 days.</p> <p>EC₅₀ >3.2mg/L</p> <p>NOEC = 3.2 based on number of non-chlorotic fronds.</p> <p>No significant difference observed in the number of normal fronds between the control and 3.2 mg/L treatment group (p=0.05); no flowers observed at any concentration; mean dry weight of fronds exposed to 3.2 mg/L (0.0239 g) was greater than mean dry weight of controls (0.0223 g) or solvent controls (0.0197 g).</p>	<p>Ward et al. 1999b MRID 45011602 (Full study from Dow)</p>
Duckweed (<i>Lemna gibba</i>)	<p>4-amino-3,5-dichloro-6-fluoro-2-methoxy-pyridine (99.9% a.i.) for 14 days under static conditions.</p> <p><u>Concentrations:</u> Nominal: 0 (control), 1.0, 2.0, 4.0, 8.0, or 16 mg/L</p> <p>Initial mean measured concentrations (used for all calculations): <0.0824 (control), 0.686, 1.18, 2.24, 4.25, or 9.23 mg/L. [Initial measured concentrations ranged from 71 to 88% of corresponding nominal concentrations.]</p>	<p>EC₅₀ = 10.6 mg/L</p> <p>NOEC = 3.52 based on number of non-chlorotic fronds.</p> <p>No significant differences observed in the numbers of normal fronds among the control and three lowest test concentrations (p=0.05); no significant decreases observed in the dry weight of fronds among the control and four lowest test concentrations (p=0.05); however, the average dry weight of fronds exposed to 3.52 mg/L as significantly greater than the control. No flowers were observed at any concentration.</p>	<p>Ward et al. 1999g MRID 45011607 (Full study from Dow)</p>

Appendix 8: Toxicity to Aquatic Plants (*continued*)

Saltwater – Algae			
<p>Marine diatom (<i>Skeletonema costatum</i>)</p>	<p>4-amino-3,5-dichloro-6-fluoro-2-pyridinol (99.5% a.i.) for 120 hours under static conditions.</p> <p>Solvent control: acetone</p> <p><u>Concentrations:</u> Nominal: 0, solvent control (0.1 mL/L acetone), 0.19, 0.38, 0.75, 1.5, or 3.0 mg/L</p> <p>Mean measured concentrations (used for all calculations): <0.0075, (control and solvent control), 0.20, 0.41, 0.83, 1.4, or 3.0 mg/L. [Measured concentrations ranged from 93 to 111% of corresponding nominal concentrations.]</p>	<p>120-hour EC₅₀ >3.0 mg/L calculated from number of cells/mL or average specific growth rate.</p> <p>120-hour NOEC = 3.0 mg/L calculated from number of cells/mL or average specific growth rate.</p> <p>No insoluble material was observed during the test.</p>	<p>Ward et al. 1999e MRID 45011605 (Full study from Dow)</p>
<p>Marine diatom (<i>Skeletonema costatum</i>)</p>	<p>4-amino-3,5-dichloro-6-fluoro-2-methoxy-pyridine (99.9% a.i.) for 120 hours under static conditions.</p> <p><u>Concentrations:</u> Nominal: 0 (control), 1, 7, 3.3, 6.5, 13, or 24 mg/L.</p> <p>Mean measured concentrations (used for all calculations): <0.0700 (control), 1.19, 2.52, 5.05, 10.2, or 21.8 mg/L.</p>	<p>120-hour EC₅₀ = 7.82 mg/L calculated from the number of cells/mL</p> <p>120-hour EC₅₀ = 11.3 mg/L calculated from the average specific growth rate.</p> <p>120-hour NOEC = 2.52 mg/L calculated from the number of cells/mL or the average specific growth rate.</p> <p>No insoluble material was observed during the test.</p>	<p>Ward et al. 1999i MRID 45011609 (Full study from Dow)</p>

Appendix 9: Gleams-Driver Simulations

Table 1: Effective Offsite Application Rate (lb/acre)			
Site	Clay	Loam	Sand
Dry and Warm Location	1.18E-06 (0 - 0.00193)	0 (0 - 0.000305)	0 (0 - 7.00E-08)
Dry and Temperate Location	0 (0 - 0.000035)	0 (0 - 2.24E-06)	0 (0 - 1.74E-09)
Dry and Cold Location	0 (0 - 0.00169)	0 (0 - 0.000104)	0 (0 - 0)
Average Rainfall and Warm Location	0.0127 (0.00041 - 0.077)	0.00229 (0.000033 - 0.0156)	1.91E-08 (0 - 0.000012)
Average Rainfall and Temperate Location	0.0074 (0.00035 - 0.07)	0.00105 (2.14E-05 - 0.0176)	4.50E-08 (0 - 1.21E-05)
Average Rainfall and Cool Location	0.0052 (2.57E-05 - 0.0242)	0.00041 (3.01E-06 - 0.0061)	0 (0 - 5.70E-07)
Wet and Warm Location	0.0059 (0.00037 - 0.046)	0.00072 (1.78E-05 - 0.0094)	5.20E-09 (0 - 3.50E-07)
Wet and Temperate Location	0.00302 (0.000034 - 0.0252)	0.000193 (7.50E-07 - 0.0062)	0 (0 - 1.60E-06)
Wet and Cool Location	0.053 (0.0271 - 0.094)	0.0111 (0.004 - 0.0203)	2.26E-08 (0 - 1.33E-05)
		Average of Central Values:	0.00381
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.094
		Summary of Values:	0.0038 (0 - 0.094)

Appendix 9: Gleams-Driver Simulations (*continued*)

Table 2: Concentration in Top 12 Inches of Soil (ppm)			
Site	Clay	Loam	Sand
Dry and Warm Location	0.206 (0.206 - 0.206)	0.205 (0.205 - 0.205)	0.217 (0.217 - 0.218)
Dry and Temperate Location	0.206 (0.202 - 0.206)	0.205 (0.203 - 0.205)	0.217 (0.217 - 0.218)
Dry and Cold Location	0.206 (0.201 - 0.206)	0.205 (0.202 - 0.205)	0.217 (0.216 - 0.217)
Average Rainfall and Warm Location	0.206 (0.201 - 0.206)	0.205 (0.203 - 0.205)	0.217 (0.216 - 0.217)
Average Rainfall and Temperate Location	0.206 (0.201 - 0.206)	0.205 (0.202 - 0.205)	0.217 (0.216 - 0.217)
Average Rainfall and Cool Location	0.206 (0.202 - 0.206)	0.205 (0.203 - 0.205)	0.217 (0.216 - 0.217)
Wet and Warm Location	0.202 (0.202 - 0.206)	0.203 (0.203 - 0.205)	0.216 (0.216 - 0.217)
Wet and Temperate Location	0.206 (0.202 - 0.206)	0.205 (0.202 - 0.205)	0.217 (0.216 - 0.217)
Wet and Cool Location	0.196 (0.188 - 0.206)	0.201 (0.198 - 0.205)	0.209 (0.195 - 0.217)
		Average of Central Values:	0.2083
		25th Percentile of Lower Bounds:	0.202
		Maximum Value:	0.218
		Summary of Values:	0.208 (0.202 - 0.218)

Appendix 9: Gleams-Driver Simulations (*continued*)

Table 3: Concentration in Top 60 Inches of Soil (ppm)			
Site	Clay	Loam	Sand
Dry and Warm Location	0.041 (0.041 - 0.041)	0.041 (0.041 - 0.041)	0.043 (0.043 - 0.044)
Dry and Temperate Location	0.041 (0.04 - 0.041)	0.041 (0.041 - 0.041)	0.043 (0.043 - 0.044)
Dry and Cold Location	0.041 (0.04 - 0.041)	0.041 (0.04 - 0.041)	0.043 (0.043 - 0.043)
Average Rainfall and Warm Location	0.041 (0.04 - 0.041)	0.041 (0.041 - 0.041)	0.043 (0.043 - 0.043)
Average Rainfall and Temperate Location	0.041 (0.04 - 0.041)	0.041 (0.04 - 0.041)	0.043 (0.043 - 0.043)
Average Rainfall and Cool Location	0.041 (0.04 - 0.041)	0.041 (0.041 - 0.041)	0.043 (0.043 - 0.043)
Wet and Warm Location	0.04 (0.04 - 0.041)	0.041 (0.041 - 0.041)	0.043 (0.043 - 0.043)
Wet and Temperate Location	0.041 (0.04 - 0.041)	0.041 (0.04 - 0.041)	0.043 (0.043 - 0.043)
Wet and Cool Location	0.039 (0.038 - 0.041)	0.04 (0.04 - 0.041)	0.043 (0.043 - 0.043)
		Average of Central Values:	0.0415
		25th Percentile of Lower Bounds:	0.04
		Maximum Value:	0.044
		Summary of Values:	0.042 (0.04 - 0.044)

Appendix 9: Gleams-Driver Simulations (*continued*)

Table 4: Maximum Penetration into Soil Column (inches)			
Site	Clay	Loam	Sand
Dry and Warm Location	12 (4 - 24)	12 (4 - 30)	18 (8 - 60)
Dry and Temperate Location	8 (4 - 12)	12 (8 - 18)	30 (12 - 60)
Dry and Cold Location	12 (8 - 24)	18 (12 - 24)	30 (18 - 42)
Average Rainfall and Warm Location	30 (24 - 36)	42 (36 - 54)	60 (60 - 60)
Average Rainfall and Temperate Location	30 (18 - 36)	36 (30 - 48)	60 (54 - 60)
Average Rainfall and Cool Location	24 (18 - 30)	36 (30 - 42)	60 (54 - 60)
Wet and Warm Location	30 (24 - 36)	48 (42 - 60)	60 (60 - 60)
Wet and Temperate Location	24 (18 - 30)	36 (30 - 42)	60 (60 - 60)
Wet and Cool Location	42 (36 - 48)	60 (54 - 60)	60 (60 - 60)
		Average of Central Values:	35.2
		25th Percentile of Lower Bounds:	12
		Maximum Value:	60
		Summary of Values:	35.2 (12 - 60)

Appendix 9: Gleams-Driver Simulations (*continued*)

Table 5: Pond, Peak Concentration in Surface Water (ug/L or ppb)			
Site	Clay	Loam	Sand
Dry and Warm Location	0.0015 (0 - 2.28)	0 (0 - 0.3)	0 (0 - 0.0012)
Dry and Temperate Location	0 (0 - 0.04)	0 (0 - 0.0023)	0 (0 - 0.001)
Dry and Cold Location	0 (0 - 1.8)	0 (0 - 0.12)	0 (0 - 9.0E-07)
Average Rainfall and Warm Location	13.2 (0.5 - 52)	2.01 (0.03 - 11.2)	0.5 (0.013 - 4.6)
Average Rainfall and Temperate Location	8 (0.4 - 52)	1 (0.017 - 11.3)	0.05 (0.00024 - 5)
Average Rainfall and Cool Location	5.2 (0.028 - 25.2)	0.4 (0.0031 - 5.3)	0.004 (0.00008 - 0.3)
Wet and Warm Location	4 (0.4 - 21.8)	0.4 (0.008 - 3.4)	2.38 (0.8 - 9.7)
Wet and Temperate Location	2.6 (0.04 - 20.2)	0.16 (0.0008 - 4.2)	0.8 (0.4 - 1.94)
Wet and Cool Location	16 (8.9 - 24.9)	3.2 (1.24 - 5.4)	25.9 (6.4 - 43)
		Average of Central Values:	3.18
		25th Percentile of Lower Bounds:	0
		Maximum Value:	52
		Summary of Values:	3.18 (0 - 52)

Appendix 9: Gleams-Driver Simulations (*continued*)

Table 6: Pond, Annual Average Concentration in Surface Water (ug/L or ppb)			
Site	Clay	Loam	Sand
Dry and Warm Location	0.00011 (0 - 0.18)	0 (0 - 0.019)	0 (0 - 0.00017)
Dry and Temperate Location	0 (0 - 0.003)	0 (0 - 0.00013)	0 (0 - 0.00018)
Dry and Cold Location	0 (0 - 0.15)	0 (0 - 0.006)	0 (0 - 1.4E-07)
Average Rainfall and Warm Location	1.28 (0.05 - 6.1)	0.14 (0.0026 - 0.8)	0.13 (0.003 - 1.16)
Average Rainfall and Temperate Location	0.8 (0.04 - 5.7)	0.06 (0.0015 - 0.9)	0.01 (0.00006 - 1.05)
Average Rainfall and Cool Location	0.5 (0.0025 - 2.28)	0.025 (0.00023 - 0.4)	0.0009 (0.000021 - 0.1)
Wet and Warm Location	0.4 (0.04 - 2.52)	0.03 (0.001 - 0.28)	0.8 (0.28 - 3.2)
Wet and Temperate Location	0.28 (0.0031 - 2.26)	0.012 (0.00005 - 0.3)	0.16 (0.04 - 0.5)
Wet and Cool Location	1.11 (0.4 - 2.31)	0.17 (0.05 - 0.4)	7.7 (2.29 - 10.9)
		Average of Central Values:	0.504
		25th Percentile of Lower Bounds:	0
		Maximum Value:	10.9
		Summary of Values:	0.5 (0 - 10.9)

Appendix 9: Gleams-Driver Simulations (*continued*)

Table 7: Stream, Maximum Peak Concentration in Surface Water (ug/L or ppb)			
Site	Clay	Loam	Sand
Dry and Warm Location	0.005 (0 - 5.8)	0 (0 - 0.8)	0 (0 - 0.002)
Dry and Temperate Location	0 (0 - 0.18)	0 (0 - 0.007)	0 (0 - 0.001)
Dry and Cold Location	0 (0 - 6.2)	0 (0 - 0.4)	0 (0 - 2.3E-06)
Average Rainfall and Warm Location	25.9 (1.2 - 75)	3.9 (0.09 - 20.2)	0.4 (0.017 - 1.99)
Average Rainfall and Temperate Location	16.4 (0.7 - 79)	1.9 (0.022 - 15.8)	0.04 (0.0003 - 2.13)
Average Rainfall and Cool Location	10.4 (0.08 - 44)	0.9 (0.008 - 9.4)	0.004 (0.00016 - 0.22)
Wet and Warm Location	11 (0.9 - 54)	1.16 (0.028 - 12.1)	1.74 (0.6 - 6.4)
Wet and Temperate Location	7.6 (0.09 - 45)	0.5 (0.0017 - 9.6)	0.7 (0.4 - 1.74)
Wet and Cool Location	51 (24 - 68)	11.6 (3.7 - 15.8)	25.8 (5.3 - 36)
		Average of Central Values:	6.33
		25th Percentile of Lower Bounds:	0
		Maximum Value:	79
		Summary of Values:	6.33 (0 - 79)

Appendix 9: Gleams-Driver Simulations (*continued*)

Table 8: Stream, Annual Average Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.000015 (0 - 0.022)	0 (0 - 0.0026)	0 (0 - 0.000006)
Dry and Temperate Location	0 (0 - 0.0005)	0 (0 - 0.000018)	0 (0 - 2.7E-06)
Dry and Cold Location	0 (0 - 0.017)	0 (0 - 0.001)	0 (0 - 6.0E-09)
Average Rainfall and Warm Location	0.09 (0.006 - 0.29)	0.013 (0.0004 - 0.07)	0.005 (0.00013 - 0.04)
Average Rainfall and Temperate Location	0.06 (0.004 - 0.23)	0.006 (0.00011 - 0.05)	0.00024 (2.3E-06 - 0.04)
Average Rainfall and Cool Location	0.04 (0.00023 - 0.16)	0.0027 (0.000027 - 0.028)	0.00004 (9.0E-07 - 0.004)
Wet and Warm Location	0.05 (0.004 - 0.23)	0.004 (0.00009 - 0.05)	0.1 (0.031 - 0.3)
Wet and Temperate Location	0.025 (0.0003 - 0.14)	0.0014 (0.000006 - 0.029)	0.04 (0.013 - 0.08)
Wet and Cool Location	0.27 (0.17 - 0.4)	0.05 (0.021 - 0.07)	1.08 (0.25 - 1.76)
		Average of Central Values:	0.0681
		25th Percentile of Lower Bounds:	0
		Maximum Value:	1.76
		Summary of Values:	0.068 (0 - 1.76)