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Scoping/Screening Level Risk Assessment on Clethodim: Final Report

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Preface

This report is based on a revision to SERA TR-056-05-01-02a, Scoping/Screening Level Risk Assessment on Clethodim, dated March 28, 2014. This document is updated to reflect the recent documents released by the U.S. EPA's Office of Pesticide Programs' registration review of clethodim (U.S. EPA/OPP/EFED 2013a, 2014a; U.S. EPA/OPP/HED 2013a,b, 2014a) as well as peer review comments.

This document is compliant with Section 508 of the Rehabilitation Act of 1973 as amended by the Workforce Investment Act of 1998. The compliance report is attached to the PDF version of this risk assessment.

Table of Contents

LIST OF TABLES vii
LIST OF FIGURES vii
LIST OF APPENDICES viii
LIST OF ATTACHMENTS viii
ACRONYMS, ABBREVIATIONS, AND SYMBOLS ix
CONVERSION OF SCIENTIFIC NOTATION xiii
EXECUTIVE SUMMARY xiv
1. INTRODUCTION 1
1.1. Chemical Specific Information 1
1.2. General Information 3
2. PROGRAMS DESCRIPTION 6
2.1. Overview 6
2.2. Chemical Description and Commercial Formulations 7
2.3. Application Methods 10
2.4. Mixing and Application Rates 11
2.5. Use Statistics 12
3. HUMAN HEALTH 14
3.1. HAZARD IDENTIFICATION 14
3.1.1. Overview 14
3.1.2. Mechanism of Action 14
3.1.3. Pharmacokinetics and Metabolism 15
3.1.3.1. General Considerations 15
3.1.3.2. Absorption 17
3.1.3.2.1. First-Order Dermal Absorption 17
3.1.3.2.2. Zero-Order Dermal Absorption 19
3.1.3.3. Excretion 19
3.1.4. Acute Oral Toxicity 20
3.1.5. Subchronic or Chronic Systemic Toxic Effects 22

3.1.6. Effects on Nervous System 23
3.1.7. Effects on Immune System 24
3.1.8. Effects on Endocrine System 25
3.1.9. Reproductive and Developmental Effects 25
3.1.9.1. Developmental Studies 25
3.1.9.2. Reproduction Studies 26
3.1.10. Carcinogenicity and Mutagenicity 27
3.1.11. Irritation and Sensitization (Effects on the Skin and Eyes) 27
3.1.11.1. Skin Irritation 28
3.1.11.2. Skin Sensitization 28
3.1.11.3. Ocular Effects 29
3.1.12. Systemic Toxic Effects from Dermal Exposure 29
3.1.12.1. Acute Studies 29
3.1.12.2. Repeated Dose Studies 30
3.1.13. Inhalation Exposure 30
3.1.14. Adjuvants and Other Ingredients 31
3.1.14.2. Other Ingredients 31
3.1.14.2. Adjuvants 33
3.1.15. Impurities and Metabolites 34
3.1.15.1. Metabolites 34
3.1.15.2. Impurities 34
3.1.16. Toxicological Interactions 35
3.2. EXPOSURE ASSESSMENT 36
3.2.1. Overview 36
3.2.2. Workers 36
3.2.2.1. General Exposures 37
3.2.2.2. Accidental Exposures 39
3.2.3. General Public 40
3.2.3.1. General Considerations 40
3.2.3.1.1. Likelihood and Magnitude of Exposure 40
3.2.3.1.2. Summary of Assessments 41
3.2.3.2. Direct Spray 42
3.2.3.3. Dermal Exposure from Contaminated Vegetation 43
3.2.3.4. Contaminated Water 43
3.2.3.4.1. Accidental Spill 43
3.2.3.4.2. Accidental Direct Spray/Drift to a Pond or Stream 44
3.2.3.4.3. GLEAMS-Driver Modeling 44

3.2.3.4.4. Other Modeling Efforts 45
3.2.3.4.5. Monitoring Data 46
3.2.3.4.6. Concentrations in Water Used for Risk Assessment 47
3.2.3.5. Oral Exposure from Contaminated Fish 47
3.2.3.6. Dermal Exposure from Swimming in Contaminated Water 48
3.2.3.7. Oral Exposure from Contaminated Vegetation 49
3.3. DOSE-RESPONSE ASSESSMENT 51
3.3.1. Overview 51
3.3.2. Chronic RfD 51
3.3.3. Acute RfD 51
3.3.4. Surrogate RfD for Occupational Exposures 52
3.3.5. Dose-Severity Relationships 52
3.4. RISK CHARACTERIZATION 54
3.4.1. Overview 54
3.4.2. Workers 54
3.4.2.1. Accidental Exposures 54
3.4.2.2. General Exposures 55
3.4.3. General Public 56
3.4.1.1. Accidental Exposures 56
3.4.1.2. Non-Accidental Exposures 56
3.4.4. Sensitive Subgroups 57
3.4.5. Connected Actions 57
3.4.6. Cumulative Effects 57
4. ECOLOGICAL RISK ASSESSMENT 59
4.1. HAZARD IDENTIFICATION 59
4.1.1. Overview 59
4.1.2. Terrestrial Organisms 60
4.1.2.1. Mammals 60
4.1.2.2. Birds 60
4.1.2.3. Reptiles and Amphibians (Terrestrial-Phase) 61
4.1.2.4. Terrestrial Invertebrates 62
4.1.2.5. Terrestrial Plants (Macrophytes) 62
4.1.2.5.1. General Considerations 62
4.1.2.5.2. Toxicity Data 63
4.1.2.5.3. Field Studies/Observations 64
4.1.2.5.4. Resistance 66
4.1.2.6. Terrestrial Microorganisms 66

4.1.3. Aquatic Organisms 67
4.1.3.1. Fish 67
4.1.3.1.1. Acute toxicity in fish 67
4.1.3.1.2. Longer-term toxicity in fish 67
4.1.3.2. Amphibians 69
4.1.3.3. Aquatic Invertebrates 69
4.1.3.4. Aquatic Plants 70
4.1.3.4.1. Algae 70
4.1.3.4.2. Aquatic Macrophytes 71
4.1.3.5. Surfactants 72
4.2. EXPOSURE ASSESSMENT 74
4.2.1. Overview 74
4.2.2. Mammals and Birds 74
4.2.2.1. Direct Spray 75
4.2.2.2. Dermal Contact with Contaminated Vegetation 75
4.2.2.3. Ingestion of Contaminated Vegetation or Prey 76
4.2.2.4. Ingestion of Contaminated Water 77
4.2.2.5. Consumption of Contaminated Fish 77
4.2.3. Terrestrial Invertebrates 78
4.2.3.1. Direct Spray and Drift 78
4.2.3.2. Ingestion of Contaminated Vegetation or Prey 78
4.2.3.3. Contaminated Soil 78
4.2.4. Terrestrial Plants 79
4.2.4.1. Direct Spray 79
4.2.4.2. Off-Site Drift 79
4.2.4.3. Runoff and Soil Mobility 80
4.2.4.4. Contaminated Irrigation Water 81
4.2.4.5. Wind Erosion 81
4.2.5. Aquatic Organisms 82
4.3. DOSE-RESPONSE ASSESSMENT 83
4.3.1. Overview 83
4.3.2. Toxicity to Terrestrial Organisms 84
4.3.2.1. Mammals 84
4.3.2.2. Birds 84
4.3.2.3. Reptiles and Amphibians (Terrestrial Phase) 84
4.3.2.4. Terrestrial Invertebrates 85

4.3.2.5. Terrestrial Plants (Macrophytes) 85
4.3.2.5.1. Vegetative Vigor 85
4.3.2.5.2. Seedling Emergence 86
4.3.2.6. Terrestrial Microorganisms 86
4.3.3. Aquatic Organisms 86
4.3.3.1. Fish 86
4.3.3.1.1. Acute Toxicity 86
4.3.3.1.2. Longer-term Toxicity 87
4.3.3.1.2.1. EPA Assessment 87
4.3.3.1.2.2. Acute to Chronic Ratios (ACRs) 88
4.3.3.1.2.3. Daphnid to Minnow Correlations 89
4.3.3.1.2.4. Quantitative Structure Activity Relationships (QSAR) 90
4.3.3.1.2.5. Weight of Evidence Assessment 91
4.3.3.1.2.6. Alternative Dose-Response Assessment 91
4.3.3.2. Amphibians (Aquatic-Phase) 92
4.3.3.3. Aquatic Invertebrates 92
4.3.3.4. Aquatic Plants 93
4.3.3.4.1. Algae 93
4.3.3.4.2. Aquatic Macrophytes 94
4.4. RISK CHARACTERIZATION 95
4.4.1. Overview 95
4.4.2. Terrestrial Organisms 96
4.4.2.1. Mammals 96
4.4.2.2. Birds 97
4.4.2.3. Reptiles and Amphibians (Terrestrial Phase) 98
4.4.2.4. Terrestrial Invertebrates 98
4.4.2.5. Terrestrial Plants 98
4.4.2.5.1. Direct Spray and Spray Drift 98
4.4.2.5.2. Soil Exposures by Runoff 99
4.4.2.5.3. Contaminated Irrigation Water 99
4.4.2.5.4. Wind Erosion 100
4.4.2.6. Terrestrial Microorganisms 100
4.4.3. Aquatic Organisms 100
4.4.3.1. Fish 100

4.4.3.1.1. Acute Exposures 100
4.4.3.1.2. Longer-term Exposures 101
4.4.3.2. Amphibians 102
4.4.3.4. Aquatic Invertebrates 102
4.4.3.4. Aquatic Plants 102
4.4.3.4.1. Algae 102
4.4.3.4.2. Macrophytes 102
5. REFERENCES 104

LIST OF TABLES

Table 1: Key Reviews and Related Documents on Clethodim 125
Table 2: Chemical and Physical Properties of Clethodim and Selected Metabolites 126
Table 3: Clethodim Formulations Listed on Greenbook.net 132
Table 4: Representative Clethodim Formulations 133
Table 5: Disclosed Inerts in Clethodim Formulations 138
Table 6: Toxicity Data on formulations from MSDSs 139
Table 7: Target Species for Clethodim Identified by the Forest Service 140
Table 8: Dermal Absorption of Clethodim by Male Rats 141
Table 9: Excretion of clethodim by rats 142
Table 10: Worker Exposure Rates 143
Table 11: Precipitation, Temperature and Classifications for Standard Test Sites 144
Table 12: Input Parameters for Fields and Waterbodies Used in Gleams-Driver Modeling 145
Table 13: Chemical parameters used in Gleams-Driver modeling 146
Table 14: Summary of Modeled Concentrations in Surface Water 147
Table 15: Concentrations in surface water used in this risk assessment 148
Table 16: Estimated residues in food items per lb a.i. applied 149
Table 17: Summary of toxicity values used in human health risk assessment 150
Table 18: Risk Characterization for Workers 151
Table 19: Risk Characterization for the General Public – One Application 152
Table 20: Risk Characterization for the General Public – Two Applications 153
Table 21: Comparison of Toxicity Values in Mammals 154
Table 22: Terrestrial Nontarget Animals Used in Ecological Risk Assessment 155
Table 23: Diets: Metabolizable Energy of Various Food Commodities 156
Table 24: Summary of toxicity values used in ecological risk assessment 157
Table 25: Acute to Chronic Ratios in Fish 158
Table 26: QSAR Estimates of Toxicity from EPI Suite 159
Table 27: Summary of Weight of Evidence for Chronic NOAEC in Fish 160
Table 28: Summary of Hazard Quotients for Longer-term Exposures of Fish 161

LIST OF FIGURES

Figure 1: Structures of Clethodim and Sethoxydim 162
Figure 2: Lower Bound Estimated Agricultural Use in the United States for 2009 163

Figure 3: Upper Bound Estimated Agricultural Use in the United States for 2009 164
Figure 4: Proposed metabolic pathway for clethodim in rats. 165
Figure 5: Whole body excretion of clethodim by rats 166
Figure 6: Increase in peak residues on vegetation following multiple applications 167

LIST OF APPENDICES

Appendix 1: Toxicity to Mammals. 168
Appendix 2: Toxicity to Birds 180
Appendix 3: Toxicity to Terrestrial Invertebrates. 183
Appendix 4: Toxicity to Terrestrial Plants..... 184
Appendix 5: Toxicity to Fish. 191
Appendix 6: Toxicity to Aquatic Invertebrates 194
Appendix 7: Toxicity to Aquatic Plants..... 197
Appendix 8: Gleams-Driver Modeling, 1 Application 200
Appendix 9: Gleams-Driver Modeling, 2 Applications..... 208
Appendix 10: Gleams-Driver Modeling, 4 Applications..... 216
Appendix 11: Gleams-Driver Modeling, 18 Applications..... 224

LIST OF ATTACHMENTS

Attachment 1: Clethodim, One Applications at 0.25 lb a.i./acre.
Attachment 2: Clethodim, Two Applications at 0.25 lb a.i./acre with a 14-Day Application Interval
Attachment 3: Clethodim, Four Applications at 0.25 lb a.i./acre with 14-Day Application Intervals
Attachment 3: Clethodim, 18 Applications at 0.25 lb a.i./acre with 14-Day Application Intervals

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACCase	acetyl coenzyme-A carboxylase
ACGIH	American Conference of Governmental Industrial Hygienists
ACR	acute to chronic ratios
AEL	adverse-effect level
a.e.	acid equivalent
a.i.	active ingredient
ALS	acetolactate synthase
APHIS	Animal and Plant Health Inspection Service
a.s.	active substance (European literature)
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
COC	crop oil concentrates
DAA	days after application
DAT	days after treatment
DER	data evaluation record
d.f.	degrees of freedom
EC	emulsifiable concentrate
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
HRAC	Herbicide Resistance Action Committee
HTD	highest dose tested
IARC	International Agency for Research on Cancer
IRED	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
m	meter
M	male
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
mPa	millipascal, (0.001 Pa)
MOS	margin of safety
MRID	Master Record Identification Number
MSDS	material safety data sheet
MSO	methylated seed oil
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
NIS	nonionic surfactant
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 Pesticide Planning and Toxic Substances
OSHA	Occupational Safety and Health Administration
Pa	Pascal
PBPK	physiologically-based kinetic
ppm	parts per million
QSAR	Quantitative Structure Activity Relationships
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SDS	Safety Data Sheet
SERA	Syracuse Environmental Research Associates
TEP	typical end-use product
T.G.I.A.	Technical grade active ingredient
TIPA	Triisopropanolamine

TRED	Tolerance Reassessment Eligibility Decision
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
WWSA	Weed Science Society of America

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℃+32
centimeters	inches	0.3937
cubic meters (m^3)	liters (L)	1,000
Fahrenheit	centigrade	0.556℉-17.8
feet per second (ft/sec)	miles/hour (mi/hr)	0.6818
gallons (gal)	liters (L)	3.785
gallons per acre (gal/acre)	liters per hectare (L/ha)	9.34
grams (g)	ounces, (oz)	0.03527
grams (g)	pounds, (oz)	0.002205
hectares (ha)	acres	2.471
inches (in)	centimeters (cm)	2.540
kilograms (kg)	ounces, (oz)	35.274
kilograms (kg)	pounds, (lb)	2.2046
kilograms per hectare (hg/ha)	pounds per acre (lb/acre)	0.892
kilometers (km)	miles (mi)	0.6214
liters (L)	cubic centimeters (cm^3)	1,000
liters (L)	gallons (gal)	0.2642
liters (L)	ounces, fluid (oz)	33.814
miles (mi)	kilometers (km)	1.609
miles per hour (mi/hr)	cm/sec	44.70
milligrams (mg)	ounces (oz)	0.000035
meters (m)	feet	3.281
ounces (oz)	grams (g)	28.3495
ounces per acre (oz/acre)	grams per hectare (g/ha)	70.1
ounces per acre (oz/acre)	kilograms per hectare (kg/ha)	0.0701
ounces fluid	cubic centimeters (cm^3)	29.5735
pounds (lb)	grams (g)	453.6
pounds (lb)	kilograms (kg)	0.4536
pounds per acre (lb/acre)	kilograms per hectare (kg/ha)	1.121
pounds per acre (lb/acre)	mg/square meter (mg/m^2)	112.1
pounds per acre (lb/acre)	µg/square centimeter ($\mu g/cm^2$)	11.21
pounds per gallon (lb/gal)	grams per liter (g/L)	119.8
square centimeters (cm^2)	square inches (in^2)	0.155
square centimeters (cm^2)	square meters (m^2)	0.0001
square meters (m^2)	square centimeters (cm^2)	10,000
yards	meters	0.9144

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

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

This document provides a screening level/scoping risk assessment for human health effects and ecological effects as consequences of using clethodim in Forest Service vegetation management programs. The most relevant literature on clethodim comes from studies submitted to the U.S. EPA in support of the registration of clethodim. Copies of these studies are not publically available and have not been reviewed in the conduct of this risk assessment. Summaries of these studies in the U.S. EPA human health and ecological risk assessments are the primary sources of information used in the current Forest Service risk assessment.

At the central estimates of exposure, there is no basis for asserting that workers would be adversely impacted during applications of clethodim. Workers involved in either ground broadcast or aerial applications do not appear to be at risk even at the upper limits of estimated non-accidental exposures. Workers involved in backpack applications have an HQ of 1.3 based on the upper bound of the prediction interval for estimated exposures. This HQ is not likely to be associated with overt signs of toxicity; however, covert effects (e.g., effects on the liver) cannot be ruled out. For backpack applications the upper bound prediction interval for exposures could be associated with applications in rough terrain or with poor personal hygiene practices during application. The upper bound of the standard accidental exposure scenario for a worker wearing contaminated gloves leads to an HQ of 4. This exposure scenario can be mitigated by washing contaminated hands and promptly replacing contaminated gloves.

For members of the general public, none of the exposure scenarios result in HQs that exceed the level of concern. The highest non-accidental HQs involve the acute consumption of contaminated vegetation which approach but do not exceed the level of concern—i.e., upper bound HQs of 0.3 following one application and 0.4 following two applications.

Clethodim is an effective herbicide for the control of many grass weeds (i.e., monocots of the family Poaceae). Clethodim, however, is relatively nontoxic to dicots and non-Poaceae monocots. Consequently, applications of clethodim do not appear to pose a substantial risk to dicots or non-Poaceae monocots. Risks to sensitive nontarget monocots (true grasses) could occur due to drift, runoff, or the use of contaminated surface water for irrigation. The risks to sensitive nontarget plants from the wind erosion of contaminated soil appear to be low. Risks to sensitive species of monocots will be highly dependent on site-specific conditions as well as specific application methods. In directed foliar applications, the potential for damage to nontarget plants species appears to be low. Risks to sensitive species of monocots could be substantial, however, from drift following aerial applications and/or in applications at sites with high runoff potential (i.e., high rates of rainfall and clay soils).

While risks to grasses are to be expected given the labelled uses of clethodim (i.e., the control of grasses), the limited data also suggest that longer-term exposures associated with applications of clethodim may adversely impact sensitive species of fish. Confidence in the risk characterization for longer-term exposures of fish to clethodim is low, however, due to limitations in the toxicity data. Confidence in the risk characterization for fish would be enhanced substantially by a confirming early life stage study in fathead minnows and by early life stage studies in other

potentially more sensitive species of fish such as trout. Risks to other groups of aquatic organisms appear to be minimal.

For terrestrial animals, risks to mammals can be well characterized but it is more difficult to characterize risks to other groups of terrestrial animals because of limitations in the available data on birds and terrestrial insects as well as the lack of toxicity data on amphibians and reptiles. Some acute exposure scenarios for a small (20 g) mammal modestly exceed the level of concern at the upper bound of plausible exposures but serious effects on mammals do not seem likely. Similarly, the potential for direct effects on birds associated with acute exposures appears to be low. Longer-term exposures for a small (10 g) bird, however, exceed the level of concern by factors of about 2 to 4 for two applications of clethodim. While the magnitude of these HQs is not substantial, serious adverse effects on the offspring of birds (i.e., mortality and decreased hatching) cannot be ruled out.

This risk assessment focuses on the potential for direct toxic effects associated with applications of clethodim. Nonetheless, there is a potential for secondary effects in virtually all groups of nontarget organisms. Terrestrial applications of any effective herbicide, including clethodim, are likely to alter vegetation within the treatment area. This alteration could have secondary effects on terrestrial or aquatic animals, including changes in food availability and habitat quality. These secondary effects may be beneficial to some species and detrimental to others; moreover, the magnitude of secondary effects is likely to vary over time. While these concerns are acknowledged, they are not specific to clethodim or herbicide applications in general. Any effective method for vegetation management, including mechanical methods which do not involve clethodim or any other herbicide, could be associated with secondary effects on both nontarget animals and vegetation.

Another limitation with the risk assessment on clethodim involves the small number of species on which toxicity data are available relative to the large number of species that may be exposed during and following applications of clethodim. While this limitation is common to virtually all ecological risk assessments, concern with this limitation is exacerbated by the lack of field studies relevant to the assessment of the effects of clethodim applications on most groups of nontarget species with the notable exception of terrestrial plants.

1. INTRODUCTION

1.1. Chemical Specific Information

This document provides a screening level/scoping risk assessment for human health effects and ecological effects as consequences of using clethodim in Forest Service vegetation management programs.

The open literature on clethodim covered in the current risk assessment is modest and primarily focused on efficacy studies (Appendix 4, Table A4-4). Most of the studies on other groups of organisms that are used quantitatively in this risk assessment are studies submitted by the registrants to the U.S. EPA in support of the registration of clethodim.

The registrant studies are classified as Confidential Business Information (CBI) and are not publically available. Consequently, the Forest Service elected to conduct a screening level/scoping risk assessment rather than a full risk assessment on clethodim. In contrast to full risk assessments, scoping/screening level risk assessments are designed to determine if there are adequate data on which to base full risk assessment (scoping effort), and, if possible, to give the Forest Service an indication of the most likely risks associated with the use of the pesticide under consideration (screening effort). The most significant differences between scoping/screening level and full Forest Service risk assessments is that scoping/screening level risk assessments rely more on secondary sources rather than the primary studies (most of which are not available for clethodim). Notwithstanding this limitation, the Forest Service has elected to have the current risk assessment subject to a standard external peer-review. Based on the outcome of the current scoping/screening level risk assessment, the Forest Service may elect to have a more detailed and elaborated risk assessment prepared if primary studies are available in the future.

The key reviews on the toxicity and environmental fate of clethodim are summarized in Table 1. Clethodim is currently under registration review by the U.S. EPA/OPP. The U.S. EPA registration review program operates on a 15-year cycle. The most recent human health risk assessment (U.S. EPA/OPP/HED 2014a) and the most recent ecological risk assessments (U.S. EPA/OPP/EFED 2014a) are both preliminary risk assessments associated with the registration review of clethodim. While the registration review of clethodim had been scheduled for completion in June 2014 (U.S. EPA/OPP 2009a), the chemical review manager for clethodim at the U.S. EPA/OPP has indicated that the final registration review will not be completed until March 2015 (Jones 2014a,c). While the Forest Service has elected to complete the current risk assessment, individuals using this risk assessment after March 2015 may wish to consult the U.S. EPA/OPP's final registration review documents for clethodim.

The recent preliminary risk assessments on clethodim in support of the registration review of clethodim (U.S. EPA/OPP/HED 2014a; U.S. EPA/OPP/EFED 2014a) are key sources of information in the current Forest Service risk assessment. The recent risk assessment by U.S. EPA/OPP/HED (2014a) contains reevaluations of several registrant studies which differ from evaluations given in previous risk assessments. The study reevaluations (U.S. EPA/OPP/HED 2010c, 2013b) are well-documented and were reviewed in the conduct of the current Forest Service risk assessment. In addition to the reevaluations, the 2014 risk assessments by EPA also contain summaries of new studies not summarized in previous EPA risk assessments.

Other detailed and well-documented reviews on clethodim prepared by U.S. EPA's Office of Pesticide Programs (U.S. EPA/OPP) include several human health risk assessments prepared by the Health Effects Division (U.S. EPA/OPP/HED 2008a, 2010a) and the ecological risk assessments prepared by Environmental Fate and Effects Division (U.S. EPA/OPP/EFED 2007a,b). These earlier risk assessments are specifically cited in the current Forest Service risk assessment because some of the earlier risk assessments contain details not included in the more recent preliminary risk assessments in support of the registration review of clethodim. Nonetheless, interpretations of studies contained in the most recent risk assessments on clethodim in support of the registration review of clethodim (U.S. EPA/OPP/HED 2014a; U.S. EPA/OPP/EFED 2014a) are given precedence over earlier reviews by the EPA. This approach is taken because it is not uncommon for the EPA to reevaluate studies over time as risk assessment methods and practices evolve. Unless there is a compelling reason to do otherwise, Forest Service risk assessments defer to the most recent assessments by the U.S. EPA. This deference is justified because, as noted above and discussed further in Section 1.2, the U.S. EPA/OPP has unrestricted access to all studies submitted by registrants in support of pesticide registrations and the U.S. EPA/OPP has a detailed program for evaluating and classifying these studies. Notwithstanding these considerations, several requests were made to the U.S. EPA/OPP to obtain additional documentation for some of the reevaluations given in U.S. EPA/OPP/HED (2014a) and this information was kindly supplied by Ricardo Jones, Chemical Review Manager for clethodim at U.S. EPA/OPP (i.e., Jones 2014a,b,c). This additional documentation is specified in the reference list (Section 5) with the code "EPARegRv".

In addition to the U.S. EPA/OPP reviews and risk assessments, there are numerous cleared reviews (a.k.a. Data Evaluation Records or DERs) listed at the following EPA web site: http://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:7:9096134567529::NO:1,3,31,7,12,25:P3_XCHEMICAL_ID:1847. These cleared reviews are used to expand the discussion of key registrant-submitted studies. The general utility of DERs is discussed further in Section 1.2. As a convention, registrant submitted studies are cited using standard author/date designations if DERs were used as the basis of the discussion in the current risk assessment. The MRID designation is used for a registrant submitted study if the summary of the study is based solely on an EPA risk assessment. In these cases, the EPA document as well as the MRID designation is given in the discussion of the study.

Several other reviews and/or sources of secondary information have also been consulted in the preparation of the current risk assessment (CalEPA 2010; EPI-Suite 2011; European Commission 2011; EXTOXNET 1995; FAO-IAEA 2013; HSDB 2012; Kegley et al. 2010; MAFF Canada 2004; PPDB/UK 2012; Tomlin 2004; DOE 2006; U.S. EPA/OPP 2012b; U.S. EPA/OPP/EFED 1990, 2006a. 2009a; U.S. EPA/OPP/HED 2001). Many of the other reviews are not detailed and do not provide full citations to the registrant studies on which they are based (e.g., ESFA 2011; FAO-IAEA 2013; HSDB 2012).

Two documents from the World Health Organization (WHO), FAO/WHO 1994 and IPCS 1994 provide detailed summaries of some registrant-submitted studies, but do not provide detailed citations to the original studies. In cases where the WHO summaries can be clearly linked to registrant studies on clethodim, these summaries (FAO/WHO 1994; IPCS (1994) are used to

elaborate on the discussion of the relevant studies. A more recent review available from European Food Safety Authority (ESFA 2011) is also used to elaborate on the discussion of studies summarized by U.S. EPA/OPP.

Some of the WHO and other European reviews summarize studies that are not in U.S. EPA/OPP documents. This occurs because some European countries require studies that are not required by the U.S. EPA. In these cases, the additional studies are summarized as fully as possible in the current risk assessment and are referenced directly to the WHO and other European reviews from which the study summaries are taken.

Some information discussed in this risk assessment is taken from Material Safety Data Sheets (MSDSs) which provide brief summaries of the composition and toxicity of pesticide formulations. Effective June 1, 2015, OSHA will require a reformatting of MSDSs and these reformatted MSDSs will be referenced as Safety Data Sheets (https://www.osha.gov/Publications/HazComm_QuickCard_SafetyData.html ; https://www.osha.gov/Publications/OSHA3514.html). For the current risk assessments, all data sheets cited are specifically labelled as Material Safety Data Sheets (MSDSs) rather than Safety Data Sheets (SDSs). Consequently, the term *MSDS* rather than *SDS* is used throughout this risk assessment.

1.2. General Information

As noted in Section 1.1, the risk assessment on clethodim is based largely on studies submitted by registrants in support of the registration of clethodim. In any risk assessment based largely on registrant-submitted studies, as is the case with clethodim, the Forest Service is sensitive to concerns of potential bias. The general concern might 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. While any study (published or unpublished) can be falsified, concerns with the design, conduct and reporting of studies submitted to the U.S. EPA for pesticide registration are minor. The design of the studies submitted for pesticide registration is based on strict guidelines for both the conduct and reporting of studies. These guidelines are developed by the U.S. EPA and not by the registrants. Full copies of the guidelines for these studies are available at http://www.epa.gov/ocspp/pubs/frs/home/guidelin.htm. Virtually all studies accepted by the U.S. EPA/OPP are conducted under Good Laboratory Practices (GLPs). GLPs are an elaborate set of procedures which involve documentation and independent quality control and quality assurance that substantially exceed the levels typically seen in open literature publications. As a final point, the EPA reviews each submitted study for adherence to the relevant study guidelines. These reviews most often take the form of Data Evaluation Records (DERs). While the nature and complexity of DERs varies according to the nature and complexity of the particular studies, each DER involves an independent assessment of the study to ensure that the EPA Guidelines are followed and that the results are expressed accurately. In many instances, the U.S. EPA/OPP will reanalyze raw data from the study as a check or elaboration of data analyses presented in the study. In addition, each DER undergoes internal review (and sometimes several layers of review). The DERs prepared by the U.S. EPA form the

basis of EPA risk assessments and, when available, DERs are used in Forest Service risk assessments.

Despite the real and legitimate concerns with risk assessments based largely on registrant-submitted studies, data quality and data integrity are not substantial concerns. The major limitation of risk assessments based solely on registrant-submitted studies involves the nature and diversity of the available studies. The studies required by the U.S. EPA are based on a relatively narrow set of criteria in a relatively small subset of species and follow standardized protocols. The relevance of this limitation to the current risk assessment on clethodim is noted in various parts of this risk assessment as appropriate.

This document has 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, an assessment of potential exposure to this compound, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure.

This is a technical support document which addresses some specialized technical areas. Nevertheless 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 2014a). The human health and ecological risk assessments presented in this document are not, and are not intended to be, comprehensive summaries of all of the available information. The information presented in the appendices and the discussions in chapters 2, 3, and 4 of the risk assessment are intended to be detailed enough to support a review of the risk analyses.

As discussed in Section 1.1, the Forest Service may update and/or expand this risk assessment and welcomes input from the general public and other interested parties on the selection of studies included in the risk assessment. This input is helpful, however, only if recommendations for including additional studies specify why and/or how the new or not previously included information would be likely to alter the conclusions reached in the risk assessments.

As with all Forest Service risk assessments, 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 which are relatively simple. Simple calculations are included in the body of the document [typically in brackets]. The results of some calculations within brackets may contain an inordinate number of significant figures in the interest of transparency – i.e., to allow readers to reproduce and check the calculations. In all cases, these numbers are not used directly but are rounded to the number of significant figures (typically two or three) that can be justified by the data.

Some of the calculations, however, are cumbersome. For those calculations, EXCEL workbooks (i.e., sets of EXCEL worksheets) are included as attachments to this risk assessment. The workbooks included with the current risk assessment are discussed in Section 2.4. The worksheets in these workbooks provide the detail for the estimates cited in the body of the document. Documentation for the use of these workbooks is presented in SERA (2011a).

The EXCEL workbooks are integral parts of the risk assessment. The worksheets contained in these workbooks are designed to isolate the numerous calculations from the risk assessment narrative. In general, all calculations of exposure scenarios and quantitative risk characterizations are derived and contained in the worksheets. In these worksheets as well as in the text of this risk assessment, the hazard quotient is the ratio of the estimated exposure to a toxicity value, typically a no adverse effect level or concentration (i.e., NOAEL or NOAEC). Both the rationale for the calculations and the interpretation of the hazard quotients are contained in this risk assessment document.

2. PROGRAMS DESCRIPTION

2.1. Overview

Clethodim is a selective postemergence herbicide used for the control of annual or perennial grass weeds. Formulations of clethodim are not specifically labeled for applications to forests but are used in forestry related applications including the control of grasses in tree farms, conifer nurseries, and conifer plantations as well as applications to rights-of-way, utility lines, fence lines, and several other non-crop sites.

Clethodim was developed in the late 1980's and is currently off patent, which means the formulations of clethodim are quite numerous. The formulations likely to be used in forestry related applications are liquids containing either 12.6% (≈1 lb a.i./gallon) or 26.4% a.i. (≈2 lbs a.i./gallon). All formulations of clethodim explicitly covered in this risk assessment contain petroleum solvents. The potential impact of these inert components on this risk assessment is discussed further in Section 3.1.14 (human health) and Section 4.1 (ecological effects).

All indications from the Forest Service are that the most common method of application for clethodim will involve either directed foliar or ground broadcast foliar applications. Clethodim is also labeled for aerial applications, which are considered in this risk assessment. Clethodim is labeled for single application rates of about 0.1 to 0.25 lb a.i./acre. Based on current product labels, the maximum seasonal application rate for clethodim is 0.5 lb a.i./acre with a minimum application interval of 14 days.

Based on the recent preliminary risk assessments from EPA supporting the registration review of clethodim (Table 1), the maximum seasonal application rate for clethodim is being increased to 4.5 lbs a.i./acre (e.g., 18 applications at a maximum single application rate of 0.25 lb a.i./acre). The Forest Service has indicated that the maximum cumulative application rate that would be used in most Forest Service programs is 0.5 lb a.i./acre – i.e., two applications at 0.25 lb a.i./acre per application. A greater number of applications in Forest Service programs appears to be extremely unlikely.

Typically, the Forest Service would use only one or two applications of clethodim. A single application at the rate of 0.25 lb a.i./acre and two applications with a 14-day application interval at an application rate of 0.25 lb a.i./acre are considered in Attachment 1 and Attachment 2, respectively. Attachment 3 considers four applications at an application rate of 0.25 lb a.i./acre per application with 14-day application intervals. Four applications are not likely to be used in Forest Service programs but are considered to encompass rare circumstances which might occur.

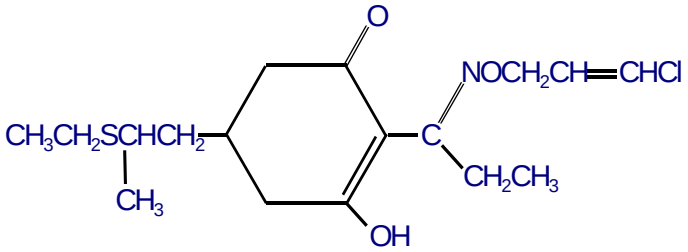
An additional set of exposure scenarios covering 18 applications are detailed in Attachment 4. The Forest Service does not anticipate using 18 applications. Risks associated with 18 applications are not discussed in detail but are included merely to illustrate patterns in the relationship of potential exposures to the number of applications, as discussed further in Section 3.2).

Because clethodim has not been used extensively by the Forest Service, the impact of the Forest Service use of clethodim relative to agricultural use cannot be directly assessed. Based on use

statistics from California, however, it appears that agricultural uses of clethodim are much greater than uses in applications related to forestry.

2.2. Chemical Description and Commercial Formulations

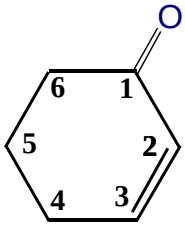
Clethodim is the common name for 2-(1-(((3-chloro-2-propenyl)oxy)imino)propyl)-5-(2-(ethylthio)propyl)-3-hydroxy-2-cyclohexen-1-one:



Selected chemical and physical properties of clethodim are summarized in Table 2.

Clethodim is a member of the cyclohexanedione/cyclohexene oxime herbicides, which include sethoxydim. The Forest Service has a full risk assessment on sethoxydim (SERA 2001). Other cyclohexanedione/cyclohexene oxime herbicides include alloxydim, butroxydim, cloproxydim, cycloxydim, profoxydim, tepraloxydim, and tralkoxydim (Mallory-Smith and Retzinger 2003; Wood 2013).

As illustrated in Figure 1, clethodim and sethoxydim differ only in the groups attached to the 2-carbon of the cyclohexen-1-one ring.



Clethodim and other similar cyclohexanedione herbicides are classified as selective herbicides for the post-emergent control of annual and perennial grasses (e.g., U.S. EPA/OPP/HED 2001, 2014a; Valent 2010a). Clethodim, other cyclohexanedione herbicides, and aryloxyphenoxy propionate herbicides are phytotoxic through the inhibition of acetyl coenzyme-A carboxylase (ACCase) activity (Mallory-Smith and Retzinger 2003). The phytotoxicity of clethodim is discussed further in Section 4.1.2.5.

The herbicidal properties of clethodim were first reported in 1987 (Kincade et al. 1987), and the original patent in Great Britain (GB 2090246) appears to have been issued to Chevron (Tomlin 2004). Based on Valent product labels for the Prism® and Envoy® formulations of clethodim, Valent Professional Products, a subsidiary of the Valent Biosciences Corporation has held the patent for clethodim in the United States—i.e., U.S. Pat. No. 4,440,566, RE - 32,489. The U.S. patent for clethodim, however, has expired (Zollinger and Howatt 2005, p. 74). As discussed below, several formulations of clethodim are available from suppliers other than Valent Professional Products.

As indicated by the (±) designation in the IUPAC and CAS names for clethodim, the current commercial formulations of clethodim are racemic mixtures enantiomers. Enantiomers are compounds that rotate polarized light. If enantiomers rotate light to the right, they are designated as (+), *dextro*, or (R) enantiomers, and if they rotate light to the left, they are designated as (-), *levo*, or (S) enantiomers. Albeit somewhat peripheral to the current risk assessment, technical grade clethodim used in commercial formulations appears to consist of a racemic mixture of both (-) clethodim and (+) clethodim enantiomers. Valent U.S.A. corporation has applied for a patent for optically pure (-) clethodim (U.S. Patent Application Number EP20010952398). Optically pure (-) clethodim is presumably more active than the mixture of (-) clethodim and (+) clethodim enantiomers. References to commercially available formulations of pure (-) clethodim were not encountered in the preparation of the current risk assessment, and the stereoisomers of clethodim are not discussed in a U.S. EPA/OPP analytical chemistry chapter on clethodim (U.S. EPA/OPP/HED 2010b) or the U.S. EPA/OPP risk assessments on clethodim listed in Section 5 and summarized in Table 1.

Formulations of clethodim listed at www.greenbook.net are summarized in Table 3, which lists the name of the formulation, the supplier, and the U.S. EPA registration number of the formulation. Typically, the registration number has two components, the company code and the formulation code, which are separated by hyphens. For example, the EPA registration number for Envoy Plus, a Valent formulation, is 59639-132, with 59639 as the company code for Valent and 132 the product code for Envoy Plus.

Some formulations have product codes that consist of three elements. These are repackaging formulation codes and indicate that the formulation is produced by one company and then repackaged and sold by another—i.e., a supplemental distributor (U.S. EPA/OPP 2010d, p. 3-7). For example, the EPA registration number for Select 2 EC is 59639-3 indicating that Valent is the formulator and supplier of this product for which the product code is 3. Identical but repackaged formulations are supplied by WinField (company code 1381) sold as Select (EPA code 59639-3-1381) and Tenkoz (company code 55467) sold as Volunteer or Volunteer CA, both of which are designated by EPA code 59639-3-55467.

The U.S. EPA/OPP formulation registration number is intended to be unique to the formulation and the supplier. Nevertheless, some formulations have identical registration numbers, as summarized in Table 3. For example, the Valent formulations of Envoy Plus and Select Max are both assigned Registration Number 59639-132 by U.S. EPA/OPP. Similarly, four formulations named Shadow are provided by three different suppliers (Arysta LifeScinece, Micro Flow, and Arvesta), but have the same registration number (66330-353). These formulations appear to be examples of "Me-Too Registrations" which indicate that the formulations are functionally identical. As detailed in the U.S. EPA label review manual, "Me-Too" registrations are only granted if the formulations are …*identical or substantially similar to a currently registered pesticide or may differ only in ways that would not significantly increase the risk of unreasonable adverse effects on the environment* (U.S. EPA/OPP 2010d, p. 4 7). Thus, while Table 3 lists 29 different formulations of clethodim, several of these formulations appear to be either identical or nearly so.

In addition to www.greenbook.net, there are many sources of information on pesticides formulations—e.g., http://iaspub.epa.gov, http://www.cdms.net/LabelsMsds, and http://www.cdpr.ca.gov/docs/label/. As discussed above, the patent for clethodim is expired; hence, there are numerous formulations of clethodim cited in the literature (e.g., HSDB 2012 and Kegley et al. 2010). As reviewed by U.S. EPA/OPP/HED (2014a, p. 10), current formulations of clethodim contain 12.4% a.i. to 36.7% a.i. as either suspension concentrates or emulsifiable concentrates. A complete listing of all formulations of clethodim currently registered by the EPA is given in Appendix 1 of U.S. EPA/OPP/HED (2014a). It is beyond the scope of the current Forest Service risk assessment to cover all commercially available formulations of clethodim, which would serve little purpose anyway, since pesticide formulations are constantly being developed and/or changed, particularly those that are off patent.

The formulations most likely to be used in Forest Service vegetation management programs are listed at www.greenbook.net. These formulations (n=10) are indicated by bold font in Table 3 and additional details on these formulations are given in Table 4. An additional formulation, Tapout, supplied by Helena, is added to Tables 3 and 4 at the request of Forest Service Region 5 (Bakke 2013).

As summarized in Table 4, no formulations of clethodim are labeled for applications directly to forests. The application sites that appear to be most relevant to forestry programs include the control of grasses in tree farms, conifer nurseries, and conifer plantations as well as applications to rights-of-way. All of the formulations are liquids which contains either 12.6% clethodim (≈1 lb/gallon w/w) or 26.4% clethodim (≈2 lbs/gallon).

Differences among pesticide formulations are important to risk assessments as they may relate to the use of inerts. Based on information on the MSDSs, none of the formulations of clethodim appears to be substantially different from the others based on the densities (0.93-0.98 g/mL) and pH (3.6 to 4.5) of the formulations. Some MSDSs report densities and pH as ranges, presumably reflecting batch-to-batch variability, and these ranges encompass most of the values for other formulations reported as single values. Furthermore, density and pH, which may vary according to the temperature and dilution of the formulation, are not specified on most MSDSs. Thus, except for differences in the percent active ingredient (a.i.), differences among clethodim formulations do not appear to be remarkable.

As discussed further in Section 3.1.14, pesticide formulations contain other ingredients, sometimes referred to as *inerts*, and the identity of the other ingredients is typically classified as proprietary or Confidential Business Information (CBI). U.S. EPA/OPP (2010d, p. 5-14) encourages but does not require the disclosure of most inerts on product labels. One exception, however, involves petroleum distillates, xylene or xylene range aromatic solvents at ≥10% (U.S. EPA/OPP 2010d, p. 5-7), which must be specified on product label. As detailed in Table 5, formulations of clethodim explicitly covered in this risk assessment (Table 4) contain other ingredients that are specified as petroleum distillates, hydrocarbons, aromatic hydrocarbons, and/or xylene range aromatic solvents and these inert ingredients are typically listed on the MSDS for the formulation. One exception is Tapout (Helena). Although petroleum distillates are not present on the MSDS for Tapout, they are clearly indicated on the product label, as required.

As summarized in Table 4 and discussed further in Section 2.4, all formulations of clethodim explicitly covered in this risk assessment also recommended adjuvants, specifically crop seed oils with emulsifiers, methylated seed oils, and/or nonionic surfactants. The impact of inerts and adjuvants on the human health risk assessment is addressed specifically in Section 3.1.14 and data on the impact of inerts and adjuvants on the ecological risk assessment are addressed in Section 4.1 as the available data warrant.

The list of formulations in Table 4 is not intended to be exclusive. Other formulations of clethodim are available commercially, and new formulations of clethodim may become available at some point in the future. The Forest Service may elect to use any formulation of clethodim registered for applications relevant to forestry. If other formulations are used in Forest Service programs attempts should be made to identify information on the inerts in the formulations as well as the toxicity of the formulations to ensure that the formulation under consideration is comparable to the formulations explicitly designated in Table 4. MSDSs for formulations will contain some information on the toxicity of the formulation and/or ingredients in the formulation. Table 6 provides a summary of this information for the formulations explicitly considered in the current risk assessment (i.e., those formulations listed in Table 4). This information is discussed further by topic in Section 3.1, the hazard identification for human health effects.

The U.S. EPA sometimes issues Special Local Need registrations and labels. As the name implies, these labels are typically issued to address specific pests and/or application methods not covered by standard labels in cases required to meet issues in specific geographic areas (e.g., CDPR 2011). The U.S. EPA/OPP (2014a) has filed a notice indicating voluntary recalls of Special Local Need registrations for several formulations of clethodim. None of these formulations, however, include the clethodim formulations likely to be used in Forest Service programs (Table 4).

2.3. Application Methods

Forest Service Region 5 (California and Hawaii) indicated that clethodim is most likely to be applied along roadsides, power lines, pipelines, rights-of-way, and other disturbance areas that are being restored back to chaparral (VinZant 2013). The target species identified by the Forest Service are summarized in Table 7.

The clethodim formulations listed in Table 4 may be applied by ground or aerial broadcast or by directed foliar application (e.g., spot treatments). Region 5 of the Forest Service indicated that clethodim will be most commonly applied by backpack spray (directed foliar) or off-highway vehicle tank spray (ground broadcast) (VinZant 2013).

As with sethoxydim, formulations of clethodim are labeled for aerial applications. For the risk assessment on sethoxydim, the Forest Service indicated that aerial applications would not be used (SERA 2001, Section 2.3). For clethodim, however, aerial applications are being considered (Bakke 2013) and aerial applications are specifically considered in the current risk assessment.

Different application methods involve different estimates of the amount of herbicide used by workers in a single day based on the number of acres treated per day and the application rate. Application rates are discussed in Section 2.4, and assumptions about the number of acres treated by a worker in a single day are discussed further in Section 3.2.2 (worker exposure assessments).

2.4. Mixing and Application Rates

As summarized in Table 4, the recommended labeled rates for formulations of clethodim in single applications relevant to Forest Service activities range from about 0.1 to 0.25 lb a.i./acre. Based on current product labels, the maximum seasonal application rate—i.e., the total cumulative application rate for a given year—for all formulations is 0.5 lb a.i./acre. Based on the recent preliminary risk assessments supporting the registration review of clethodim (U.S. EPA/OPP/HED 2014a; U.S. EPA/OPP/EFED 2014a), the maximum seasonal application rate for clethodim is being increased to 4.5 lbs a.i./acre (e.g., 18 applications at a maximum single application rate of 0.25 lb a.i./acre).

A representative of Region 6 of the Forest Service (i.e., Pacific Northwest) has indicated that the maximum cumulative application rate that would be used in Forest Service programs would rarely exceed 0.5 lb a.i./acre – i.e., two applications are a rate of 0.25 lb a.i./acre (Bautista 2014). Comments from Region 5 of the Forest Service (Pacific Southwest) indicate that multiple applications (not otherwise specified) would be typical for the control of invasive plants including invasive grasses (Bakke 2013; VinZant 2013).

The current Forest Service risk assessment on clethodim focuses on both a single application at the rate of 0.25 lb a.i./acre and two applications at this rate with a 14-day application interval, the latter meeting but not exceeding the current maximum labeled rate and the maximum seasonal rate. These exposure scenarios are detailed in EXCEL workbooks—i.e., Attachment 1 for the single application and Attachment 2 for two applications. To accommodate the potential for a greater number of applications, exposure scenarios for 4 applications at 0.25 lb a.i./acre with 14-day application intervals are considered in Attachment 3. Lastly, 18 applications at 0.25 lb a.i./acre with 14-day application intervals are considered in Attachment 4. Attachment 4 is not discussed extensively in the current Forest Service risk assessment because 18 applications would not be used in Forest Service programs. The scenarios involving 18 applications are included only to illustrate the relationships between potential risk and the number of applications over the spectrum of the number of applications considered in the most recent EPA risk assessments (U.S. EPA/OPP/HED 2014a; U.S. EPA/OPP/EFED 2014a).

Several formulations of clethodim listed in Table 4 are registered for application to food crops. For various food crops, applications intervals of 14 days are recommended. Application intervals for conifers are not specified on the product labels for the formulations listed in Table 4. The product label for Envoy Plus does recommend an application interval of 14 days for non-crop areas and ornamentals, and the product label for Intensity One indicates that the maximum seasonal application rate does specifically apply to conifers. As noted above, however, it appears that the maximum seasonal application rate for clethodim is being increased and this increase will likely be reflected in new product labels once the registration review of clethodim is completed.

In addition to application rates, application volumes, meaning the number of gallons of pesticide solution applied per acre, have an impact on the estimates of potential risk. The extent to which a formulation of clethodim is diluted prior to application primarily influences dermal and direct spray scenarios, both of which depend on 'field dilution' (i.e., the concentration of clethodim in the applied spray). In all cases, the higher the herbicide concentration (i.e., equivalent to the lower dilution of the herbicide), the greater is the risk. As summarized in Table 4, the recommended application volumes for clethodim formulations range from 5 to 40 gallon/s acre for ground applications and 3 to 10 gallons per acre for aerial applications.

In the EXCEL workbooks that accompany this risk assessment, the range of application volumes is taken as 3 to 40 gallons per acre to encompass the application volumes that could be used in both aerial and ground applications – i.e., 3 gallons per acre is the lower bound for aerial applications and 40 gallons per acre is the upper bound for ground applications (Table 4). The central estimate of the application volume is taken as 10 gallons/acre, the maximum application volume for aerial applications and close to the geometric mean of the range of application volumes [$(3 \times 40)^{0.5} \approx 10.95$]. The dilution volumes used in the workbooks are intended only to encompass the ranges of the clethodim concentration in field solutions likely to be used in Forest Service programs.

The selection of application rates and dilution volumes in this risk assessment is intended to reflect plausible estimates of potential exposures. In the assessment of specific program activities, the application rates and volumes can be changed in Worksheet A01 of the EXCEL workbooks to reflect the rates and volumes that are actually used.

As indicated in Table 4, the product labels for clethodim formulations explicitly covered in this risk assessment recommend the use of crop oil concentrates, methylated seed oil, or nonionic surfactants. The impact of the use of these adjuvants on the current risk assessment is discussed further in Section 3.1.14.2 with respect to the human health risk assessment and Section 4.1.3.5 with respect to the ecological risk assessment.

2.5. Use Statistics

Forest Service risk assessments attempt to characterize the use of an herbicide or other pesticide in Forest Service programs relative to the use of the herbicide or other pesticide in agricultural applications. Forest Service pesticide use reports up to the year 2004 are available on the Forest Service web site (http://www.fs.fed.us/ foresthealth/pesticide/reports.shtml). This dated information is not clearly relevant to the current use of pesticides by the Forest Service. A query of the Forest Service's ACtivity Tracking System (FACTS) – i.e., a more current database on pesticide use in Forest Service programs – indicates that 22.28 lbs. a.i. of clethodim has been used by the Forest Service between 2000 and 2013 (Lake 2013). Most of this use – i.e., 18.24 lbs a.i. – occurred in Forest Service Region 9 (Eastern Region) with the remainder used in Region 8 (Southern Region).

Information on the agricultural use of pesticides is compiled by the U.S. Geological Survey (USGS) (http://water.usgs.gov/nawqa/pnsp/usage/maps/). The agricultural use of clethodim in 2009 (the most recent year for which data are available) is estimated by the USGS (2013) to range from about 600,000 lbs (Figure 2) to about 900,000 lbs (Figure 3). The greatest use of clethodim is in the north central to central United States (North Dakota, Minnesota, Iowa,

Illinois, Indiana, and Ohio) as well as parts of California. Based on use data by crop (also summarized in Figure 2 and Figure 3), clethodim is most commonly used on soybeans. A recent ecological risk assessment from U.S. EPA/OPP/EFED (2014a, p. 12) estimates a somewhat lower annual use of 400,000 lbs than that given by the USGS (2013).

Detailed pesticide use statistics are compiled by the state of California. The use statistics from California for 2011, the most recent year for which statistics are available, indicate that a total of about 59,924 pounds of clethodim were used in California (CDPR 2013, p. 233). The major use relevant to Forest Service programs appears to be rights-of-way management (about 1573 lbs or 2.6% of total use in California). Application to alfalfa is the major use of clethodim in California (i.e., 39,385 lbs or about 65% of total use in California). Based on these use statistics from California, it appears that agricultural uses of clethodim are much greater than forestry related uses.

As discussed further in Section 3.2.3.6 (Oral Exposure from Contaminated Vegetation), crop treatments may be conducted on some Forest Service lands by individuals or organizations with authorization from the Forest Service to use Forest Service lands for the cultivation of crops. In terms of use statistics, agricultural applications are not considered as forestry applications.

3. HUMAN HEALTH

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

Based on acute assays for systemic toxicity, clethodim is relatively nontoxic. The U.S. EPA uses a classification system for acute responses ranging from Category I (most severe response) to Category IV (least severe response). Clethodim is classified as Category III to Category IV for acute oral (Category III), acute dermal (Category IV), and inhalation exposures (Category IV). Clethodim may cause moderate skin irritation (Category III) and mild eye irritation (Category III).

Subchronic and chronic toxicity studies are available in dogs, mice, and rats. The duration of exposure ranges from 4 weeks to 90 days in subchronic studies and 1 to 2 years in chronic studies. The most common signs of toxicity in the subchronic and chronic studies are decreases in body weight or body weight gain and increases in relative or absolute liver weights. There are, however, no reports of liver necrosis (i.e., cell death) associated with clethodim exposure.

Clethodim has not been specifically tested for effects on endocrine function, although these tests are now being required by the U.S. EPA. Clethodim has been assayed specifically for effects on the nervous system and immune system and there is no evidence that clethodim causes adverse effects on these systems. Clethodim has been adequately tested for carcinogenicity, reproductive effects, and developmental effects and no adverse effects have been noted.

Clethodim formulations contain petroleum solvents that include naphthalene. The primary effects of naphthalene and petroleum solvents involve CNS depression or other signs of neurotoxicity. While clethodim is rapidly degraded in the environment, some of the degradation products are much more persistent than the parent compound; accordingly, this pattern is considered quantitatively in the risk assessment.

3.1.2. Mechanism of Action

The mechanism of action of clethodim in mammals has not been identified (U.S. EPA/OPP/HED 2014a, p. 8). As discussed further in Section 3.4.6 (Cumulative Effects), the U.S. EPA/OPP had not made a determination on a common mechanism of action for clethodim with other pesticides.

As noted in Section 2.2 and as discussed further in Section 4.1.2.5 (hazard identification for terrestrial plants), the phytotoxicity of clethodim is based on the inhibition of acetyl coenzyme-A carboxylase (ACCase) activity. ACCase occurs in mammals, plants, bacteria, yeast, and fungi (More et al. 2012; Tong 2005). Deficiencies in ACCase in mammals have been associated with decreased body weight and reduced body fat. ACCase enzymes in mammals, however, are substantially different from ACCase enzymes in plants (Gronwald 1991; Tong 2005).

As discussed in several sections below, decreases in body weight or body weight gain are noted in many toxicity studies on clethodim (e.g., U.S. EPA/OPP/HED 1990, 2010a, p. 6 and Table A.2; U.S. EPA/OPP/HED 2014a, p. 4). Decreases in body weight or body weight gain are common signs of toxicity observed in pesticide exposure studies. As discussed further in the Section 3.1.5, a decrease in food conversion efficiency—i.e., decreased weight gain that is

greater than would be expected based on the level of food consumption—has been noted in male but not female rats in a chronic feeding study (i.e., MRID 410301-21). Decreases in food conversion efficiency, however, have not been noted in chronic studies in female rats, mice, or dogs. In addition, decreases in food conversion efficiency have not been reported in subchronic studies in rats, mice, or dogs.

As reviewed by Tong (2005), ACCase is a key enzyme in fatty acid metabolism and catalyzes the carboxylation of acetyl-CoA to produce malonyl-CoA. Consequently, compounds which inhibit mammalian ACCase are potentially useful drugs to control obesity. There are, however, no studies available on the inhibition of mammalian ACCase by clethodim. While weight loss and decreases in body weight gain are frequently noted in toxicity studies with clethodim, there is no information linking these effects to the inhibition of mammalian ACCase.

As detailed further in Section 3.1.5, another common group of effects associated with repeated oral and dermal exposure to clethodim involve changes in the liver. These effects include increases in liver weight, increases in the size of some liver cells, and changes in associated clinical chemistry values. As discussed by U.S. EPA /OPP/HED (2014a, p. 11; 2010c, p. 1), these changes are classified as adaptive rather than as signs of toxicity. While the Agency does not provide a detailed discussion of the rationale for this reevaluation, clethodim does induce liver mixed-function oxidases (i.e., cytochrome P450 enzymes). This effect is typically accompanied by an increase in the number and size of liver cells which will lead to an increase in gross liver weight without signs of frank liver pathology (e.g., liver necrosis). As detailed in Section 3.3.4 (Surrogate RfD for Occupational Exposures), the classification of these liver effects as adaptive rather than as signs of toxicity is central to the U.S. EPA's recent revision of the dose-response assessment for workers.

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 clethodim 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, is important to this risk assessment because many of the exposure scenarios (Section 3.2) involve dermal exposure. Rates of excretion are generally used in Forest Service risk assessments to evaluate the likely body burdens associated with repeated exposure.

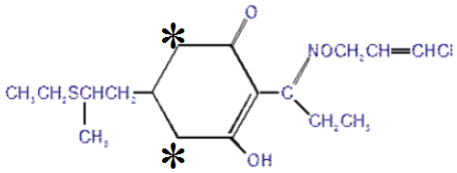
In addition to the general consideration about how clethodim behaves in the body, another consideration is the behavior of clethodim in the environment and the extent to which the metabolism of clethodim in the environment must be considered quantitatively in the risk assessment. The consideration of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

3.1.3.1. General Considerations

For pesticide registration, the U.S. EPA/OPP generally requires a relatively standard metabolism study in rats in which the compound is administered by both intravenous and oral routes. There is one available study on the metabolism of clethodim in rats (Rose and Griffis 1988, MRID 410301-32), and a detailed Data Evaluation Record (DER) for this study is included in U.S.

EPA/OPP/HED (1990). Although the EPA classified the study as "Acceptable" (U.S. EPA/OPP/HED 2010a, p. 49), it is, nevertheless, atypical in that no intravenous dosing was used. The rationale given in the DER for omitting an intravenous study is …*clethodim's poor solubility in water and saline.*

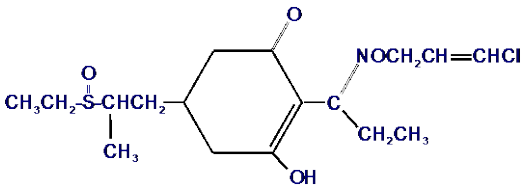
The oral administration study involved pure (99%) clethodim labeled in the 4 and 6 carbons of the cyclohexen-1-one ring, as illustrated below.



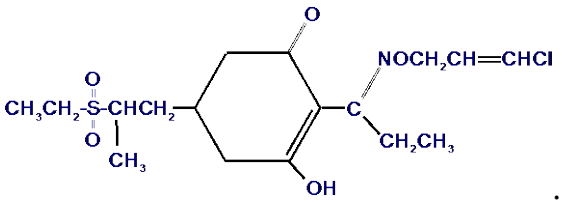
Single doses were administered to groups of five male and five female rats at 4.5 or 450 mg/kg bw. Repeated doses of 4.5 mg/kg/day unlabeled clethodim were given to groups of 10 male and 10 female rats for 14 days after which five animals per sex were administered a single dose of 4.5 mg/kg bw radiolabelled clethodim. Finally, an additional group of 10 male rats was dosed with 450 mg/kg radiolabelled clethodim for the identification of urinary metabolites.

In the metabolism study by Rose and Griffis (1988, MRID 410301-32), clethodim was absorbed rapidly following oral administration, and the absorption efficiency was estimated at 89 to 96%. In addition, as discussed further in Section 3.1.3.3, clethodim and clethodim metabolites were rapidly excreted in both the urine (≈90% of the administered dose) and feces (≈10 of the administered dose). Very little clethodim or clethodim metabolites were exhaled (<1%).

As illustrated in Figure 4, clethodim was metabolized extensively in rats, and only about 5-10% of the administered dose was excreted as clethodim. The primary metabolite (≈60% of the administered dose) was clethodim sulfoxide,



which is in turn metabolized to clethodim sulfone



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As illustrated in Figure 4, the metabolites found in the study by Rose and Griffis (1988) suggest that mammals do not cleave the 2-cyclohexen-1-one moiety. As discussed further in Section 3.1.15.1 (Environmental Metabolites), plants and soil generate metabolites in which the 2-cyclohexen-1-one moiety is cleaved.

By day 7 after dosing, very little clethodim or clethodim metabolites (<1%) remained in the rats. In the high dose groups, the highest level of radioactivity at 7 days after dosing was noted in the adrenals, followed by the liver and the kidney. The concentration of radioactivity in the adrenals was higher in females (13 ppm) than males (7 ppm) in the high dose group. Differences between concentrations of radioactivity in the low dose group were not substantial—i.e., 0.079 ppm for females and 0.068 ppm for males.

As reviewed by U.S. EPA/OPP (2010a), the clethodim sulfoxide and clethodim sulfone are also the major metabolites of clethodim in both goats and chickens. Moreover, clethodim sulfoxide and clethodim sulfone are the major environmental metabolites of clethodim (Section 3.1.15, (Impurities and Metabolites).

3.1.3.2. Absorption

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 toxicity studies in animals. It is, therefore, necessary to assess the consequences of dermal exposure relative to oral exposure and the extent to which clethodim is likely to be absorbed from the skin surface.

Two types of dermal exposure scenarios are considered: immersion and accidental spills. In the scenarios involving immersion, the concentration of the chemical in contact with the surface of the skin is assumed to remain constant or at least nearly so. As detailed in SERA (2014a), the calculation of absorbed dose for dermal exposure scenarios involving immersion requires an estimate of the dermal permeability coefficient (K_p) expressed in cm/hour, and the rate of absorption is assumed to be essentially constant (i.e., zero-order kinetics as discussed in Section 3.1.3.2.2). In exposure scenarios involving direct sprays or accidental spills where the compound is deposited directly on the skin, the concentration or amount of the chemical on the surface of the skin is assumed to be the limiting factor in dermal absorption. For these scenarios first-order dermal absorption rate coefficients (k_a), expressed as a proportion of the deposited dose absorbed per unit time—e.g., $hour^{-1}$—are used in the exposure assessment.

3.1.3.2.1. First-Order Dermal Absorption

Human studies involving the dermal absorption of clethodim are not available in the open literature or in U.S. EPA and other risk assessments (Table 1). One registrant-submitted dermal absorption study in rats (MRID 410302-02) is available. Although a full DER for this study has not been identified, the study is adequately summarized in U.S. EPA/OPP/HED (1996, p. 2) and U.S. EPA/OPP/HED (1990, p. 15). In this study, radiolabelled (NOS) clethodim (98.7% purity) was applied to 10 cm^2 areas of the back of male rats (12 rats/dose) at doses of 0.05, 0.5, or 5 mg/rat, and dermal absorption was assayed at 2, 10, and 24 hours by sacrificing four rats/dose at each time interval. U.S. EPA/OPP/HED (1990) classifies this study as “Acceptable”.

As summarized in Table 8, rats in the lowest dose group absorbed 28.4% of the clethodim at 10 hours after dosing. Based on this data point, U.S. EPA/OPP/HED selected a dermal absorption factor of 30% for risk assessment (U.S. EPA/OPP/HED 1996, p. 2). Presumably, the 10-hour value was selected because it roughly corresponds to a work day and the value for the lowest

dose group was selected because it was the highest absorption rate among the three dose groups. ESFA (2011, p. 30) cites a dermal absorption factor of 15% for an undiluted formulation and 42% for dilute spray (not otherwise specified). The estimate of 42% is identical to the value given in the U.S. EPA/OPP/HED (2014, p. 12) risk assessment.

Forest Service risk assessments typically do not use absorption factors analogous to those used by U.S. EPA, because Forest Service risk assessments include accidental exposure scenarios involving exposure periods from 1 minute to 1 hour (Section 3.2.2.2). As an alternative and as noted above, dermal absorption rate coefficients (k_a) are derived based on the following equation:

$$\ln \frac{M_t}{M_0} = Ln(P_{unabsorbed}) = -k_a t \qquad (1)$$

where M_0 is the amount applied and M_t is the amount unabsorbed at time, t, after application. In practice, the analysis involves the regression of the natural log of the proportion of the compound unabsorbed against time and k_a is estimated from the slope of the regression.

The analyses of the dermal absorption study in rats are summarized in the bottom section of Table 8. A clear dose-dependent effect on dermal absorption rates is apparent with the central estimate of the k_a in the low dose group being almost twice that in the high dose group [0.025 $hour^{-1}$ ÷ 0.014 $hour^{-1}$ ≈ 1.79].

As discussed by Kissel (2010), higher absorption rates with lower skin loadings are common observations and are most often associated with the saturation of dermal absorption processes at higher doses. In the rat dermal absorption study, the skin loadings were 0.005, 0.05, and 0.5 mg/cm^2—i.e., doses of 0.05, 0.5, and 5 mg applied to a 10 cm^2 area of skin. As summarized in Worksheets C03a and C03b of the attachments, the skin loadings in the relevant accidental worker exposure scenarios are 0.024 (0.006 to 0.08) mg/cm^2. In terms of skin loading, the dermal absorption rate from the mid-dose group is most relevant to the current risk assessment.

In the absence of information on first-order dermal absorption rates on the pesticide under consideration, Forest Service risk assessments will typically use quantitative structure activity relationships (QSAR) as detailed in SERA (2014a, Section 3.1.3.2.2). The QSAR method is based exclusively on dermal absorption data from studies in humans involving a wide variety of chemicals. As detailed in Worksheet B03b of Attachments 1 and 2, the QSAR methods yield a much lower estimate of the dermal absorption rate—i.e., about 0.003 (0.001 – 0.009) $hour^{-1}$—using a K_{ow} value of 31,600 and a molecular weight of 359.92. These properties are within the range of values on which the algorithm is based—i.e., K_{ow} values ranging from 0.0015 to 3,000,000 and molecular weights ranging from 60 to 400 g/mole.

In general, experimental data are given preference over QSAR estimates in selecting kinetic or toxicological inputs. This approach is taken in the current risk assessment, albeit with some reservation. Based on the rats in mid-dose group from MRID 410302-02, the first-order dermal absorption rate coefficients are 0.017 (0.015-0.019) $hour^{-1}$. The central estimate is about a factor of 6 higher than the central estimate based on QSAR relationships in humans [0.017 $hour^{-1}$ ÷ 0.003 $hour^{-1}$ ≈ 5.6667]. Dermal absorption rates in rats are typically greater and sometimes much greater than those in humans (European Commission 2004). For example, van

Ravenzwaay and Leibold (2004) compared dermal absorption rates *in vitro* using preparations of rat and human skin and observed that rat skin about 3 to more than 30 times more permeable than human skin (Ravenzwaay and Leibold 2004, Table 3, p. 222). This finding is consistent with the analysis in SERA (2013, Table 7) in which the first-order dermal absorption rates for several pesticides in rats are from about 3 to 11 times higher than the QSAR estimates based on human data.

Notwithstanding the above reservation with the absorption data on clethodim in rats, the first-order dermal absorption rate coefficients of 0.017 (0.015-0.019) $hour^{-1}$ from MRID 410302-02 are used in the current risk assessment. This approach is taken because Forest Service risk assessments are at least as conservative as risk assessments conducted by the U.S. EPA unless there is a compelling reason to do otherwise. In the absence of experimental data on clethodim absorption rates in humans, using the experimental data from rats is more appropriate than relying on QSAR estimates.

3.1.3.2.2. Zero-Order Dermal Absorption

Exposure scenarios involving the assumption of zero-order dermal absorption require an estimate of dermal permeability (K_p) in units of cm/hour. No experimental data are available on the dermal permeability rate of clethodim. In the absence of experimental data, Forest Service risk assessments generally use a QSAR algorithm developed by the EPA (U.S. EPA/ORD 1992, 2007). This approach is discussed in further detail in SERA (2014a, Section 3.1.3.2.1). As with the algorithm for estimating the first-order dermal absorption rate constant, the EPA algorithm is based on molecular weight and K_{ow} (U.S. EPA/ORD 1992, 2007). The molecular weight and K_{ow} values used for estimating the K_p are identical to those used in the estimate of the first-order dermal absorption rate constants (i.e., a K_{ow} value of 31,600 and a molecular weight of 359.92).

The EPA algorithm is derived from an analysis of 95 organic compounds with K_{ow} values ranging from about 0.0056 to 309,000 and molecular weights ranging from approximately 30 to 770 (U.S. EPA/ORD 1992, 2007). These ranges of K_{ow} and molecular weight values encompass the estimates of the corresponding values for clethodim.

Details of the implementation of the algorithms are given in Worksheet B03a in the EXCEL workbooks for clethodim (Attachments 1 and 2). Using the EPA algorithm results in an estimated dermal permeability (K_p) of about 1.7×10^{-2} (8.3×10^{-3} to 3.6×10^{-2}) cm/hour.

As discussed in Section 3.1.3.2.1, the QSAR algorithms used to estimate the first-order dermal absorption rate for clethodim yield higher estimates than those based on the dermal absorption study in rats. It is possible that the QSAR methods developed by the EPA (U.S. EPA/ORD 1992, 2007) overestimate the K_p for clethodim in humans. In the absence of any experimental data, however, the QSAR estimates of the K_p for clethodim are used without modification.

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, p. 320 ff). Under the assumption of first-order elimination, the first-order elimination rate coefficient ($\boldsymbol{k}$) is inversely related to the half-life ($\boldsymbol{T_{50}}$) [$\boldsymbol{k} = \ln(2) \div \boldsymbol{T_{50}}$]. If a chemical with a first-order elimination rate

constant of $\boldsymbol{k}$ is administered at fixed time interval ($\boldsymbol{t^*}$) between doses, the body burden after the $\boldsymbol{N^{th}}$ dose ($\boldsymbol{X_{N\ Dose}}$) relative to the body burden immediately following the first dose ($\boldsymbol{X_{1\ Dose}}$) is:

$$\frac{X_{N\,Dose}}{X_{1Dose}} = \frac{(1-\left(e^{-kt^*}\right)^N)}{1-e^{-kt^*}} \tag{2}$$

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

$$\frac{X_{Inf}}{X_1} = \frac{1}{1-e^{-kt^*}} \tag{3}$$

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

As discussed in Section 3.1.3.1, Rose and Griffis (1988, MRID 410301-32) conducted a metabolism study in rats in which clethodim was extensively metabolized and rapidly excreted. Data on the excretion of clethodim and clethodim metabolites (i.e., total radioactivity) from the study by Rose and Griffis (1988) are summarized in Table 9. In Table 9, the excretion at 168 hours is summarized only for the high dose groups, because clethodim was completely excreted by 168 hours in the low dose groups. Even in the high dose group, the estimated excretion in the urine and feces combined totaled to over 100% of the administered dose. The excretion of total radioactivity for the high dose group (excluding males at 168 hours) is illustrated in Figure 5. The data are consistent with first-order excretion with a half-life of about 11.8 hours or 0.49 days with a corresponding first-order elimination rate coefficient ($\boldsymbol{k}$) of 1.4 day^{-1} [ln(2) ÷ 0.49 days ≈ 1.415 day^{-1}]. Substituting this rate coefficient into Equation 3, the estimated plateau for clethodim and clethodim metabolites is about 1.3. In other words, over very prolonged periods of exposure, the maximum increase in the body burden of clethodim should be no more than a factor of about 1.3.

3.1.4. Acute Oral Toxicity

Standard acute oral toxicity studies are typically used to determine LD_{50} values—i.e., the treatment dose estimated to be lethal to 50% of the animals. LD_{50} values are not used directly to derive toxicity values as part of the dose-response assessment in Forest Service risk assessments. Even so, comparing the LD_{50} values for the active ingredient to the LD_{50} values for the formulations or metabolites of the active ingredient may be useful in assessing the potential impact of inerts or metabolites on potential risks. LD_{50} values as well as other measures of acute toxicity discussed in following sections are used by the U.S. EPA/OPP to categorize potential risks. U.S. EPA/OPP uses a ranking system for response ranging from Category I (most severe response) to Category IV (least severe response). Details of the categorization system used by the Agency are detailed in SERA (2014a, Table 4) as well as the U.S. EPA/OPP (2010d) label review manual.

The acute oral LD_{50} values for clethodim are summarized in Appendix 1, Table A1-1. Acute oral LD_{50} values are available in mice, rats, and rabbits. No systematic differences in toxicity are apparent among these three species. Although differences between male and female mammals

are not substantial, definitive oral LD_{50} values within studies consistently indicate that females are somewhat more sensitive than males—i.e., a factor of about 1.1 in mice [2579÷2430 ≈ 1.06], 1.20 in rats for technical grade clethodim [1630÷1360 ≈ 1.198], and a factor of 1.24 in rats for Select 2.0 EC [3610÷2920 ≈ 1.236].

One acute oral toxicity study is available on a clethodim formulation—i.e., Select 2.0 EC. Although Select 2.0 EC, which is manufactured by Valent, is not specifically labeled for forestry uses, Select 2.0 EC appears to be similar to formulations that the Forest Service may elect to use (Table 4). Based on a summary of MRID 409745-06 in (U.S. EPA/OPP/HED 1990), the acute LD_{50} values for Select 2.0 EC in rats are 3610 mg/kg for males and 2920 mg/kg for females. The EPA summary, however, does not specifically indicate whether the LD_{50} values are expressed in units of formulation or active ingredient (a.i.). EPA documents typically express LD_{50} and similar toxicity values in the units of the material that was tested unless the document explicitly indicates otherwise. This suggests that the LD_{50} values from MRID 409745-06 are in units of mg formulation/kg bw. As summarized in Appendix 1, Table A1-1, the LD_{50} values of about 3000 to 3600 mg/kg for Select 2.0 EC are higher than those for technical grade clethodim. When converted to a.i., however, the LD_{50} values for Select 2.0 EC are somewhat lower than those for technical grade clethodim. Based on a comparison to the relevant data from MRID 409745-07, the formulation is more toxic when units are expressed as a.i. than for technical grade clethodim by a factor of about 1.4 in male rats [1358 mg a.i./kg ÷942 mg a.i./kg ≈1.442] and a factor of about 1.5 in female rats [1133 mg a.i./kg ÷ 762 mg a.i./kg ≈1.487]. These differences in toxicity between technical grade clethodim and the Select 2.0 EC formulation are relatively modest. As discussed in Section 3.1.14.2 (Other Ingredients), these toxicity values suggest that technical grade clethodim is more toxic than the other ingredients in the Select 2.0 EC formulation by a factor of about 4.

Intraperitoneal LD_{50} values for male and female rats are summarized in IPCS (1994) (see Appendix 1, Table A1-1). These LD_{50} values are about 2 to 3 times lower than corresponding LD_{50} values for oral exposure. While these differences should not be overly interpreted, the differences are consistent with the rapid detoxification of clethodim in the liver following oral dosing—i.e., first-pass metabolism. As discussed in Section 3.1.3.1, clethodim is rapidly and almost completely metabolized following oral dosing. While this supposition may be somewhat speculative, it is consistent with the indefinite oral LD_{50} values for clethodim imine sulfone and clethodim 5-hydroxy sulfone, both with have reported LD_{50} values of >1400 mg/kg (Appendix 1, Table A1-1).

Based on the oral LD_{50} values for clethodim in male and female rats, the U.S. EPA/OPP/HED (2014a, p. 33) classifies clethodim as Category III (the second to the least toxic category) for acute oral exposure. As summarized in Table 6, the formulation toxicity data from the MSDS reflect and/or are consistent with the EPA classification of the acute oral toxicity of clethodim. The Shadow formulation from Arysta cites the LD_{50} of 1630 for male rats from MRID 409745-07 (Appendix 1, Table A1-1). Several of the other MSDS report LD_{50} values of >5000 mg/kg bw, and the MSDS for Envoy reports a definitive oral LD_{50} value of 4800 for female rats. These toxicity values cannot be specifically associated with studies summarized in U.S. EPA risk assessments or other reviews on clethodim (Table 1).

3.1.5. Subchronic or Chronic Systemic Toxic Effects

As discussed in SERA (2014a, Section 3.1.5), *subchronic* and c*hronic* are somewhat general terms which refer to studies involving repeated dosing. Some repeated dose studies are designed to detect specific toxic endpoints, like reproductive and neurological effects. Except for some comments in this subsection on general signs of toxicity, these more specialized studies are discussed in subsequent subsections of this hazard identification. The focus of this subsection is toxicity studies designed to detect more general signs of systemic toxicity and to quantify no-observable-effect levels (NOAELs) for the identified endpoints as well as levels associated with adverse effects—i.e., lowest-observed-effect-levels (LOAELS).

The subchronic and chronic toxicity studies on clethodim are summarized in Appendix 1, Table A1-2. Since there are no subchronic or chronic toxicity studies available in the published open literature, all of the toxicity studies relevant to the current risk assessment were submitted to the U.S. EPA/OPP in support of the registration of clethodim. The summaries of these studies given in Appendix 1, Table A1-2 are taken primarily from U.S. EPA/OPP/HED (1990) with some updated evaluations, discussed below, from more recent EPA risk assessments (U.S. EPA/OPP/HED 2007a, 2010a; 2014a).

The most common signs of toxicity in the subchronic and chronic studies are decreases in body weight or body weight gain and increases in relative or absolute liver weights. There are, however, no reports of liver necrosis (i.e., cell death). The increase in liver weights and the sizes of liver cells is consistent with the induction of mixed-function oxidases in the liver. As discussed in Section 3.1.3.1, clethodim is extensively metabolized, and substrates that are metabolized by liver mixed-function oxidases (i.e., cytochrome P450 enzymes) often induce liver mixed-function oxidases (e.g., Coon 2005; Denisov et al. 2005). Nonetheless, as reviewed by IPCS (1994, p. 8), clethodim was shown to increase both liver cytochrome P450 and liver protein; however, the levels of cytochrome P450 per mg of liver protein were not increased.

Subchronic studies in rats are available on three metabolites of clethodim—i.e., clethodim imine sulfone and clethodim 5-hydroxy sulfone (both a which are mammalian and environmental metabolites) as well as M17R, a plant metabolite (Appendix 1, Table A1-2). Summaries of subchronic studies in rats are available in U.S. EPA/OPP/HED (1990) and the European Food Safety Authority (EFSA 2011).

Based on the summaries from U.S. EPA/OPP/HED (1990), the two mammalian metabolites appear to be less toxic than clethodim. The 13-week NOAEL in rats for technical grade clethodim is 500 ppm with a LOAEL of 2500 ppm based on liver toxicity (MRID 410301-07). For clethodim imine sulfone, the 5-week NOAEL is 1000 ppm with a LOAEL of 8000 ppm, also based on liver toxicity (MRID 410301-04). For clethodim 5-hydroxy sulfone, the NOAEL from a 5-week feeding study in rats is 8000 ppm, the highest dose tested (MRID 410301-05). Based on the NOAELs, clethodim appears to be more toxic than clethodim imine sulfone by a factor of 2 [1000 ppm ÷ 500 ppm] and more toxic than clethodim 5-hydroxy sulfone by a factor of 16 [8000 ppm ÷ 500].

The utility of comparisons of NOAELs and LOAELs are admittedly limited because NOAELs and LOAELs rely on the doses used in the particular studies rather than statistically derived

endpoints such as LD_{50}s. As discussed further in Section 3.1.15.1, all of the available LD_{50} values for clethodim metabolites are indefinite. In other words, the LD_{50} values are expressed as *greater than* (>) values which typically reflect the highest dose tested. Notwithstanding these limitations and as detailed in in Section 3.1.15.1, the acute toxicity data are consistent with the subchronic studies on clethodim metabolites in that neither set of studies indicate that the metabolites of clethodim are more toxic than clethodim itself.

The summaries of subchronic studies from EFSA (2011) differ from those summarized by the EPA. The very brief study summaries in EFSA (2011) indicate a 90-day rat NOAEL of 25 mg/kg bw/day for clethodim (p. 28), a subacute NOAEL of 70 mg/kg bw/day for clethodim imine sulfone (p. 29), and a subacute NOAEL of 5.94 mg/kg bw/day for clethodim 5-hydroxy sulfone (p. 29). EFSA (2011) does not specify the duration of the subacute studies.

The studies summarized by EFSA (2011) indicate that clethodim is more toxic than clethodim imine sulfone but by a factor of about 3 [70 mg/kg bw/day ÷ 25 mg/kg/day ≈ 2.8]. For clethodim 5-hydroxy sulfone, however, the EFSA (2011) summaries indicate that clethodim 5-hydroxy sulfone is more toxic than clethodim by about a factor of nearly 12 [70 mg/kg bw/day ÷ 5.94 mg/kg bw/day ≈ 11.7]. The EFSA (2011) also summarizes a study not covered in the EPA documents, which indicates that the plant metabolite M17R has a 28-day rat NOAEL of 400 mg/kg bw/day.

The reason(s) for the discrepancies between the metabolite studies summarized by U.S. EPA/OPP/HED (1990) and ESFA (2011) are not clear. As noted in Table 1, ESFA (2011) provides only brief study summaries, and the original studies are not referenced.

3.1.6. Effects on Nervous System

In severely poisoned animals, virtually any chemical may cause gross signs of toxicity which might be attributed to neurotoxicity—e.g., incoordination, tremors, or convulsions. A direct neurotoxicant, however, is defined as a chemical that interferes with the function of nerves, either by interacting with nerves directly or by interacting with supporting cells in the nervous system. This definition of a direct 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). U.S. EPA has developed a battery of assays to test for neurotoxicity (Group E in U.S. EPA/OCSPP 2010), and U.S. EPA/OPP requires neurotoxicity studies for pesticides when standard toxicity studies or other considerations such as chemical structure suggest that concerns for effects on the nervous system are credible.

As noted in U.S. EPA/OPP/HED (2010a, p. 6), changes to pesticide regulations (40 CFR § 158) now require batteries of acute and subchronic neurotoxicity assays as a requirement for pesticide registration. As summarized in the human health risk assessment for the registration review on clethodim (U.S. EPA/OPP/HED 2014a), two acute oral (gavage) neurotoxicity studies in rats have been conducted on clethodim (MRID 487885-02 in 2012 and MRID 481418-01 in 2006). Both studies evidenced an acute NOAEL of 100 mg/kg bw/day with a corresponding LOAEL of 1000 mg/kg bw/day based on decreased spontaneous activity, ruffled fur, head tilt, and hunched posture (U.S. EPA/OPP/HED 2014a, p. 31). As discussed further in Section 3.3.3, the acute NOAEL of 100 mg/kg bw/day is the basis for the acute RfD for clethodim derived by U.S.

EPA/OPP/HED (2014a) and adopted without modification in the current Forest Service risk assessment.

In addition to the acute toxicity assays for neurotoxicity, one subchronic neurotoxicity study in rats has been conducted (MRID 487885-03) and is summarized in U.S. EPA/OPP/HED (2014a). No signs of neurotoxicity were observed at dietary concentrations of clethodim up to 5000 ppm (equivalent to 331 mg/kg bw/day in males and 380 mg/kg bw/day in females).

Based on the general toxicity studies on clethodim, U.S. EPA/OPP/HED (2010a, p. 6) concludes that the available toxicity data on clethodim do not provide evidence that clethodim is a specific neurotoxin. This conclusion is also expressed in several other EPA risk assessments (U.S. EPA/OPP/HED 2001a, 2007a, 2008a). In an earlier assessment (U.S. EPA/OPP/HED 1990, p. 2), the EPA expresses concern for neurotoxicity based on ataxia, salivation, and other related signs of toxicity observed in an acute oral toxicity study in rats (MRID 409745-07) as well as neuropathology in the spinal cord in 2/5 female rats following an oral dose of 1450 mg/kg bw. The identity of the latter study is not specified in U.S. EPA/OPP/HED (1990), and a more detailed description of this study has not been located. Some incidents involving human exposures to clethodim report symptoms that could be interpreted as signs of neurotoxicity (U.S. EPA/OPP 2008c). Nonetheless, the EPA offers the following conclusion: *The types of effects reports appear to vary from general malaise to neurological symptoms that may not be associated with exposure to clethodim products* (U.S. EPA/OPP 2008c, p. 2).

The European Food Safety Authority review of clethodim concurs with the U.S. EPA/OPP/HED (2010a; 2014a) risk assessments concluding that there is no evidence that clethodim is a neurotoxin (ESFA 2011). Other European assessments of clethodim do not address the topic of neurotoxicity (European Commission 2011, FAO/IAEA 2013; FAO/WHO 1994; IPCS 1994).

3.1.7. Effects on Immune System

There is very little direct information on which to assess the potential immunotoxicity of clethodim. The only studies specifically related to the effects of clethodim on immune function are skin sensitization studies (Section 3.1.11). While these studies provide support for asserting that clethodim is not likely to cause skin sensitization, they provide no information useful for directly assessing the potential for clethodim to impair immune function.

Risk assessments from EPA prior to 2010 (i.e., U.S. EPA/OPP/HED 1990, 1996, 2000a, 2001a, 2007a) do not specifically address immunotoxicity. As with neurotoxicity, recent changes to pesticide regulations (40 CFR § 158) now require immunotoxicity assays as a condition for pesticide registration; however, these regulations were not in effect when clethodim was registered (U.S. EPA/OPP/HED 2010a, p. 6). The most recent EPA risk assessment indicates that an immunotoxicity study in mice (MRID 487885-05) was conducted and that a preliminary evaluation of the study …*showed that clethodim did not produce immunotoxicity*… at doses of up to 1312 mg/kg bw/day (U.S. EPA/OPP/HED 2014a, p. 37).

Subchronic or chronic animal bioassays typically involve 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 lymphoid tissue and blood, indicative of a possible immune system stimulation or suppression, can also be detected. As summarized in Appendix 1, Table A1-2 (Subchronic and Chronic Toxicity Studies), repeated doses of clethodim have been shown to decrease red blood cell counts and associated parameters, but no effects on white blood cells (leukocytes) have been reported. In the 1-year feeding study in dogs (MRID 410301-11), there was slight hypercellularity in the sternal marrow of all dogs treated with 300 mg/kg bw/day.

3.1.8. Effects on Endocrine System

Assessments 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 synthesis, hormone receptor binding, or post-receptor processing). U.S. EPA/OPP has developed a battery of screening assays for endocrine disruption which can be found at: http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series890.htm. Clethodim has been selected as one of the pesticides in the second tier for which the screening assays are being required (U.S. EPA/OPP 2010e, p. 70252); however, the results from the screening assays were not located in the available data. The EPA expressed no specific rationale for selecting clethodim for screening of endocrine disruption. As with neurotoxicity and immunotoxicity, recent changes to U.S. EPA's regulatory policy require that all pesticides be tested for potential effects on endocrine function (U.S. EPA/OPP/HED 2010a, p. 17). None of the U.S. EPA/OPP risk assessments or European risk assessments (Table 1) express concern for the potential effects of clethodim on endocrine function.

In a chronic feeding study in rats (MRID 410301-21 summarized in Appendix 1, Table A1-2), a decrease in food conversion efficiency was observed in male but not female rats in the high dose group—i.e., 2500 ppm in food corresponding to a dose of about 100 mg/kg bw/day. While effects on the endocrine system can be associated with decreases in growth and food conversion efficiency (e.g., Sohlstrom et al. 1998), the single observation of decreased food conversion efficiency cannot be used as a basis to conclude that clethodim is an endocrine disruptor.

3.1.9. Reproductive and Developmental Effects

3.1.9.1. Developmental Studies

Developmental studies are used to assess the potential of a compound to cause malformations and signs of toxicity during fetal development. These studies typically entail gavage administration of the chemical compound 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 by the EPA for the registration of pesticides.

As summarized in Appendix 1, Table A1-3, standard developmental studies on clethodim were conducted with rats (MRID 410301-14/16) and rabbits (MRID 410301-13/15). In addition, developmental studies on the two major *in vivo* metabolites of clethodim were conducted with rats—i.e., clethodim imine sulfone (MRID 410301-17) and clethodim 5-hydroxy sulfone (MRID 410301-18). While no differences in the systematic toxicity of clethodim are apparent in the acute toxicity studies with mice, rats, and rabbits (Section 3.1.4), rabbits appear to be somewhat more sensitive than rats in terms of maternal toxicity—i.e., 100 mg/kg bw/day is a LOAEL for rabbits but a NOAEL for rats. In terms of effects on offspring, however, rats may be somewhat more sensitive than rabbits—i.e., 350 mg/kg bw/day is a LOAEL for rats and 300 mg/kg bw/day

is a NOAEL for rabbits. Tail defects in rats (classified as rare in the DER for MRID 410301-14/16), which was observed in the 700 mg/kg bw/day dose group, was the most severe effect noted.

As discussed in Section 3.1.5, the 90-day feeding study in dogs (MRID 410301-06) was selected as the basis for the dose-response assessment for occupational exposure using a dog NOAEL of 75 mg/kg bw/day in the most recent EPA risk assessment (U.S. EPA/OPP/HED 2014a). The developmental study in rabbits (MRID 410301-15) notes adverse systemic effect in adults (reduced weight gain and food consumption) at 100 mg/kg bw with a NOAEL of 25 mg/kg bw/day. The proximity of the LOAEL of 100 mg/kg bw/day from the developmental study in rabbits to the subchronic NOAEL in dogs of 75 mg/kg bw/day is discussed further in Section 3.3.5 (Dose-Severity Relationships).

As summarized in Appendix 1, Table A1-3, developmental studies in rats are also available for the two major mammalian metabolites of clethodim—i.e., clethodim imine sulfone and clethodim 5-hydroxy sulfone. Clethodim 5-hydroxy sulfone did not cause adverse developmental effects or parental toxicity at doses up to 700 mg/kg bw/day (MRID 410301-18).

The toxicity of clethodim imine sulfone relative to clethodim is less straightforward. Based on assessments in U.S. EPA/OPP/HED (1990), clethodim imine sulfone might be considered somewhat more toxic than clethodim. In terms of parental toxicity, clethodim caused no adverse effects at a dose of 100 mg/kg bw/day. The EPA classifies the same dose of clethodim imine sulfone as a parental LOAEL, based on reduced body weight gain and reduced food consumption, although these effects were not statistically significant (U.S. EPA/OPP/HED 1990, p. 12, MRID 410301-17). At higher doses, both clethodim and clethodim imine sulfone caused a significant reduction in body weight and food consumption as well as salivation—i.e., a dose of 350 mg/kg bw/day for clethodim and 700 mg/kg bw/day for clethodim imine sulfone. In terms of fetal effects, the NOAEL for both clethodim and clethodim imine sulfone is 100 mg/kg bw/day. The LOAELs are based on reduced fetal body weights and delayed growth observed at 350 mg/kg bw for clethodim and 700 mg/kg bw/day for clethodim imine sulfone. The lower LOAEL for clethodim reflects differences in the highest doses used in the two studies and cannot be clearly interpreted as an indication that clethodim is more toxic than clethodim imine sulfone. In other words, the differences in the LOAELs may simply reflect differences in the highest doses tested in the two studies.

The European Food Safety Commission (ESFA 2011) review of clethodim and its metabolites also summarizes several of the developmental studies on clethodim and clethodim metabolites (Appendix 1, Table A1-3). The ESFA (2011) review, however, reports somewhat lower doses for some of the studies. As noted in Table 1 of the current risk assessment, the ESFA (2011) review does not contain detailed study summaries, and the reason for the discrepancy between the ESFA (2011) document and the U.S. EPA documents is not clear. The more recent and more detailed review by FAO/IAEA (2013) as well as the review by IPCS (1994) are consistent with the data given in U.S. EPA/OPP/HED (1990, 2010a;2014a).

3.1.9.2. Reproduction Studies

Multi-generation reproduction studies typically involve dietary exposures of a group of rats referred to as the *parental generation* or P_1. Male and female animals are selected from this

group and mated. Exposure of the female continues through gestation and after delivery. Offspring from the parental generation, typically referred to as F_1, are then continued on dietary exposure through sexual maturity. The F_1 offspring are mated (and then referred to as the P_2 generation) producing an F_2 generation. This is the basic design of a "2-generation" study, although variations on this design are sometimes used, and occasionally the study is carried over to a third generation. Multi-generation reproduction studies typically focus on effects on reproductive capacity—i.e., the number of young produced and their survival.

As detailed in Appendix 1, Table A1-3, U.S. EPA/OPP/HED (2010a) summarizes the results of a 2-generation reproduction study in rats, and a full DER of this study is available in U.S. EPA/OPP/HED (1990). In this study, rats were exposed to clethodim in the diet at concentrations of 0, 5, 20, 500, or 2500 ppm. No adverse effects were noted in offspring. In both generations, parental effects included reduced food consumption and reduced body weight at 2500 ppm. This dietary concentration is expressed as a LOAEL of 263 mg/kg bw, and the NOAEL (500 ppm) is expressed as a dose of 51 mg/kg bw/day in the full DER (U.S. EPA/OPP/HED (1990, pp. 415-436).

Summaries of a reproduction study in rats are also given in the European literature (ESFA 2001, FAO/IAEA 2013, IPCS 1994). These summaries are relatively brief but for the most part are consistent with the summaries discussed above from U.S. EPA/OPP/HED (1990, 2010a;2014a). There are minor differences, however, in the conversion of the dietary concentrations to mg/kg bw/day doses. These minor differences do not have a quantitative impact on the current risk assessment because the reproduction study in rats is not used in the dose-response assessment (Section 3.3).

3.1.10. Carcinogenicity and Mutagenicity

As summarized in Appendix 1 (Table A1-2), clethodim has been assayed for carcinogenicity in chronic studies with both rats (MRID 410301-21) and mice (MRID 410301-12). No increases in the incidences of tumors were observed in either species. Based on these studies, the most recent EPA risk assessment notes that clethodim …is classified as …*not likely to be carcinogenic to humans* (U.S. EPA/OPP/HED 2014a, p. 11). This position is repeated in other EPA risk assessments on clethodim (Table 1) as well as all of the European reviews and assessments that address carcinogenicity (i.e., ESFA 2011; IPCS 1994).

A number of different test systems for mutagenicity are required for pesticide registration and none of these assays indicate that clethodim is mutagenic (U.S. EPA/OPP/HED 2010a, 2014a). A complete listing of the assays for mutagenicity is given in U.S. EPA/OPP/HED (2014a, pp. 35-36). Similarly, no mutagenic activity was observed in assays with clethodim imine sulfone, clethodim 5-hydroxy sulfone, and the M17R plant metabolite of clethodim (ESFA 2011).

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

The U.S. EPA/OPP requires standard studies with pesticide formulations for skin and eye irritation as well as skin sensitization (U.S. EPA/OCSPP 2010). As with acute oral toxicity, the U.S. EPA/OPP uses a ranking system for responses ranging from Category I (most severe response) to Category IV (least severe response) for all three groups of endpoints discussed in this subsection (e.g., U.S. EPA/OPP 2010d).

3.1.11.1. Skin Irritation

Assays for skin irritation and sensitization are summarized in Appendix 1, Table A1-4. One standard registrant submission (MRID 409745-16) is available on skin irritation in rabbits following dermal exposure to technical grade clethodim. A full Data Evaluation Record (DER) for this submission is included in U.S. EPA/OPP/HED (1990). This submission involves two replicate and standard studies involving a 4-hour dermal exposure period in six rats followed by a 14-day observation period. In the first study, signs of dermal irritation, including severe reddening of the skin and slight to moderate edema at 72 hours after dosing and slight reddening and edema in one rabbit at 14 days after dosing, are more severe than the signs of dermal irritation observed in the second study. The study authors suggest that the more severe and prolonged signs of dermal irritation may be attributable to incomplete removal of clethodim from the test animals following the 4-hour exposure period. Similar but less severe effects were noted in the second study up to 72 hours post-dosing, and no skin irritation was apparent at 14 days post-dosing.

The most recent EPA human health risk assessment (U.S. EPA/OPP/HED 2014a, p. 33) appears to consider both studies from this submission and classifies clethodim as a Category III skin irritant. As summarized in Table 6, the MSDSs for Envoy and Envoy Plus a Category II determination that was made in U.S. EPA/OPP/HED (2010a). Most other formulations indicate that moderate skin irritation may occur. Nonetheless, the MSDS for Tapout indicates that this formulation causes only mild skin irritation. As summarized in Table 5, the inerts profile given on the MSDS for Tapout is different from that of other formulations, and the notation for mild skin irritation on the MSDS for Tapout may be based on a dermal study on this formulation. This study, however, was not identified in the literature on clethodim.

3.1.11.2. Skin Sensitization

One standard assay for skin sensitization in guinea pigs was conducted on technical grade clethodim (MRID 409745-18), and a full Data Evaluation Record (DER) for this submission is included in U.S. EPA/OPP/HED (1990) (Appendix 1, Table A1-4). This study was conducted with 0.5% and 5% solutions of clethodim. While skin irritation was observed during the induction period for the 5% solution of clethodim, no signs of skin sensitization were observed in the challenge period. Citing this study on technical grade clethodim, U.S. EPA/OPP/HED (2010a; 2014a) concludes that clethodim is not a skin sensitizer.

FAO/IAEA (2013, p. 2) and IPCS (1994, p. 8) review a skin sensitization study in guinea pigs that is probably the same study reviewed by U.S. EPA; moreover, both the European reviews reach the same conclusion as the U.S. EPA (Appendix 1, Table A1-4). The review by the European Food Safety Authority, however, indicates that clethodim is a skin sensitizer (EFSA 2011, p. 28) but this review does not provide any details on or a citation to support this conclusion.

As indicated in Table 6, two formulations of clethodim—i.e., Envoy Plus and Intensity One—indicate that these formulations are skin sensitizers and two other formulations—i.e., Envoy and Select 2 EC—indicate that these formulations may be skin sensitizers. This language appears to reflect the study by Blaszak (1998, MRID 446865-01) in which Select 2 EC was classified as a skin sensitizer in a standard guinea pig assay. A full DER of this study is available and the DER indicates that the study by Blaszak (1998) was classified as acceptable. This study, however, is

not cited in any of the EPA risk assessments listed in Table 1, including the most recent human health risk assessment in support of the registration review of clethodim (U.S. EPA/OPP/HED 2014a). While somewhat speculative, the statements in EFSA (2011, p. 28) indicating that clethodim is a skin sensitizer may refer to the Blaszak (1998) assay on Select 2 EC.

3.1.11.3. Ocular Effects

A standard eye irritation study in rabbits was conducted with technical grade clethodim (MRID 409745-14). The summary of this study in Appendix 1, Table A1-5 is based on the full Data Evaluation Record (DER) in U.S. EPA/OPP/HED (1990). This assay involved a short period of exposure (30 seconds) to 0.1 mL of technical grade clethodim inserted into the conjunctival sac of one eye. A total of six rabbits were assayed, and the treated eyes of three of the rabbits were washed immediately following the exposure period. Eye irritation was observed in both groups of rabbits (i.e., washed and unwashed eyes), but was much more severe in the unwashed eyes. Based on this study, U.S. EPA/OPP/HED (2014a, p. 32) classifies clethodim as a Category III irritant to the eyes. A summary of an eye irritation study consistent with the DER in U.S. EPA/OPP/HED (1990) is given in IPCS (1994, p. 7), which concludes that clethodim is a mild eye irritant. The review by ESFA (2011, p. 28) indicates that clethodim is a *non-irritant* to the eyes; however, there are no data to support this statement.

3.1.12. Systemic Toxic Effects from Dermal Exposure

As summarized in Appendix 1, Table A1-6, the acute dermal toxicity data include a study on technical grade clethodim (MRID 409745-10) and 21-day repeated dose studies on technical grade clethodim (MRID 410301-09) and the Select 2.0 EC formulation (MRID 410302-01). A DER for the acute toxicity study on clethodim is available in U.S. EPA/OPP/HED (1990). The acute and repeated dose studies on clethodim are cited in the most recent EPA risk assessment (i.e., U.S. EPA/OPP/HED 2014a). A full DER for the repeated dose study on Select 2.0 EC is not included in U.S. EPA/OPP/HED (1990) but this study is cited in U.S. EPA/OPP/HED (2014a). An additional 28-day dermal toxicity study is briefly summarized in ESFA (2011).

3.1.12.1. Acute Studies

In the acute study involving single dermal doses of 0, 2500, or 5000 mg/kg bw/day, skin irritation was noted in all treated animals. This finding is consistent with the dermal irritancy of technical grade clethodim (Section 3.1.11.1). Of the 12 animals tests (six males and six females per dose), only one animal in the high dose group displayed signs of toxicity and eventually died. The signs of toxicity included decreased food consumption, decreased activity, and diarrhea. Clethodim is classified as Category IV for dermal toxicity with an LD_{50} of >5000 mg/kg bw (U.S. EPA/OPP/HED 2014a, p. 33). This LD_{50} value is also cited by IPCS (1994, p. 4). ESFA (2011) cites a dermal LD_{50} in rats of >4167 mg/kg bw, but does not provide additional details. FAO/IAEA (2013, p.1) indicates that clethodim is *virtually non-toxic* to rabbits following acute dermal administration, but does not cite a supporting study.

As summarized in Table 6, the MSDS for most of the formulations explicitly covered in the current risk assessment report LD_{50} values of >5000 mg/kg bw or indicate that the dermal toxicity of clethodim is *minimal*. These reports are consistent with the acute dermal toxicity data on clethodim from the U.S. EPA (e.g., U.S. EPA/OPP/HED 1990, 2010a, 2014a). The MSDS for Intensity and Section 2EC formulations indicate that dermal toxicity data are not available, and it may be that the U.S. EPA/OPP waived studies on these formulations.

3.1.12.2. Repeated Dose Studies

As summarized in Appendix 1 (Table A1-6), a 21-day study on technical grade clethodim (Hedhecock 1987, MRID 410301-09) reports skin irritation but no adverse systemic effects at doses of up to 1000 mg/kg bw/day. Similarly, a 21-day on Select 2.0 EC (MRID 410302-01) noted no systemic effects at doses of up to 2000 mg/kg bw/day. Both studies noted dermal irritation at 10 mg/kg bw/day, the lowest dose in the dermal studies on both technical grade clethodim and Select 2.0 EC.

In addition to the 21-day studies discussed and summarized in EPA risk assessments, ESFA (2011) briefly summarizes a 28-day dermal toxicity study in rats and reports a NOAEL of 83 mg/kg bw/day, but provides no further details. Specifically, ESFA (2011) does not indicate whether the NOAEL is based on systemic toxicity or dermal irritation and does not specify a LOAEL for systemic toxicity.

As discussed further in Section 3.2 (exposure assessment for human health effects), many of the exposure scenarios considered in this risk assessment involve dermal exposures. The failure to note signs of systemic toxicity in repeated-dose dermal toxicity studies on clethodim diminishes concern that longer-term dermal exposures to clethodim have the potential to cause systemic toxicity.

3.1.13. Inhalation Exposure

As summarized in Appendix 1, Table A2-7, standard acute inhalation toxicity studies are available on both technical grade clethodim (MRID 409745-12) and Select 2.0 EC (MRID 409745-13). DERs for these studies are included in U.S. EPA/OPP/HED (1990). For technical grade clethodim, the acute LC_{50} is >3.9 mg/L in rats. Based on this study (MRID 409745-12), U.S. EPA/OPP/HED (2014a, p. 33) classifies clethodim as Category IV for acute inhalation exposures.

There is an available study on a 1% solution of Select 2.0 EC with a reported LC_{50} of >5.4 mg/L. Based on the DER for this study in U.S. EPA/OPP/HED (1990), the reported LC_{50} is clearly in units of test solution (i.e., 5.4 mg of test solution) rather than in units of either a.i. or formulation.

In the acute study on technical grade clethodim (MRID 409745-12), salivation was noted in 3/10 rats during exposure and in all rats after exposure. Salivation was also noted in the study on Select 2.0 EC in 9/10 rats during exposure and in all rats (10M/10F) after exposure. Salivation was not noted in any of the control groups.

IPCS (1994, p. 3) cites the same rat inhalation study as the U.S. EPA. EFSA (2011) reports an indefinite inhalation LC_{50} of >3.25 mg/L in rats, only somewhat lower than the LC_{50} of >3.9 mg/L from MRID 409745-12. EFSA (2011) does not provide a reference for the study, but the magnitude of the difference between the EPA and ESFA values suggests that EFSA may be citing a different study. Both IPCS (1994, p. 3) and FAO/IAEA (2013, p. 5) state that clethodim is *"virtually non-toxic"* to rats following inhalation exposures.

As summarized in Table 6, the MSDS for most of the formulations explicitly covered in the current risk assessment report LC_{50} values of >2 mg/L for a 4-hour exposure. These reports are consistent with the acute inhalation toxicity data on clethodim from the U.S. EPA (e.g., U.S.

EPA/OPP/HED 1990, 2010a, 2014a). The MSDS for Envoy specifically references the LC_{50} of >5.4 mg/L. As discussed above, this LC_{50} is from MRID 409745-13 and the concentration refers to a 1% solution of Select 2.0 EC.

The MSDSs for two formulations, Envoy and Select 2 EC, note that these formulations may be respiratory irritants. According to the DER for the inhalation study on clethodim (MRID 409745-12), interstitial pneumonia was observed in five of five treated males and two of five male controls but …*these lesions …were spontaneous in nature and were not unusual for rats of this strain and age*. No lung pathology was attributed to clethodim. The DER for the inhalation study on Select 2.0 EC (MRID 409745-13) notes … *no apparent compound-related changes observed during gross necropsy or microscopy of the lungs and trachea*. In addition, the hazard identification by U.S. EPA/OPP/HED (1996, p. 3) notes that …*no appropriate dose or end-point*… was identified for inhalation exposures. Finally, the most recent EPA human health risk assessment (U.S. EPA/OPP 2014a) expresses concern for both skin and eye irritation but not for lung irritation. The basis for the specific concern for lung irritation expressed in the MSDS for Envoy and Select 2 EC cannot be identified. Nonetheless, the information on the MSDS cannot be ignored; accordingly, respiratory irritation is considered an endpoint of concern.

The U.S. EPA/OPP has waived the requirement for a subchronic inhalation study (U.S. EPA/OPP/HED 2014a, p. 11).

3.1.14. Adjuvants and Other Ingredients

3.1.14.2. Other Ingredients

U.S. EPA is responsible for regulating both the active ingredients (a.i.) in pesticide formulations as well as any other chemicals that may be added to the formulation. As implemented, these regulations affect only pesticide labeling and testing requirements. The term *inert* was used to designate compounds that are not classified as active ingredient on the product label. 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 components.

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. Material Safety Data Sheets (MSDS) sometimes specify inerts used in pesticide formulations. U.S. EPA/OPP (2010d, p. 5-14) encourages but does not generally require expanded inert statements on product labels which specifically identify the inert ingredients in the product. One notable exception, however, involves petroleum distillates including xylene or xylene range solvents that are part of the formulation and at a concentration of ≥10%. In this case, the product label must contain the following statement: *Contains petroleum distillates, xylene or xylene range aromatic solvents* (U.S. EPA/OPP 2010d, p. 5-7).

Table 5 summarizes the product labels of all of the clethodim formulations that contain petroleum distillates explicitly covered in the current risk assessment. The MSDS for all formulations, except Tapout and Section 2EC, list petroleum distillates among the other ingredients.

Petroleum distillates, including aromatic hydrocarbons, are complex mixtures (e.g., ATSDR 1995). It is possible that the specific constituents in the different liquid formulations of clethodim differ at least somewhat from one another. As reviewed by ATSDR (1999), petroleum distillates can induce a wide range of toxic effects, particularly effects on the nervous system. The U.S. EPA/OPP has not yet completed their RED for aromatic hydrocarbons (http://www.epa.gov/pesticides/reregistration/status.htm). Petroleum distillates may also contain naphthalene as well as other aromatics. As detailed in U.S. EPA/OPP (2008b), naphthalene is registered for use as an insecticide and insect repellant. For example, naphthalene is the active ingredient in mothballs.

Given the complexity and variability of petroleum distillates as well as the limited information available on the identity of the petroleum components in clethodim formulations, it is difficult to assess the extent to which the other ingredients in clethodim formulations contribute to their toxicity. One approach is to compare the toxicity of the formulations, expressed in units of active ingredient, to the toxicity of the active ingredient itself. As discussed in Section 3.1.4, the comparison of oral LD_{50} values on technical grade clethodim with the Select 2 EC formulation suggests that clethodim does not completely account for the toxicity of the formulation. This assessment can be elaborated by more quantitatively considering the Select 2 EC formulation as a mixture containing two components, clethodim and the *other ingredients*. While this is clearly a simplification, it is the only other approach to quantitatively assessing the significance of the *other ingredients* relative to clethodim.

As summarized in Table 9, oral LD_{50} values are available on both technical grade clethodim and the Select 2 EC formulation. Toxicity data, however, are not available on the inerts in clethodim—i.e., the formulation constituents without clethodim. Nonetheless, the toxicity of the other ingredients in Select 2 EC can be estimated based on the assumption of relative potency and dose-additivity. A general discussion of these concepts is given in Finney (1971, pp. 210-282) and the symbols used below are taken from Finney (1971, p. 233). Under the assumption of dose addition, relative potency is defined as:

$$\rho = \frac{\zeta_1}{\zeta_2} \tag{4}$$

where ζ_1 is a toxicity value (such as the LD_{50}) for chemical 1 and ζ_2 is a comparable toxicity value for chemical 2. In the above equation, potency is defined as the toxicity of chemical 2 relative to chemical 1. In other words, if the LD_{50} of chemical 2 is twice that of chemical 1, the potency of chemical 2 relative to chemical 1 is 0.5.

Under the assumption of dose addition (Equation 11.8 in Finney 1971, p. 233), a toxicity value for a mixture (ζ_M) of chemical 1 and chemical 2 can be estimated from the toxicity values of the two chemicals and the proportions of the two chemicals (i.e., π_1 and π_2 in the mixture):

$$\zeta_{M=} = \frac{\zeta_1}{\pi_1 + (\pi_2 \rho)} \tag{5}$$

In the case of clethodim, LC_{50} values are available on the mixture (i.e., Select 2 EC in MRID 409745-06) as well as technical grade clethodim (MRID 409745-07). From these data, the LC_{50} values for the other ingredients in clethodim can be estimated. Substituting the right hand side of the equation for relative potency into the above equation of dose addition and solving for ζ_2,

$$\zeta_{2=} = \frac{\zeta_1 \pi_2 \zeta_M}{\zeta_1 - \pi_1 \zeta_M} \tag{6}$$

As summarized in Table 9, the proportion of technical grade clethodim in the Select 2 EC formulation on which LD_{50} values are available is 0.261. Thus, the proportion of *other ingredients* may be taken as 0.739 [1-0.261]. The LC_{50} values for Select 2 EC (ζ_M) are 3610 and 2920 mg formulation/kg in male and female rats, respectively. The LC_{50} values for technical grade clethodim (ζ_1) are 1630 and 1360 mg a.i./kg in male and female rats, respectively. Substituting the appropriate values into the above equation for ζ_2, the LC_{50} values for the other ingredients in clethodim may be estimated at about 6322 mg/kg for male rats and 4909 mg/kg for female rats. Using the above definition of relative potency, the potency of the other ingredients relative to technical grade clethodim is about 0.25 for male rats [1630 mg/kg ÷ 6,322 mg/kg ≈ 0.2578] and 0.27 for female rats [1360 mg/kg ÷ 4909 mg/kg ≈ 0.2770]. In other words, technical grade clethodim appears to be about 4 times more toxic than the other ingredients in Select 2 EC based on the acute oral LD_{50} values for technical grade clethodim and Select 2 EC.

3.1.14.2. Adjuvants

As summarized in Table 4, adjuvants, including nonionic surfactants, methylated seed oils, or vegetable oil concentrates are recommended for applications of clethodim. These adjuvants are commonly used with herbicides to improve efficacy. Product labels recommend the use of nonionic surfactants at a concentration of 0.25% v/v, methylated seed oil, vegetable oil at a concentration of 1% (v/v), or other commercially available adjuvants. These recommendations are supported by several studies in the open literature documenting the enhancement of weed control by these adjuvants (e.g., Bohannan and Jordan 1995; Bridges et al. 1991; Jordan 1995; Jordan et al. 1996; McMullan 1996; McWhorter et al. 1992).

Although methylated seed oils and vegetable oil concentrates are somewhat vague terms, there is no basis for asserting that these adjuvants are likely to enhance the toxicity of clethodim to humans. Several seed and vegetable oils are approved food additives (Clydesdale 1997); moreover, many vegetable and fruit oils are classified as *minimal risk inerts* (U.S. EPA/OPPTS 2009). Nonionic surfactants comprise a large and complex group of materials (e.g., Kosswig 1994). In the absence of mammalian studies regarding the potential toxicity of clethodim in combination with various nonionic surfactants, it is not possible to generalize about potential hazards to human health. As discussed further in the ecological risk assessment, some nonionic surfactants are much more toxic than clethodim to aquatic species (Section 4.1.3.5).

3.1.15. Impurities and Metabolites

3.1.15.1. Metabolites

As illustrated in Figure 4 and discussed in Section 3.1.3.1, clethodim is extensively metabolized in rats, primarily to clethodim sulfoxide which is in turn metabolized to clethodim sulfone. As also discussed in Section 3.1.3.1, the available study in rats indicates that rats do not cleave the 2-cyclohexen-1-one moiety. The EPA has elected to consider metabolites with the intact 2-cyclohexen-1-one moiety semi-quantitatively by adjusting the inputs for exposure models so that the degradation rates used in exposure modeling account for the degradation times of major metabolites with the 2-cyclohexen-1-one moiety (U.S. EPA/OPP 2010b).

In terms of toxicity, this approach appears to be reasonable. Based on acute oral toxicity (Section 3.1.4, Appendix 1, Table A1-1), the sulfone metabolites do not appear to be more toxic than clethodim. This comparison is compromised because all of the LD_{50} values for the metabolites are indefinite, and the studies were conducted at doses below the definite LD_{50} values for clethodim. Based on subchronic studies (Section 3.1.5, Appendix 1, Table A1-1) summarized in U.S. EPA/OPP/HED (1990), the sulfone metabolites are less toxic than clethodim by factors of 2 to 16. As also detailed in Section 3.1.5, the review by the European Food Safety Authority (ESFA 2012) indicates that 5-hydroxy sulfone is more toxic than clethodim by about a factor of nearly 12. The reason for the discrepancy between the U.S. EPA assessment and the ESFA assessment cannot be determined. The ESFA document, however, does not provide sufficient detail to assess the identity or quality of the studies reviewed by ESFA. In the absence of more detailed information, the determinations from the U.S. EPA are given preference.

3.1.15.2. Impurities

There is no information in the published literature concerning the manufacturing impurities in clethodim. Nonetheless, virtually no chemical synthesis yields a totally pure product. Technical grade clethodim, like other technical grade products, contains some impurities. These impurities are disclosed to U.S. EPA but are not made publically available. Because specific information concerning impurities may provide insight into the manufacturing process used to synthesize clethodim, it is considered proprietary, is protected under FIFRA (Section 10), and was not available for the preparation of the current Forest Service risk assessment. Nonetheless, the U.S. EPA has reviewed information on the impurities in technical grade clethodim and has determined that the known impurities are not of toxicologic concern (U.S. EPA/OPP/HED 2014a, p. 9, Table 3.1).

In addition to the determination from the EPA, concern for impurities in technical grade clethodim is reduced because most of the existing toxicity studies were conducted with the technical grade product or formulated products. Thus, toxic impurities present in the technical grade product are likely to be encompassed by the available toxicity studies. In addition and as summarized in Appendix 1, Table A1-2, the subchronic toxicity of purified clethodim (96.2%, MRID 410301-08) appears to be comparable to technical grade clethodim (83.4%, MRID 410301-07).

3.1.16. Toxicological Interactions

Data regarding the possible interactions of clethodim with other compounds were not identified in the available literature. Consequently, there is no basis for inferring toxicological interactions of clethodim with other agents.

As discussed in Section 3.1.2, clethodim is a substrate for cytochrome P450. Cytochrome P450 is a variable set of enzymes that are both induced by and involved in the metabolism of many naturally occurring as well as man-made compounds (e.g., Coon 2005). Thus, exposures to other compounds that serve as inducers or substrates for cytochrome P450 could impact the metabolism or excretion of clethodim. In the absence of other information, the impact that these interactions might have on the toxicity of clethodim cannot be further characterized. Metabolic reactions involving cytochrome P450 are saturable processes. Thus, it seems reasonable to suggest that these interactions would be substantial only at relatively high levels of exposure in which cytochrome P450 would be induced or the metabolism of clethodim would be competitively inhibited by other substrates of cytochrome P450.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview

The exposure assessments used in the current risk assessment are given in the accompanying EXCEL workbooks: Attachment 1 for a single application of 0.25 lb/acre and Attachment 2 for two applications of 0.25 lb/acre with a 14-day application interval. These workbooks contain a set of worksheets that detail each exposure scenario discussed in this risk assessment as well as summary worksheets for both workers (Worksheet E01) and members of the general public (Worksheet E02). Documentation for these worksheets is presented in SERA (2011a).

Worker exposures are modeled for backpack spray, broadcast ground spray, and aerial spray. In non-accidental scenarios involving the normal application of clethodim, central estimates of exposure for workers are approximately 0.09 mg/kg/day for backpack applications, 0.03 mg/kg/day for ground broadcast applications, and 0.02 mg/kg bw/day for aerial spray. Upper prediction intervals of exposures are approximately 1 mg/kg/day for backpack applications, 0.21 mg/kg/day for ground broadcast applications, and 0.16 mg/kg/day for aerial applications.

For the general public (Worksheet E03), acute non-accidental exposure levels associated with terrestrial applications range from very low (e.g., $\approx 1 \times 10^{-8}$ mg/kg/day) to about 0.4 mg/kg bw. The upper bound of exposure of about 0.4 mg/kg bw is associated with the consumption of contaminated vegetation. The other acute exposure scenarios lead to lower and often much lower dose estimates. The lowest acute exposure levels are associated with swimming in or drinking contaminated water. For the accidental exposure scenarios, the greatest exposure levels are associated with the consumption of contaminated water by a small child following an accidental spill, for which the upper bound dose is about 0.9 mg/kg bw/day.

The highest longer-term exposure levels are associated with the consumption of contaminated vegetation, and the upper bound for this scenario is about 0.06 mg/kg/day, which is followed by the scenario for the longer-term consumption of contaminated fruit with an upper bound of 0.009 mg/kg/day. The lowest longer-term exposure levels are associated with the consumption of contaminated fish.

3.2.2. Workers

Two types of exposure assessments are considered for workers: general exposure and accidental/incidental exposure. 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 as well as members of the general public and ecological receptors) are based on the maximum annual application scenario, two applications of 0.25 lb. a.i./acre with the minimum application interval of 14 days (Section 2.4). These exposure scenarios are detailed in Attachment II. For most exposure scenarios, exposure and consequent risk will scale linearly with the application rate. The consequences of using lower application rates or only a single application in one season are considered in the risk characterization (Section 3.4).

3.2.2.1. General Exposures

As described in SERA (2014a), worker exposure rates 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, exposure rates are estimated for three different types of applications: directed foliar (backpack), boom spray (hydraulic ground spray), and aerial. The worker exposure rates are summarized in Table 10 of the current Forest Service risk assessment. The worker exposure rates in Table 10 are taken from a recent update and reevaluation of the methods used to estimate worker exposure (SERA 2013). All exposure rates are based on biomonitoring studies of worker exposures during pesticide applications.

As discussed further in Section 3.2.3.1.1 (Likelihood and Magnitude of Exposure), most exposure scenarios included in the current risk assessment are accompanied by estimates of variability and/or uncertainty and are expressed as a central value (most likely exposure) as well as estimates of the upper and lower bounds of exposure. The revised worker exposure rates from SERA (2013) are elaborated to include both 95% confidence intervals as well as 95% prediction intervals. As discussed in SERA (2013), the 95% confidence intervals should be interpreted as the region for average exposures in groups of workers. The 95% prediction intervals should be interpreted as the region in which most exposures for individual workers may occur.

Another elaboration in the new worker exposure methods involves the adjustment for exposure rates in backpack workers based on differences in dermal absorption. As Section 4.2.1.1 of SERA (2013) explains, different exposure rates are developed for backpack workers applying glyphosate, 2,4-D, and triclopyr BEE. In developing backpack worker exposure rates for another pesticide, one of these three rates is selected based on the first-order dermal absorption rate coefficients for these pesticides and the pesticide under consideration. As discussed in Section 3.1.3.2.1, the central estimate of the first-order dermal absorption rate coefficient for clethodim is taken as 0.017 $hour^{-1}$ based on a dermal absorption study in rats. Section 3.1.3.2.1 also discusses the substantial reservations with this approach because this first-order dermal absorption rate coefficient is about a factor of 6 higher than rate coefficient based on QSAR estimates using human data [0.017 $hour^{-1} \div 0.003\ hour^{-1} \approx 5.66$]. Based on the higher dermal absorption rate for rats, clethodim is most similar to triclopyr BEE for which the first-order dermal absorption rate coefficient based on human data is 0.0021 $hour^{-1}$ (SERA 2013, Table 7). Thus, the first-order dermal absorption rate coefficient for clethodim is estimated to be greater than that for triclopyr BEE by about a factor of 8 [0.017 $hour^{-1} \div 0.0021\ hour^{-1} \approx 8.0952$]. Following the approach detailed in SERA (2013, Equation 22), the exposure rates for triclopyr BEE derived in SERA (2013) are multiplied by the adjustment factor of about 8, and the worker exposure rates for backpack workers applying clethodim are estimated as 0.08 with 95% confidence intervals of 0.06 to 0.1 and 95% prediction intervals of 0.02 to 0.5 mg/kg bw/day per lb a.i. handled. Details of these calculations are provided in Worksheet C01a-Sup of Attachments 1 and 2.

In addition to the application rate and absorbed dose rate, the other factor affecting worker exposure is the number of acres per day that a worker will treat. Estimates of the number of acres per day that a worker might treat are also given in Table 10. These values are based on treatment rates used in several Forest Service Environmental Impact Statements (USDA/Forest Service 1989a,b,c).

As discussed in SERA (2013), the U.S. EPA/OPP uses a different method in estimating worker exposures—i.e., deposition-based methods, which typically use the Pesticide Handlers Exposure Database (PHED, Keigwin 1998). Accordingly, the EPA conducted exposure assessments for workers applying clethodim by ground broadcast and aerial applications (U.S. EPA/OPP/HED 2002a, 2007a, 2008a, 2013a).

The worker exposure assessments conducted using PHED typically involve assessments of both dermal and inhalation exposure. These types of exposure assessments were conducted in all EPA occupational exposure assessments up to U.S. EPA/OPP/HED (2008a). As part of the registration review of clethodim, however, the EPA reevaluated the 28-day dermal toxicity study in rats (MRID 410301-09 summarized in Appendix 1, Table A1-6) and reclassified the highest dose tested (1,000 mg/kg bw/day) as a NOAEL (U.S. EPA/OPP/HED 2013a). In all previous EPA risk assessments, the 1,000 mg/kg bw/day dose had been classified as a LOAEL …*based on anogenital discharge and anogenital staining on males and females, decreased food efficiency and body weight gain for males, and increased absolute and relative liver weight in females* (U.S. EPA/OPP/HED 2010a). In the conduct of the current Forest Service risk assessment, the U.S. EPA/OPP was queried concerning the basis for this reclassification and provided a memorandum containing executive summaries of revised DERs (U.S. EPA/OPP/HED 2013b). In the discussion of MRID 410301-09, the EPA document notes the following: *The systemic NOAEL was 1000 mg/kg/day based on absence of any adverse compound-related effect seen in any treatment groups. The dermal irritation was seen in all compound treated rats* (U.S. EPA/OPP/HED 2013b, p. 3). No additional details of the reevaluation are provided.

Because of the NOAEL of 1000 mg/kg bw/day, the occupational exposure assessment in U.S. EPA/OPP/HED (2013a) did not consider dermal exposure. In order to offer a more direct comparison of the PHED method used by EPA to the methods for assessing occupational exposures used in Forest Service risk assessments, the comparison is based on the worker exposure assessment from U.S. EPA/OPP/HED (2008a) rather than the most recent assessment U.S. EPA/OPP/HED (2014a).

The worker exposure methods from U.S. EPA/OPP/HED (2008a, Table 10, p. 32) are summarized in a custom worksheet named “PHED EPA” which follows Worksheet C01c in the EXCEL workbooks which accompany this risk assessment. These exposure estimates are not directly comparable to those given in the current Forest Service risk assessment, because the U.S. EPA uses somewhat higher estimates of the number of acres a worker will treat (and hence the amount of pesticide that a worker will handle) in agricultural applications compared with the Forest Service estimates, which are applicable to forestry applications.

A more direct comparison of the EPA and Forest Service methods for estimating worker exposures is given in custom worksheet “PHED Comp”, which follows worksheet “PHED EPA”, in Attachments 1 and 2. This worksheet uses all of the assumptions for estimating worker exposure using PHED as used in U.S. EPA/OPP/HED (2008a) for ground broadcast and aerial applications, except that the number of acres treated per day as based on the central estimates given in Table 10 of the current risk assessment—i.e., the values based on forestry applications. The EPA assessments do not include backpack applications. The estimate for backpack exposure given in worksheet “PHED Comp” is based on the inputs for a standard backpack

exposure scenario (i.e., Scenario 34) used in other EPA worker exposure assessments (Keigwin 1998). Note that the U.S. EPA does not provide estimates of the variability in worker exposures and all comparisons given in "PHED Comp" are based on the central estimates of exposure given in the current risk assessment.

As indicated in worksheet "PHED Comp", the exposure assessments given in the current risk assessment are very similar to the corresponding estimates from U.S. EPA/OPP/HED (2008a) for ground broadcast and aerial applications. Rounding to one significant digit, the estimates for ground broadcast are 0.003 mg/kg bw in the current risk assessment and 0.002 mg/kg bw in U.S. EPA/OPP/HED (2008a). For aerial applications, the exposure estimates are 0.002 in the current risk assessment and 0.003 mg/kg bw in U.S. EPA/OPP/HED (2008a). Given the differences in the methods used in the current risk assessment and those used in U.S. EPA/OPP/HED (2008a), the similarities in the exposure estimates are striking.

For backpack applications, however, the central estimate of exposure given in the current risk assessment (about 0.088 mg/kg bw) is higher than the estimate based on PHED (i.e., about 0.012 mg/kg) by about a factor of 7. This difference is very similar to the adjustment factor—i.e., a factor of 8 as discussed above and derived in worksheet C01a-Sup—used to estimate the exposure rates for clethodim based on exposure rates for triclopyr BEE. It should be emphasized that this adjustment is an extrapolation rather than an interpolation—i.e., triclopyr BEE has the highest dermal absorption rate coefficient of the compounds for which backpack worker exposure rates are derived in SERA (2013). As discussed further in Section 3.4.2 (risk characterization for workers), this extrapolation adds uncertainty to the exposure assessment and risk characterization for backpack workers.

3.2.2.2. Accidental Exposures

Irritation to the skin and eyes of workers are most likely to be associated with accidental spills or splashes of pesticide solutions. Quantitative exposure scenarios for skin and eye irritation are not developed in this or other Forest Service risk assessments. Clethodim and formulations of clethodim may cause moderate skin irritation (Section 3.1.11.1) and mild eye irritation (Section 3.1.11.3). Quantitative exposure and dose-response assessments for skin and eye irritation are not developed but these effects are considered qualitatively in the risk characterization (Section 3.4.2).

Generally, dermal exposure is the predominant route of exposure for pesticide applicators (Ecobichon 1998; van Hemmen 1992), and accidental dermal exposures are considered quantitatively in all Forest Service risk assessments. The two types of dermal exposures modeled in the risk assessments include direct contact with a pesticide solution and accidental spills of the pesticide onto the surface of the skin. In addition, 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 of the EXCEL workbooks that accompany this risk assessment—i.e., Attachments 1 and 2. Additionally, Worksheet E01 references other worksheets in which the calculations of each exposure assessment are detailed.

Exposure scenarios involving direct contact with solutions of clethodim are characterized either by immersion of the hands in a field solution for 1 minute 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 possible 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 clethodim are provided in Section 3.1.3.2.2.

The amount of the pesticide absorbed per unit time depends directly on the concentration of the chemical in solution. For terrestrial applications, the current risk assessment uses an application volume of 10 gallons/acre with a range of 3 to 40 gallons per acre, which encompasses the potential range of applications to be used in ground, aerial, and aquatic applications (Section 2.4). At an application rate of 0.25 lb a.i./acre, the estimated concentrations in a field solution are 3 mg/mL with a range of 0.75 to 10 mg/mL (Worksheet A01 in Attachment 1 and Attachment 2).

The details of the accidental dermal exposure scenarios for workers consist of spilling a chemical solution on to the lower legs as well as spilling a chemical solution on to the hands, at least some of which adheres to the skin. The absorbed dose is then calculated as the product of the amount of chemical on the skin surface (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 coefficient, and the duration of exposure. The first-order dermal absorption rate coefficient (k_a) is derived in Section 3.1.3.2.1.

3.2.3. General Public

3.2.3.1. General Considerations

3.2.3.1.1. Likelihood and Magnitude of Exposure

As noted in Section 2.3, the Forest Service may wish to apply clethodim along roadsides, power lines, pipelines, and rights-of-way. Although some of these applications may be made at locations remote from the general public, exposures to members of the general public cannot be excluded. 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 (2014a, 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 credible exposure levels.

This Extreme Value approach is essentially an elaboration on the concept of the *Most Exposed Individual* (MEI), sometimes 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 limits of exposures. 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 intended to encompass exposures to 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, the point of using the central estimate, and especially the lower bound estimate, is not 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. Conversely, if the upper bound estimates do not exceed the level of concern, there is strong indication that the pesticide can be used without posing undue risks based on the exposure assumptions used in the risk assessment.

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 clethodim exposure. This concern is considered in the dose-response assessment (Section 3.3) which bases exposures on the most sensitive endpoint in the most sensitive species and uses an uncertainty factor for sensitive individuals. 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).

3.2.3.1.2. Summary of Assessments

The exposure scenarios developed for the general public are summarized in Worksheet E03 of the EXCEL workbooks that accompany this risk assessment. As with the worker exposure scenarios, details about the assumptions and calculations used in these assessments are given in the detailed calculation worksheets in the EXCEL workbook (Worksheets D01–D10).

For clethodim, a standard set of exposure assessments used in all Forest Service risk assessments for broadcast applications are considered. 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. Non-accidental exposures involve dermal contact with contaminated vegetation as well as the consumption of contaminated fruit, vegetation, water, or fish. The longer-term or chronic exposure scenarios parallel the acute exposure scenarios for the consumption of contaminated fruit, water, or fish. All of the non-accidental exposure scenarios are based on levels of exposure to be expected following two applications of clethodim at 0.25 lb a.i./acre with an application interval of 14 days. 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*). The impact of lower application rates or single applications of clethodim on the risk characterization is discussed in Section 3.4.

The nature of the accidental exposure scenarios is intentionally extreme. The non-accidental, acute exposure scenarios are intended to be conservative but plausible, meaning that it is not unreasonable to assume that the magnitude of exposures in the non-accidental exposure scenarios could occur in the routine use of clethodim. This interpretation does not extend to the longer-term exposure scenarios. The longer-term exposure scenarios essentially assume that an individual will consume either treated vegetation, fruits, or water from a treated area every day over a prolonged period of time. While this type of exposure cannot be completely ruled out, the likelihood that such exposures will occur seems to be low. As discussed further in Section 3.4.3, this is an important consideration in the interpretation of hazard quotients associated with longer-term exposures to contaminated vegetation.

3.2.3.2. Direct Spray

Direct sprays involving ground applications are modeled in a manner similar to accidental spills for workers (Section 3.2.2.2). In other words, it is assumed that the individual is sprayed with a solution containing the compound and that an amount of the compound remains on the skin and is absorbed by first-order kinetics. Two direct spray scenarios are given, one for a young child (D01a) and the other for a young woman (D01b).

For the young child, it is assumed that a naked child is sprayed directly during a ground broadcast application and that the child is completely covered (that is, 100% of the surface area of the body is exposed). This 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. In this scenario, it is assumed that the lower legs and feet of a woman are accidentally sprayed with a pesticide. The choice of a young woman rather than an adult male in this scenario is common to many of the exposure assessments and relates to concerns for both the *Most Exposed Individual* (MEI) as well as the most sensitive individual. As discussed in Section 3.1.9 and detailed further in Appendix 1 (Table A1-3), clethodim has not been shown to cause adverse effects in offspring but has been associated with signs of maternal toxicity. Consequently, the exposure of a young woman of reproductive age is used to better assess the potential for adverse effects in the population at risk of effects associated with exposures during pregnancy—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 using specific values in these and other exposure scenarios as well as the sources of the specific values is provided in documentation for the preparation of Forest Service risk assessments and the worksheets that accompany Forest Service risk assessments (SERA 2010a,b).

3.2.3.3. Dermal Exposure from Contaminated Vegetation

In this exposure scenario, it is assumed that clethodim is sprayed on to vegetation and that a young woman comes in contact with sprayed vegetation or other contaminated surfaces at some period after the spray operation (D02). For these exposure scenarios, some estimates of dislodgeable residue (a measure of the amount of the chemical that could be freed from the vegetation) and the rate of transfer of the chemical from the contaminated vegetation to the surface of the skin must be available.

No data are available on dermal transfer rates for clethodim. This is not a severe limitation in this risk assessment. As detailed in Durkin et al. (1995), dermal transfer rates are reasonably consistent for numerous pesticides, and the methods and rates derived in Durkin et al. (1995) are used as defined in Worksheet D02. Similarly, no data are available on dislodgeable residues for clethodim. This is a somewhat greater source of uncertainty. For this exposure scenario, a default dislodgeable residue rate of 0.1 of the nominal application rate is used.

The exposure scenario assumes a contact period of 1 hour and further assumes that the chemical is not effectively removed by washing for 24 hours. Other approximations used in this exposure scenario include estimates of body weight, skin surface area, and first-order dermal absorption rates, as discussed in Section 3.2.3.2 (Direct Spray).

3.2.3.4. Contaminated Water

3.2.3.4.1. Accidental Spill

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 calculation of the concentration of clethodim in water following the spill is given in Worksheet B04b, and the estimate of the dose to a small child is 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, the scenario 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 that is consumed. All Forest Service risk assessments assume that the accidental spill occurs in a small pond with a surface area of about one-quarter of an acre (1000 m^2) and a depth of 1 meter. Thus, the volume of the pond is 1000 m^3 or 1,000,000 liters.

A spill volume of 100 gallons with a range of 20 to 200 gallons is used to reflect plausible spill events. These spill volumes are used in all Forest Service risk assessments involving terrestrial applications. The clethodim 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 clethodim in a small pond ranges from about 0.06 to about 7.5 mg/L, with a central estimate of about 1.1 mg/L (Worksheet B04b).

3.2.3.4.2. Accidental Direct Spray/Drift to a Pond or Stream

This scenario involves the accidental direct spray or incidental spray drift to a small pond and a small stream. The exposure scenarios involving drift are less severe but more plausible than the accidental spill scenario described in the previous section. For each water body, two sets of drift scenarios are given, one based on fine droplets and the other on coarse droplets. All of the product labels for clethodim clearly indicate that applications should be made using coarse droplets to minimize drift. The use of fine droplets would essentially involve a misapplication of clethodim. The distinction between fine and coarse droplet sizes applies only to aerial and ground broadcast applications. Drift from backpack applications are always modeled using coarse droplet sizes.

U.S. EPA typically uses a 2-meter-deep pond to develop exposure assessments. If such a pond is directly sprayed with clethodim at an application rate of 0.25 lb a.i./acre, the peak concentration in the pond would be about 0.028 mg/L (Worksheet B04c1 and B04c2). This concentration is a more than 250 times less than the upper bound of the peak concentration of 7.5 mg/L after the accidental spill (Section 3.2.3.4.1, Worksheets B04a) [7.5 mg/L ÷ 0.028 mg/L ≈ 267.86]. Worksheets B04c1 (fine droplets) and B04c2 (coarse droplets) also model concentrations at distances of from 25 to 900 feet downwind based on standard values adapted from AgDrift for the different terrestrial broadcast application methods considered in this risk assessment (SERA 2011a). Based on these estimates, clethodim concentrations in a small pond contaminated by drift from at an application made 25 feet upwind would be 0.0009 mg/L for backpack applications (coarse droplets). For broadcast applications, the concentrations at 25 feet downwind would range from about 0.001 mg/L (low boom ground applications) to 0.006 mg/L (aerial) using fine droplets and about 0.0003 mg/L (low boom ground applications) to 0.004 mg/L (aerial) using coarse droplets.

Similar calculations can be made for scenarios involving a stream contaminated either by direct spray or drift (Worksheets B04d1 and B04d2). 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 in Gleams-Driver simulations (Section 3.2.3.4.3) 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 0.023 mg/L. For broadcast applications, the concentrations at 25 feet downwind would range from about 0.0008 mg/L (low boom ground applications) to 0.005 mg/L (aerial) using fine droplets and about 0.0002 mg/L (low boom ground applications) to 0.003 mg/L (aerial) using coarse droplets.

3.2.3.4.3. GLEAMS-Driver 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 2007a, 2011b).

Gleams-Driver offers the option of conducting exposure assessments using site-specific weather files from Cligen, a climate generator program developed and maintained by the USDA

Agricultural Research Service (USDA/NSERL 2004). Gleams-Driver was used in the current risk assessment to model clethodim concentrations in a small stream and a small pond.

As summarized in Table 11, nine locations are used in the Gleams-Driver modeling. These locations are standard sites used in Forest Service risk assessments for Gleams-Driver simulations and are intended to represent combinations of precipitation (dry, average, and wet) and temperature (hot, temperate, and cool) (SERA 2007a). The characteristics of the fields and bodies of water used in the simulations are summarized in Table 12. For each location, simulations were conducted using clay (high runoff, low leaching potential), loam (moderate runoff and leaching potential), and sand (low runoff, high leaching potential) soil textures. For each combination of location and soil, Gleams-Driver was used to simulate pesticide losses to surface water from 100 modeled applications at a unit application rate of 1 lb a.i./acre, and each of the simulations was followed for a period of about 1½ years post application. Note that an application rate of 1 lb a.i./acre is used as a convention in all Forest Service risk assessments in order to avoid rounding limitations in GLEAMS outputs. All exposure concentrations discussed in this risk assessment are based on an application rate of 0.25 lb a.i./acre.

Table 13 summarizes the chemical-specific values used in Gleams-Driver simulations. For the most part, the chemical properties used in the Gleams-Driver simulations are based on the parameters used by the Environmental Fate and Effects Division (EFED) of the U.S. EPA's Office of Pesticides Programs modeling of clethodim (U.S. EPA/OPP/EFED 2009a, 2014a). As discussed by U.S. EPA/OPP/EFED (2014a, p. 24), these input values are intended to encompass not only clethodim but also total residues/metabolites of concern. The EPA modeling efforts are discussed below (Section 3.2.3.4.4). In the current risk assessment, most of the model input values are based on the environmental fate studies submitted to the U.S. EPA by registrants as well as standard values for GLEAMS modeling recommended by Knisel and Davis (2000). The notes to Table 13 indicate the specific sources of the chemical properties used in the GLEAMS modeling effort.

Details of the results for the Gleams-Driver runs are provided in Appendix 8 (single application), Appendix 9 (two applications with a 14 day application interval), and Appendix 10 (four applications with 14 day application intervals). A summary of the results for the Gleams-Driver runs are presented in Table 14, along with a summary of other modeling efforts which are discussed further in the following subsection. The use of these estimates in developing the exposure assessments for the current risk assessment is discussed in Section 3.2.3.4.6.

3.2.3.4.4. Other Modeling Efforts

Other efforts to model clethodim concentrations in surface water are summarized in Table 14, which also summarizes the surface water modeling conducted for the current risk assessment (Section 3.2.3.4.3). To estimate concentrations of a pesticide in ambient water as part of a screening level risk assessment, the U.S. EPA typically uses Tier 1 screening models (e.g., GENEEC, FIRST, SCIGROW, and PRZM-GW). For more refined and extensive risk assessment, the Agency will typically use PRZM/EXAMS, a more Tier 2 modeling system. The U.S. EPA/OPP typically models pesticide concentrations in water at the maximum labeled rate. All of the concentrations given in Table 14 are expressed as Water Contamination Rates (WCRs)—i.e., the modeled concentration divided by the application rate. This adjustment

results in values expressed as µg/L per lb/acre, which are directly comparable to the other modeling values summarized in Table 14.

In support of human health and ecological risk assessments conducted by the U.S. EPA prior to 2014 (Table 1), the EPA used the FIRST and SCIGROW Tier 1 screening models. All EPA modeling was conducted for two applications with a 14-day application interval. In these simulations, the EPA estimated peak concentration in surface water is approximately 150 µg/L. This concentration is somewhat higher than the central estimates from Gleams-Driver (i.e., about 87 µg/L for a pond) but is well below the upper bound estimate from Gleams-Driver (i.e., about 1,200 µg/L for a pond). A similar pattern is apparent for longer-term concentrations in surface water. Using FIRST, the EPA estimates longer-term concentrations of 30.5 and 52 µg/L. The average of these two values, 41.25 µg/L, is virtually identical to the central estimate of longer-term concentrations from Gleams-Driver for two applications (i.e., about 41.8 µg/L for the pond).

The recent drinking water assessment for the registration review of clethodim (U.S. EPA/OPP/EFED 2013a), used PRZM-GW, a relatively new Tier 1 model analogous to GENEEC but designed to estimated upper bound concentrations of pesticides in ground water (U.S. EPA/OPP/EFED 2012a). As discussed in Section 2, the registration review documents from EPA indicated that the maximum number of applications per year for clethodim may be increased from 2 applications at 0.25 lb a.i./acre to 18 applications at 0.25 lb a.i./acre. Thus, the modeling with PRZM-GW is based on 18 applications at 0.25 lb a.i./acre. The values reported in U.S. EPA/OPP/EFED (2013a) adjusted to approximate 2 applications as indicated in the footnote to Table 14. While the water contamination rates from PRZM-GW are the highest estimates from U.S. EPA/OPP modeling, the upper bound concentrations from the GLEAMS-Driver simulations – i.e., about 1,160 µg/L – substantially exceed the estimates from PRZM-GW (635.6 µg/L). In the recent ecological risk assessment in support of the registration review of clethodim (U.S. EPA/OPP/EFED 2014a), the estimated concentrations of clethodim in surface water following two applications range from 16 to 26 µg/L in using PRZM (Tier 2). The upper bound of this range is similar to the central estimate for streams from GLEAMS-Driver (i.e., 25.6 µg/L) but a factors of about 2 to 3 below central estimate for ponds from GLEAMS-Driver (i.e., 43.5 µg/L).

The comparisons of the simulations produced by EPA and Gleams-Driver for clethodim are similar to many other comparisons noted in other Forest Service risk assessments. Because Gleams-Driver is applied to numerous site/soil combinations and because 100 simulations are conducted for each site/soil combination, the upper bound values from Gleams-Driver often exceed the concentrations obtained from conservative Tier 1 models. Because the overall intent of Gleams-Driver is to estimate both central estimates and uncertainty bounds associated with the central estimates, the conservative Tier I models from EPA typically yield concentrations higher than the central estimate from Gleams-Driver.

3.2.3.4.5. Monitoring Data

As noted in U.S. EPA/OPP (2006a, p. 3) there is a general lack of monitoring data on clethodim in surface water and groundwater, which is underscored by the lack of data in the compendia on pesticide concentrations in streams and groundwater (USGS 2007).

3.2.3.4.6. Concentrations in Water Used for Risk Assessment

The modeled surface water concentrations of clethodim used in the current risk assessment are summarized in Table 15. 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 14, the summary of all of the modeling efforts, units of exposure are expressed as ppb or µg/L, as a matter of convenience. In Table 15, however, ppb is converted to mg/L (ppm) because mg/L is the unit of measure used in the EXCEL workbooks for contaminated water exposure scenarios in both the human health and ecological risk assessments. The water contamination rates are entered in Worksheet B04Rt in Attachment 1 (single application) and Attachment 2 (two applications with a 14-day application interval). The values in Worksheet B04Rt are linked to the appropriate scenario-specific worksheets in the EXCEL workbooks.

As discussed previously and summarized in Table 15, the Gleams-Driver simulations of the small pond provide the highest estimates of clethodim concentrations in surface water. Consequently, the Gleams-Driver simulations serve as the primary basis for the water concentrations of clethodim used in the current risk assessment. As noted in 3.2.3.4.5, monitoring data on concentrations of clethodim in surface water are not available in the literature. While the Gleams-Driver estimates are reasonably consistent with U.S. EPA/OPP modeling (Section 3.2.3.4.4), the lack of monitoring data adds uncertainty to this risk assessment.

3.2.3.5. Oral Exposure from Contaminated Fish

Many chemicals may be concentrated or partitioned from water into the tissues of aquatic animals or plants. This process is referred to as bioconcentration. Generally, bioconcentration is measured as the ratio of the concentration in the organism to the concentration in the water. For example, if the concentration in the organism is 5 mg/kg and the concentration in the water is 1 mg/L, the bioconcentration factor (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. Details regarding the relationship of the bioconcentration factor to standard pharmacokinetic principles are provided in Calabrese and Baldwin (1993).

Three sets of exposure scenarios are presented: one set for acute exposures following an accidental spill (Worksheets D08a and D08b), one set for acute exposures based on expected peak concentrations of clethodim in water (Worksheets D09c and D09d), and another set for chronic exposures based on estimates of longer-term concentrations in water (Worksheets D09a and D09b). The two worksheets for each set of scenarios are included to account for different consumption rates of caught fish among the general population and subsistence populations. Details of these exposure scenarios are provided in Section 3.2.3.5 of SERA (2014a).

The scenarios associated with consumption of contaminated fish are based on the same concentrations of clethodim in water used for the accidental spill scenario (Section 3.2.3.4.1.) and the drinking water exposure estimates (Section 3.2.3.4.6).

Experimental bioconcentration factors are required by the EPA as part of the registration process. As summarized in Table 2, two bioconcentration studies were submitted to the U.S. EPA/OPP, MRID 409745-31and MRID 409745-24. For edible tissue (i.e., the portion of the fish that would

be consumed by humans), the reported bioconcentration factors are 0.71 (MRID 409745-31) and 2.1 (MRID 409745-24). While these values do not differ substantially, the lower value is used for acute exposure scenarios and the upper value is used for longer-term exposure scenarios. This approach is identical to the approach used for the consumption of fish by wildlife (Section 4.2.2.5), except that whole fish bioconcentration factors are used.

3.2.3.6. Dermal Exposure from Swimming in Contaminated Water

Some geographical sites maintained by the Forest Service or Forest Service cooperators include surface water in which members of the general public might swim. The extent to which this might apply to areas treated with clethodim is unclear, and this exposure scenario is included in the current risk assessment.

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 D10). 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 in the corresponding worker exposure scenario, the 1-hour period of exposure is somewhat arbitrary given that longer periods of exposure are plausible. Nonetheless, the 1-hour period is intended as a unit exposure estimate. In other words, both the absorbed dose and consequently the risk will increase linearly with the duration of exposure, as indicated in Worksheet D10. Thus, a 2-hour exposure would lead to an HQ 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). For clethodim, however, the HQs for this scenario are far below the level of concern.

As with the exposure scenarios for the consumption of contaminated fish, the scenarios for exposures associated with swimming in contaminated water are based on the peak water concentrations of clethodim used to estimate acute exposure to drinking water (Section 3.2.3.4.6).

3.2.3.7. Oral Exposure from Contaminated Vegetation

Although none of the Forest Service applications of clethodim will involve crop treatment, crop treatments may be conducted on some Forest Service lands by individuals or organizations with authorization from the Forest Service to use Forest Service lands for the cultivation of crops. All such agricultural applications are subject to U.S. EPA/OPP regulatory constraints (e.g., tolerance limits) and exposures associated with agricultural applications are not explicitly considered in Forest Service risk assessments. Nonetheless and as discussed further below, longer-term dietary exposures to clethodim associated with agricultural applications by EPA are less than the longer-term exposure assessments developed for forestry applications of pesticides.

For pesticides that may be applied to vegetation, Forest Service risk assessments 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, detailed in Worksheets D03a (fruit) and D03b (vegetation) for acute exposure and Worksheets D04a (fruit) and D04b (vegetation) for chronic exposure, apply only to terrestrial applications of clethodim (Attachment 1) and are omitted from the EXCEL workbook for aquatic applications of clethodim (Attachment 2).

The pesticide contamination on 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) at a normalized application rate of 1 lb a.i./acre. Although the EPA human health risk assessments 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 assessments of clethodim (U.S. EPA/OPP/EFED 2006a, 2007a).

The residue rates recommended by Fletcher et al. (1994) are given in Table 16 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 16 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). As summarized in Table 16, Fletcher et al. (1994) provide residue rates for four different classes of plant material, including short grass, tall grass, broadleaf vegetation, and fruits. While all four groups of plant material are used in the ecological risk assessment (Section 4.2.2), only broadleaf vegetation and fruit are used in the human health risk assessment.

For longer-term exposures, the time-weighted-average concentrations are estimated using the initial pesticide concentration, the half-life on vegetation, the number of applications, and the application interval. These calculations are detailed in Worksheet B05a (fruit) and Worksheet B05b) for broadleaf vegetation. In these worksheets, the halftimes are identical to those used in the Gleams-Driver modeling—i.e., 5.75 (5.4-6.1) days. Experimental half-lives for clethodim on fruit or broadleaf vegetation are not reported in the available literature. As noted in Table 13, the half-lives for clethodim on vegetation are based on the approximation from Juraske et al. (2008)

in which the half-lives in soil are divided by a factor of 4 to estimate the half-lives for total residues in vegetation. The soil half-lives, as summarized in Table 13, are taken from U.S. EPA/OPP/EFED (2009a, p. 4, MRIDs 409745-21 and MRID 413768-01) and the Agency adjusted these half-lives for total toxic residue. As illustrated in Figure 1 and discussed in Section 2.2, clethodim is structurally similar to sethoxydim, which has a reported foliar half-life of 3 days (Knisel and Davis 2000, p. 119). The similarity of the estimated half-lives for clethodim to the reported foliar half-life for sethoxydim supports the approximation method from Juraske et al. (2008).

Based on 2 applications at a rate of 0.25 lb a.i./acre, the U.S. EPA/OPP/HED (2010a, Table 5.2, p. 29) estimated a chronic dose to members of the general public of 0.002992 mg/kg bw/day. The comparable exposure assessment in the current Forest Service risk assessment is given Worksheet D04b of Attachment 2 – i.e., the consumption of broadleaf vegetation by a young woman following 2 applications of clethodim at a rate of 0.25 lb a.i./acre with a 14 day application interval. For this exposure scenario, the estimated doses in the current Forest Service risk assessment are about 0.0075 (0.0005 to 0.066). The central estimate is higher than the EPA estimate by about a factor of about 2.5 [$0.0075 \div 0.002992 \approx 2.507$] and the upper bound estimate is higher than the EPA estimate by about a factor of about 22 [$0.066 \div 0.002992 \approx 22.06$]. This is a common pattern. Chronic dietary exposures in Forest Service risk assessments are typically higher than corresponding estimates in EPA risk assessments because the latter are limited by agricultural tolerances, which are not limiting factors in Forest Service risk assessments.

As discussed in Section 2.4, the use of clethodim in Forest Service programs is likely to involve only 1 or 2 applications at an individual application rate of 0.25 lb a.i./acre but the U.S. EPA/OPP is in the process of permitting up to 18 applications of clethodim at this application (U.S. EPA/OPP/HED 2014a; U.S. EPA/OPP/EFED 2014a). In terms of peak residues on vegetation, it is worth noting that increasing numbers of applications have little impact. As illustrated in Figure 6, this follows directly from the estimated half-lives on vegetation as well as the plateau principle, as specified in Equation 2 and discussed in Section 3.1.3.3. For example, the upper bound peak concentration of clethodim on broadleaf vegetation is about 40.6 mg/kg following 2 applications (Attachment 2, Worksheet B05b) and 42.4 mg/kg following 18 applications (Attachment 4, Worksheet B05b).

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

Table 17 provides an overview of the dose-response assessment used in this risk assessment. The available data on the toxicity of clethodim to mammals is reasonably complete, and, as standard practice, the toxicity values derived in the most recent EPA human health risk assessment (U.S. EPA/OPP/HED 2014a) are adopted without modification. Forest Service risk assessments typically defer to the U.S. EPA in the derivation of toxicity values used in the human health risk assessment, unless there is a compelling reason to differ with the EPA. In the case of clethodim, the toxicity values derived by the U.S. EPA are preferable to toxicity values proposed by the European Food Safety Authority (EFSA 2011).

3.3.2. Chronic RfD

The U.S. EPA has not derived an agency-wide RfD for clethodim—i.e., there is no RfD for clethodim listed on the U.S. EPA Integrated Risk Information System (http://www.epa.gov/iris/).

The most recent U.S. EPA/OPP human health risk assessment derives a chronic RfD of 0.3 mg/kg/day (U.S. EPA/OPP/HED 2014a). This RfD is based on the 18 month carcinogenicity study in mice which yielded a NOAEL of 30 mg/kg bw/day with a corresponding LOAEL of 150 mg/kg bw/day based on … *treatment related effects on survival, decreased red cell mass (decreased erythrocyte counts, hemoglobin, and hematocrit values), increased liver weights, and increased foci of amphophilic alveolar macrophages in the lung, bile duct hyperplasia, and increased pigmentation in the liver* (U.S. EPA/OPP/HED 2014a, p. 35). In deriving the chronic RfD, the EPA uses an uncertainty factor of 100 (10 for species-to-species extrapolation and 10 for sensitive subgroups in the human population) [30 mg/kg/day ÷ 100 mg/kg/day = 0.3 mg/kg bw/day]. Because the available data on reproductive toxicity and teratogenicity do not indicate that young animals are more sensitive than adults to clethodim, an additional uncertainty factor for infants or children is not applied (U.S. EPA/OPP 2014a, p. 13).

The European Food Safety Authority (ESFA 2011) recommends a somewhat lower chronic value of 0.16 mg/kg/day. This value is designated as an ADI (Acceptable Daily Intake) which is essentially equivalent to a chronic RfD. The ESFA (2011, p. 10) states that this ADI is based on a chronic rat NOAEL and an uncertainty factor of 100. The ESFA, however, does not identify or provide a citation to the chronic study in rats. As summarized in Appendix 1 (Table A1-2), the chronic rat NOAEL reported by the U.S. EPA is 19 mg/kg/day (MRID 410301-21). It seems likely that ESFA (2011) is referring to MRID 410301-21 but may have used a somewhat different method to estimate the average daily dose based on the concentrations of clethodim in the diet. The EPA chronic RfD is adopted for the current Forest Service risk assessment without modification.

3.3.3. Acute RfD

The U.S. EPA/OPP/HED (2014a, p. 31) risk assessment for clethodim has derived an acute RfD of 1 mg/kg bw/day. This RfD is based on two acute neurotoxicity studies (MRID 487885-02 in 2012 and MRID 481418-01 in 2006) which yielded a NOAEL of 100 mg/kg bw/day with a corresponding LOAEL of 1,000 mg/kg bw/day based on decreased spontaneous activity, ruffled fur, head tilt, and hunched posture. In deriving the RfD, an uncertainty factor of 100 is used based a factor of 10 for extrapolation from experimental mammals to humans (i.e., interspecies

variability) multiplied by a factor of 10 for potentially sensitive individuals (i.e., intraspecies variability). This acute RfD is used without modification in the current Forest Service risk assessment.

The approach taken by U.S. EPA/OPP/HED (2014a) is more conservative than the approach taken in the recent assessment by the European Food Safety authority which notes: *Considering the toxicological profile of clethodim, the experts agreed that an Acute Reference Dose (ARfD) is not needed* (ESFA 2011, p. 10)

3.3.4. Surrogate RfD for Occupational Exposures

Instead of deriving RfDs for occupational exposure, the EPA will identify a longer-term NOAEL and recommend a margin of exposure (MOE). Often, the EPA uses the same longer-term toxicity value used to derive the chronic RfD, in which case, the recommended MOE will be identical to the uncertainty factor used to derive the chronic RfD. This, however, is not the case for clethodim.

Rather than assessing occupational exposures based on a chronic/lifetime RfD—i.e., the chronic rat NOAEL of 30 mg/kg bw/day with an acceptable MOE of 100—the most recent U.S. EPA risk assessment selected an intermediate-term exposure of 1 to 6 months using a subchronic dog NOAEL of 75 mg/kg bw/day (MRID 410301-06) with an acceptable MOE of 100. This approach is essentially equivalent to deriving an occupational RfD of 0.75 mg/kg bw/day.

This most recent occupational assessment from the U.S. EPA differs from the Occupational and Residential Exposure Assessment for clethodim (U.S. EPA/OPP/HED 2002a, p. 9) which used 25 mg/kg bw as the subchronic dog NOAEL. As noted in Section 3.1.2, however, this difference is based on a re-evaluation of the subchronic dog study in which the 75 mg/kg/day dose group was reclassified as a NOAEL. As also discussed in Section 3.1.2, the EPA does not detail the rationale for this reevaluation but it appears to reflect a consideration of effects on the liver which reflect the induction of cytochrome P450 rather than frank liver pathology.

Analogous to the approach taken with the surrogate acute RfD, 0.75 mg/kg bw/day is used in the current risk assessment as a surrogate occupational RfD for clethodim.

EFSA (2011) recommends an *Acceptable Operator Exposure* of 0.2 mg/kg bw/day, which appears to be based on their recommended ADI of 0.16 mg/kg bw/day rounded to one significant digit. As discussed in Section 3.3.2, ADI and Acceptable Operator Exposure appear to be based on the chronic rat NOAEL.

3.3.5. Dose-Severity Relationships

Forest Service risk assessments sometimes consider dose-severity relationships in an effort to more fully characterize potential risks in exposure scenarios where the doses exceed the RfD. For clethodim, however, this approach is not justified. As discussed in Section 3.4, none of the exposure scenarios for members of the general public exceed the level of concern (HQ=1). Based on the relationships of NOAELs to LOAELs (Table 17), HQs that would clearly trigger a concern for potential adverse effects are 10 for acute exposures [1000 mg/kg bw/day acute LOAEL ÷ 100 mg/kg bw/day acute NOAEL] and 5 for longer-term exposures [150 mg/kg bw/day chronic LOAEL ÷ 30 mg/kg bw/day chronic NOAEL].

As discussed in Section 3.1.9.1, the NOAEL of 75 mg/kg bw/day from the subchronic study in dogs is close to the LOAEL of 100 mg/kg bw/day in the developmental study in rabbits (MRID 410301-15). This proximity enhances concern with occupational exposures which exceed surrogate occupational RfD of 0.75 mg/kg bw/day. Conversely, the LOAEL of 100 mg/kg bw/day is based on relatively mild effects – i.e., reduced body weight gain and reduced food consumption with no signs of overt toxicity. Thus, while any occupational exceedances of the surrogate occupational RfD of 0.75 mg/kg bw/day are a concern, the plausibility of observing adverse effects following modest exceedances [100 mg/kg bw/day ÷ 75 mg/kg bw/day ≈ 1.333…] is not clear. Nonetheless, based on the relationship of the LOAEL to the NOAEL in the dog study on which the surrogate occupational RfD is based, HQs in excess of about 1.66 [LOAEL of 125 mg/kg bw/day ÷ NOAEL of 75 mg/kg bw/day] would be a cause for concern.

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 a toxicity value with an HQ of greater than 1 defined as the level of concern—i.e., the exposure exceeds the level of concern. For the human health risk assessments the toxicity values are a surrogate acute RfD of 1 mg/kg bw/day, a surrogate intermediate RfD of 0.75 mg/kg bw/day for workers, and a chronic RfD of 0.3 mg/kg bw/day for chronic exposures in members of the general public (Section 3.3).

Workers involved in either ground broadcast or aerial applications do not appear to be at risk even at the upper limits of estimated non-accidental exposures. The upper bound prediction interval of the HQ for workers involved in backpack applications is 1.3. Based on dose-severity relationships in experimental mammals (Section 3.3.5), this HQ is not likely to be associated with overt signs of toxicity; however, covert effects (e.g., effects on the liver) cannot be ruled out. For backpack applications the upper bound prediction interval for exposures could be associated with applications in rough terrain or with poor personal hygiene practices during application. The upper bound of the standard accidental exposure scenario for a worker wearing contaminated gloves leads to an HQ of 4. This exposure scenario can be mitigated by washing contaminated hands and promptly replacing contaminated gloves.

For members of the general public, none of the exposure scenarios result in HQs that exceed the level of concern. The highest HQ is the upper bound of 0.9 associated with an accidental spill. The highest HQs for non-accidental exposure scenarios are associated with the consumption of contaminated vegetation – i.e., upper bound HQs of 0.4 for acute exposures and 0.2 for longer-term exposures following two applications at the maximum application rate of 0.25 lb a.i./acre.

3.4.2. Workers

The quantitative risk characterization for workers is summarized in Table 18. The HQs given in this table are taken from Worksheets E02 in Attachments 1 and 2. Note that the HQs for workers are identical in both EXCEL workbooks, which will be true regardless of the number of applications that are made. Accidental scenarios model only a single event. The general exposure scenarios assume that the worker will repeatedly apply the pesticide—i.e., a longer-term toxicity value is used. Thus, the worker risk will be the same if the worker is repeatedly applying the pesticide to the same field or applying the pesticide to different fields.

3.4.2.1. Accidental Exposures

The only accidental exposure scenario that leads to an excursion above the level of concern [HQ=1] is the upper bound of the HQ for wearing contaminated gloves for 1 hour [HQ=4]. As summarized in Table 17, the HQ for this and other accidental exposure scenarios is based on the surrogate acute RfD of 1 mg/kg bw/day which, in turn, is based on a NOAEL of 100 mg/kg bw/day with a corresponding LOAEL of 350 mg/kg bw/day based on decreased body weight and salivation in rats. The HQ of 4 is greater than the dose spacing of the NOAEL and LOAEL [350÷100=3.5]; thus, it could be regarded with concern. As discussed in Section 3.3.2, however, the data on which this surrogate acute RfD is based are from a multiple dose study and the U.S. EPA/OPP uses this RfD for exposures ranging from 1 to 30 days. This does, at least to some

extent, diminish concern for the upper bound HQ of 4 for the acute (single event) contaminated glove scenario. The most sensible interpretation of the HQ of 4 amounts to little more than standard practice in any pesticide application—i.e., hands should be washed and gloves should be replaced as soon as possible after gloves become contaminated.

As discussed in Section 3.1.11, clethodim may cause moderate skin irritation and mild eye irritation. From a practical perspective, skin or eye irritation is likely to be the only overt effect as a consequence of mishandling clethodim. Eye irritation can be minimized or avoided by prudent industrial hygiene practices, including the use of protective eye wear. The most recent EPA human health risk assessment (U.S. EPA/OPP/HED 2014a, p. 4) specifically requires protective eyewear during application. This requirement is reflected in almost all of the product labels for the clethodim formulations summarized in Table 4 (i.e., Clethodim 2E, Clethodim 2EC, Dakota, Envoy, Envoy Plus, Intensity, Intensity One, Prism, Section 2EC, Select 2EC, Shadow, Tapout). The only formulation that does not specifically recommend or require protective eyewear on the product label is Arrow 2 EC (Manna).

3.4.2.2. General Exposures

For the general exposures, meaning exposures anticipated in the normal use and application of clethodim, the risk characterization is reasonably simple. The central estimates of the HQs are below the level of concern by factors of 10 [HQ=0.1 for backpack workers] to over 300 [HQ of 0.003 for aerial applications]. The upper bound HQs based on confidence intervals are below the level of concern by factors of about 3 [HQ=0.3 for backpack workers] to 50 [HQ of 0.02 for aerial applications]. Simply put, these HQs indicate that average exposures in groups of workers applying clethodim are likely to be well below the level of concern.

The upper bound of the prediction interval for backpack workers [HQ=1.3] does modestly exceed the level of concern. Simply put, this HQ indicates that backpack applications of clethodim could lead to levels of exposure in some workers that would be viewed as excessive and imprudent. As summarized in Table 17, the HQs for workers are based on a NOAEL of 75 mg/kg bw/day with a corresponding LOAEL of 125 mg/kg bw/day. Thus, an HQ of about 1.7 would be viewed with clear concern [125 ÷ 75 = 1.6666]. The upper bound of the prediction interval, the HQ of 1.3, is in the middle of the range between a level of concern [HQ=1] and a clearly imprudent exposure level [HQ=1.7]. At this upper bound exposure level, overt signs of toxicity seem unlikely; however, covert effects (e.g., effects on the liver) could occur. As detailed in SERA (2013), the upper bound exposures for the prediction interval would most likely reflect adverse conditions during the application (e.g., rough terrain) and/or poor worker practices in terms of limiting exposures. A mitigating factor in poor terrain could involve the assumptions on which the exposure assessment for backpack workers is based. As summarized in Table 10, the upper bound of 8 acres per day is used with the upper bound worker exposure rates for backpack applications. If backpack workers are applying clethodim in rough terrain, this upper bound treatment rate may not be realistic. This argument is not considered further in the current risk assessment but could be considered in a specific planned application of clethodim.

3.4.3. General Public

The quantitative risk characterizations for members of the general public are summarized in Table 19 for a single application at 0.25 lb a.i./acre and Table 20 for two applications at 0.25 lb a.i./acre with a 14-day application interval. The HQs given in these tables are taken from Worksheets E04 in Attachment 1 (single application) and Attachment 2 (two applications). As with workers, the quantitative risk characterizations for the general public are expressed as HQs (i.e., the estimated exposure divided by a toxicity value) using the acute RfD of 1 mg/kg/day for acute exposures and chronic RfD of 0.3 mg/kg bw/day for longer-term exposures (Table 17).

3.4.1.1. Accidental Exposures

None of the HQs for the accidental exposure scenarios exceed the level of concern (HQ=1). The scenarios of greatest concern involve the upper bounds of the HQs for a small child consuming contaminated water following an accidental spill (HQ=0.9) or the accidental direct spray of a small child (HQ=0.7). As with the accidental exposure scenarios for workers, the accidental exposure scenarios are the same for both one and two applications—i.e., accidental exposures are assumed to occur only once. Although these exposure scenarios are intentionally extreme, they could be made more extreme. While HQs for the accidental exposure scenarios do not exceed the level of concern, common sense dictates that attempts should be made to limit exposures to members of the general public after an accidental event involving any pesticide application.

3.4.1.2. Non-Accidental Exposures

None of the acute non-accidental exposure scenarios for members of the general public exceed the level of concern (HQ=1). All exposure scenarios involving contaminated water are substantially below the level of concern—i.e., factors of about 33 (the upper bound HQ of 0.03 for water consumption by a small child following two applications) to over 150 million (the lower bound HQ of $6x10^{-9}$for the consumption of contaminated fish following one application).

The HQs for the acute consumption of contaminated vegetation approach but do not exceed the level of concern—i.e., upper bound HQs of 0.3 following one application and 0.4 following two applications. As discussed in Section 2, clethodim will be used to treat grassy weeds and would not be intentionally applied to vegetation or fruits that might be consumed by humans in a treated area. While the inadvertent application of clethodim to vegetation that might be consumed by humans would not be likely in backpack (i.e., directed foliar) applications, the inadvertent application of clethodim to edible vegetation seems plausible in ground broadcast applications and likely in aerial applications if consumable vegetation or fruit occur in the treated area. For acute exposures, however, even the upper bound estimates of exposures are below the level of concern.

As with acute exposures, none of the longer-term exposure scenarios exceed the level of concern (HQ=1). Also as with the acute exposure scenarios, the highest longer-term HQs are associated with the consumption of contaminated vegetation – i.e., upper bound HQs of 0.1 following one application and 0.2 following two applications. Again, the contamination of consumable vegetation seems unlikely with backpack or other directed foliar applications, plausible in ground broadcast applications, and likely in aerial applications.

3.4.4. Sensitive Subgroups

As indicated in Section 3.1.3, the mechanism of action for the acute and chronic toxicity in mammals is unclear. Effects noted in experimental mammals include decreases in food consumption as well as decreased body weight and the occurrence of liver pathology. These effects, however, would occur only at high doses, and it is not clear that exposures to clethodim following the types of applications proposed by the Forest Service would aggravate responses in individuals with liver disease. In an evaluation of the reproductive and developmental toxicity data on clethodim (summarized in Section 3.1.9 of this document), the most recent EPA risk assessment on clethodim specifically notes young animals do not appear to be more sensitive to clethodim than adult animals (U.S. EPA/OPP/HED (2014a, p 13).

As discussed in Section 3.1.11.2, the U.S. EPA/OPP does not classify clethodim as a skin sensitizer but a skin sensitization assay on Select 2 EC (Blaszak 1998) does indicate that this formulation did induce skin sensitization in guinea pigs. In addition, the MSDS for Select 2 EC as well as MSDSs for some other clethodim formulations (i.e., Envoy, Envoy Plus, Intensity One) indicate clethodim is or may be a skin sensitizer. Consequently, the potential for skin sensitization in some individuals is a concern in the handling of these formulations. As with the application of any pesticide or other chemical, adverse skin reactions in individuals handling clethodim would warrant medical attention.

As discussed in Section 3.1.13, the MSDSs for Envoy and Select 2 EC indicate that these formulations may be respiratory irritants. While the basis for this concern has not been identified, the information on the MSDS cannot be ignored and the potential for respiratory irritation in some individuals is considered an endpoint of concern.

3.4.5. Connected Actions

There is no available data regarding the toxicity of clethodim combined with other pesticides in mammals. As noted in Section 2, formulations of clethodim contain petroleum solvents and/or surfactants. There is no information, however, suggesting that these agents have a substantial impact on the toxicity of clethodim to humans or experimental mammals. As discussed in Section 3.1.14.2, the very limited information on the toxicity of clethodim formulations suggests that the contribution of the other ingredients in the clethodim formulations is insubstantial.

3.4.6. Cumulative Effects

Cumulative effects may involve either repeated exposures to an individual agent or simultaneous exposures to the agent of concern (in this case clethodim) and other agents that may cause the same effect or effects by the same or a similar mode of action.

The most recent EPA human health risk assessment on clethodim did not make a determination of whether other pesticides may have cumulative effects with clethodim.

> *Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to clethodim and any other substances and clethodim 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 clethodim has a common mechanism of toxicity with other substances.*
>
> U.S. EPA/OPP (2014a, pp. 22-23)

In the absence of a determination of a common mechanism of action with other pesticides, the U.S. EPA/OPP has not further developed a cumulative effects determination involving clethodim.

As noted in the current risk assessment, clethodim is structurally similar to sethoxydim (Figure 1), and both clethodim and sethoxydim are cyclohexanedione oxime herbicides which have the same mechanism of action in plants and cause similar signs of toxicity in mammals. As the U.S. EPA further develops approaches for dealing with cumulative effects from substances found to have a common mechanism of action, it seems reasonable to speculate that clethodim, sethoxydim, and perhaps other cyclohexanedione oxime herbicides may be grouped together in assessing cumulative effects.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

While the mammalian data on clethodim are clearly sufficient for hazard identification, the data on most other groups of animals are limited. The limitations are particularly severe for fish and aquatic invertebrates. In addition, the hazard identification of clethodim is further limited by the lack of toxicity data on terrestrial-phase and aquatic-phase amphibians and reptiles. All of the information used in the ecological risk assessments for animals comes from studies submitted to the U.S. EPA/OPP in support of the registration of clethodim. Information on these studies is taken primarily from recent EPA ecological risk assessments on clethodim (U.S. EPA/OPP/EFED 2007a,b, 2014a).

Based on acute toxicity, U.S. EPA/OPP (2007a,b; 2014a) classifies clethodim as *practically non-toxic* to mammals, birds, and honeybees and as *slightly to practically non-toxic* to fish. Based on the available toxicity data, clethodim would be classified as *moderately toxic* to aquatic invertebrates. As with most ecological risk assessments, toxicity data are available on only a few species, relative to the numerous species which may be exposed to clethodim; thus, the assessment of the hazards or lack of hazards to most groups of terrestrial nontarget species is constrained accordingly.

The longer-term toxicity in mammals and birds is relatively well characterized by standard studies required for pesticide registration. These studies include subchronic, chronic, reproductive, and developmental studies in mammals as well as reproduction studies in birds. Toxicity studies involving longer-term exposures to aquatic organisms, however, are sparse. A single reproduction study is available in daphnids and an early life stage study is available in fathead minnows. While the daphnid reproduction study appears to have been properly conducted, the early life stage study in fathead minnows has several substantial deficiencies.

Clethodim is an effective herbicide for the control of grasses. While there is essentially no open literature on the potential effects of clethodim on nontarget animals, there is an abundant open literature demonstrating the efficacy of clethodim for the control of grass weeds (monocots) and the relative lack of phytotoxicity to nontarget plants, particularly dicots. This information form the open literature is supported by standard bioassays of clethodim in dicots which indicate that clethodim causes only slight effects on some dicots at the maximum application rate of 0.25 lb a.i./acre. While many monocots are sensitive to clethodim at much lower application rates, onions (which are monocots) appear to be relatively insensitive to clethodim.

The application of any effective herbicide will damage at least some vegetation, and this damage, in turn, may alter (either positivity or negatively) the suitability of the treated area for terrestrial and aquatic organisms in terms of habitat, microclimate, or food supply. These secondary effects (i.e., effects on the organism that are not a consequence of direct exposure of the organism to clethodim) would occur with any equally effective method of vegetation management—i.e., mechanical or herbicide use. The potential for secondary effects is acknowledged but not otherwise considered in the risk assessment for nontarget species.

4.1.2. Terrestrial Organisms

4.1.2.1. Mammals

The toxicity studies used to assess the potential hazards of clethodim to humans (Appendix 1) are applicable to the risk assessment for mammalian wildlife. While the toxicity of clethodim to plants is understood relatively well (Section 4.1.2.5), it is not clear what, if any, specific toxicity clethodim may cause in mammalian wildlife. Field studies to investigate the impact of clethodim on mammalian wildlife were not found in the available literature. As discussed in Section 3.1 and summarized in Appendix 1, body weight loss or decreased body weight gain is the most consistent effect observed in experimental mammals exposed to clethodim in acute, subchronic, and chronic toxicity studies.

While human health risk assessments typically focus on the most sensitive species, the ecological risk assessment is concerned with differences in toxicity among species. No substantial or systematic differences are apparent in the acute toxicity of clethodim to dogs, mice, rats, and rabbits. As summarized in Table 21, the chronic NOAELs and LOAELs span a relatively narrow range of doses for mice, rats, and dogs – i.e., NOAELs from 21 to 75 mg/kg bw/day and LOAELs of 113 to 150 mg/kg bw/day. The comparison of subchronic NOAELs and LOAELs is complicated by differences in the durations of the available studies. Ninety day NOAELs and LOAELs are available for rats and dogs and these values are within a factor of less than two. Given the similarities of the NOAELs and LOAELs between rats and dogs, canids are not identified as a potentially sensitive subgroup of species. Consequently, as discussed further in Section 4.3.2.1, separate dose-response assessments are not developed for chronic exposure of canids and non-canid mammals.

No acute toxicity data are available on canids, which is a circumstance common to most pesticide risk assessments. Consequently, separate acute dose-response assessments are not derived for canid and non-canid mammals. While this lack of information adds uncertainty to the risk assessment, the uncertainty is not substantial given the similarities in the subchronic and chronic NOAELs and LOAELs for rats and dogs.

4.1.2.2. Birds

As summarized in Appendix 2, a standard set of toxicity studies—i.e., acute gavage studies (Appendix 2, Table 1), acute dietary studies (Appendix 2, Table 2), and reproduction studies (Appendix 2, Table 3) were submitted to the U.S. EPA/OPP in support of the registration of clethodim. The U.S. EPA/OPP typically requires these studies to be conducted on both mallard ducks and bobwhite quail. Acute dietary and reproduction studies are available in both quail and mallards. It appears, however, that an acute gavage study was conducted with bobwhite quail, but not with mallard ducks.

Reasonably detailed Data Evaluation Records (DERs) are available for the acute gavage study in quail (Hinken and Grimes 1986, MRID 40974525 and the reproduction study in quail (Beavers 1988a, MRID 41030206). All of the other information in Appendix 2 is taken from recent EPA ecological risk assessment on clethodim (U.S. EPA/OPP/EFED 2007a,b, 2014a). The risk assessments, however, does not provide detailed discussions of the toxicity studies in birds. One limitation in comparing the dietary studies on quail and mallards is the lack of information on food consumption. The DER for the reproduction study in quail (Beavers 1988, MRID

41030206) indicates that food consumption was recorded, but does not provide such data. Furthermore, food consumption data from the other dietary studies are not reported in the available summaries of these studies. In Appendix 2, dietary concentrations for quail and mallards are estimated from acute and reproduction studies on aminopyralid in these species (SERA 2007b). In all cases, the dose in mg/kg bw/day is corrected for the reported % a.i. in technical grade clethodim.

As with studies included in the human health risk assessment, the U.S. EPA/OPP uses a classification system for categorizing the acute toxicity of pesticides to various groups of nontarget species (see SERA 2014a, Table 16 with discussion in Section 4.1.2). Based on the acute gavage study in quail with an LD_{50} of >2000 mg/kg bw/day, U.S. EPA/OPP/EFED (2007b, p. 44; 2014a, p. 40) classifies clethodim as *Practically Nontoxic* to birds. In the acute gavage study, signs of toxicity including lethargy, wing droop, and a ruffled appearance on Day 1 of the study were noted in the two high dose groups, 1650 and 2000 mg/kg bw. By day 6, however, all animals appeared normal. A transient decrease in body weight along with a decrease in food consumption was noted over the first 3 days of the study.

Based on the acute dietary studies in quail and mallards, there are no apparent differences in species sensitivity—i.e., NOAELs of about 1050 mg a.i./kg bw/day for quail and 947.1 mg a.i./kg bw/day for mallards (Appendix 2, Table A2-2). Based on the reproduction studies, however, mallards appear to be more tolerant than quail. At a dietary concentration 833 ppm, mallards evidenced no adverse effects but quail evidenced a decrease in survival, egg viability, and egg hatch (Appendix 2, Table A2-3). As discussed in Section 4.1.2.1, weight loss and decreased body weight gain are endpoints commonly observed in mammalian toxicity studies on clethodim. According to the relatively detailed DER for the reproduction study in quail (Beavers 1988, MRID 41030206), clethodim did not have an impact the body weights of adults or offspring.

4.1.2.3. Reptiles and Amphibians (Terrestrial-Phase)

There is no information regarding the toxicity of clethodim to reptiles or terrestrial-phase amphibians in the open literature or in the available EPA studies (U.S. EPA/OPP/EFED 1990b, 2007a,b, 2008a). Neither the database maintained by Pauli et al. (2000) nor the open literature includes information on the toxicity of clethodim to reptiles or terrestrial-phase amphibians.

Risks to terrestrial phase amphibians are addressed in the EPA ecological risk assessments on clethodim prepared by the Environmental Fate and Effects Division (EFED) of U.S. EPA/OPP (U.S. EPA/OPP/EFED 2007a,b, 2014a). In these ecological risk assessments as well as many similar ecological risk assessments prepared by U.S. EPA/OPP, birds are used as surrogates for terrestrial phase amphibians and reptiles (e.g. U.S. EPA/OPP/EFED 2014a, p. 64) in the absence of data on these groups of organisms. A concern with the use of birds as a surrogate for amphibians involves the permeability of amphibian skin to pesticides and other chemicals. While no data are available on the permeability of amphibian skin to clethodim, Quaranta et al. (2009) have noted that the skin of the frog *Rana esculenta* is much more permeable to several pesticides than pig skin and that these differences in permeability are consistent with differences in the structure and function of amphibian skin relative to mammalian skin.

4.1.2.4. Terrestrial Invertebrates

The honey bee is the standard test organism for assessing the potential effects of pesticides on terrestrial invertebrates. For foliar applications of pesticides, which may result in honey bee exposures, U.S. EPA requires an acute contact study with the technical grade pesticide.

As summarized in Appendix 3, Table A3-1, Data Evaluation Records (DERs) for acute contact bioassays in bees are available on both technical grade clethodim (Atkins 1986, MRID 409745-32) and Select 2.0 EC (Hoxter and Smith 1990, MRID 416851-07). In the DERs for both bioassays, the LD_{50}s are reported as >100 µg/bee. The DERs, however, do not give mortality rates for each dose level assayed and do not specify any signs of toxicity or provide a NOAEL for bees. Based on the LC_{50} of >100 µg/bee for technical grade clethodim (Atkins 1986, MRID 409745-32), U.S. EPA/OPP/EFED (2007b, p. 22) classifies clethodim as *Practically Nontoxic* to honeybees. Similarly but based on the bioassay on the Select 2 EC formulation, U.S. EPA/OPP/EFED (2014a, p. 41) also classifies clethodim as *Practically Nontoxic* to honeybees. The problem formulation from U.S. EPA/OPP/EFED (2008a, Table 1, p. 6) cites a different study for technical grade clethodim (MRID 410302-05) but reports an identical toxicity value (>100 µg/bee) and toxicity classification. As summarized in Appendix 3 (Table A3-1), ECOTOX indicates that the LOAEL is >100 µg/bee. Thus, 100 µg/bee appears to be a functional NOAEL. This interpretation is also consistent with the DER for Atkins (1986) which indicates: *Due to very low mortality at all levels, no analysis was performed*.

Typical body weights for worker bees range from 81 to 151 mg (Winston 1987, p. 54). Taking 116 mg as an average body weight, a dose of 100 µg/bee corresponds to about 860 mg/kg bw [0.1 mg ÷ 0.000116 kg ≈ 862.07 mg/kg bw]. This dose is higher than the NOAEL values reported in both canid and other experimental mammals (Appendix 1) and comparable to the acute NOAELs for birds (Appendix 2).

There are numerous terrestrial invertebrates in any diverse environment. Typically, as with clethodim, information is available on only a single terrestrial invertebrate species, the honey bee. Thus, the ability to identify potential hazards in other species of terrestrial invertebrates is limited.

4.1.2.5. Terrestrial Plants (Macrophytes)

4.1.2.5.1. General Considerations

As indicated in Section 2.2, the mechanism of action involved in the phytotoxicity of clethodim cyclohexanedione herbicide is the inhibition of acetyl coenzyme-A carboxylase (ACCase). Based on this mechanism, clethodim is categorized as a Class 1 herbicide under the system used by the Weed Science Society of America and a Class A herbicide under the system used by the Herbicide Resistance Action Committee. Other cyclohexanedione herbicides that are similarly classified include alloxydim, butroxydim, cycloxydim, sethoxydim, and tralkoxydim. Aryloxyphenoxy propionate herbicides (e.g., fluazifop-P) also act through the inhibition of ACCase (Mallory-Smith and Retzinger 2003). ACCase is key enzyme in fatty acid metabolism and catalyzes the carboxylation of acetyl-CoA to produce malonyl-CoA (Abell 1996; Burton et al. 1989; Dotray et al. 1993; Focke and Lichtenthaler 1987; Kobek and Lichtenthaler 1990; Lichtenthaler et al. 1991; Maier et al. 1994; Rendina et al. 1990; Tong 2005).

Clethodim is used for the control of grassy weeds. As noted in U.S. EPA/OPP/EFED (2008a, p. 4): *Sensitivity or selectivity of grasses has been demonstrated to be due to a greater susceptibility at the acetyl-CoA carboxylase (ACCase) enzyme of grass species*. This differential sensitivity of plant ACCases to clethodim is well documented in the published literature. ACCases from various species of grass have IC_{50} values (i.e., a 50% inhibition of ACCase activity) at concentrations ranging from 0.25 µM (≈90 µg/L) in barley (Rendina and Felts 1988) to 3.2 µM (≈1.1 mg/L) in green foxtail (Shukla et al. 1997). Intermediate IC_{50} values in sensitive species of grasses range from 0.25 µM to 1.1 µM (DiTomaso 1994; Rendina and Felts 1988; Shukla et al. 1997; Yu 2007). Corresponding IC_{50} values for dicots are not widely reported, except that Rendina and Felts (1988) assayed two species of dicots, both of which have markedly higher IC_{50} values, relative to monocots—i.e., 53 µM for mung bean and 1240 µM for spinach. The differences between ACCase sensitivity of monocots and dicots to clethodim are reflected in the sensitivity differences based on standard bioassays in terrestrial plants (Section 4.1.2.5.2) as well as observations from field applications of clethodim (Section 4.1.2.5.3).

As discussed further in Section 4.1.3.4.1, algae do not appear to be particularly sensitive to clethodim; however, quantitative comparisons to sensitive species of grasses are precluded by the difference in the units of measure expressed in standard bioassays—e.g., lb/acre for terrestrial vegetation and mg/L for aquatic organisms. Roessler (1990), however, assayed clethodim using ACCase from a diatom, *Cyclotella cryptica* and reported an IC_{50} of 23 µM. Based on this admittedly limited information, the sensitivity of algae to clethodim is more like that of dicots than monocots.

4.1.2.5.2. Toxicity Data

The testing requirements for the effects of herbicides on terrestrial plants are relatively rigorous, since terrestrial vegetation is the target for terrestrial herbicides. The testing requirements include bioassays for vegetative vigor (i.e., post-emergence applications), bioassays for seedling emergence (i.e., pre-emergence applications), and bioassays for seed germination. The seed germination studies involve Petri dish exposures—i.e., the seeds are placed on filter paper in a Petri dish, sprayed with the herbicide at various application rates, and then water is added to support germination. These studies are not used directly in most herbicide risk assessments because the exposure method is not directly relevant to plausible exposures involving the use of most herbicides. As summarized in Appendix 4, studies submitted to the EPA in support of the registration of clethodim include bioassays for vegetative vigor (Appendix 4, Table A4-1), seedling emergence (Appendix 4, Table A4-2), and seed germination (Appendix 4, Table A4-3).

The relative lack of toxicity of clethodim to dicots is evident in all the standard bioassays summarized in Appendix 4. Exposures equivalent to application rates of 0.25 lb a.i./acre caused no or very little signs of toxicity in the dicot species tested—i.e., soybean, lettuce, carrot, tomato, cucumber, and cabbage.

Responses in monocots, however, were diverse. Onion is a relatively tolerant monocot. Clethodim applied at a rate of 0.25 lb a.i., did not cause adverse effects in onions in the vegetation vigor assay, seedling emergence assay, or seed germination assay. In other words, tolerant species of monocots appear to be no more sensitive than dicots to clethodim. It should be noted that onions (*Allium cepa*) are monocots but are not true grasses – i.e., members of the

family Poaceae – and this difference is probably the basis of the tolerance of onions to clethodim.

The three other species of monocots that were assayed (i.e., corn, oats, and ryegrass all of which are true grasses/Poaceae) were much more sensitive than onions or the dicots. In the vegetative vigor assays (Chetram 1990a, MRID 416851-05), the most sensitive NOECs (plant dry weight) for these more sensitive monocot species ranged from 0.0023 to 0.013 lb a.i./acre—i.e., more sensitive than onion or the dicots by factors of about 20 to over 100 [0.25 ÷ 0.013 or 0.0023 ≈ 19.2 to 108.7]. In the seedling emergence studies (Chetram 1990b, MRID 416851-04), the differences in sensitivity were more variable with the most sensitive NOECs (plant height) for the sensitive monocot species ranging from 0.0004 to 0.0313 lb a.i./acre—i.e., more sensitive than onion or the dicots by factors of about 8 to over 600 [0.25 ÷ 0.0313 or 0.0004 ≈7.99 to 625]. While seed germination studies are not used quantitatively in the current risk assessment and are not discussed in the EPA ecological risk assessments (U.S. EPA/OPP /EFED 2007a,b), the sensitive monocots had NOECs as low as 0.0031 lb a.i./acre, a factor of about 80 below the NOEC of 0.25 lb a.i./acre in dicots.

As with several of the studies cited in the human health risk assessment (Section 3), the EPA appears to have reassessed some of the studies on terrestrial plants. Details of reanalysis are given in Wendel and Anderson (2012). As discussed further in Section 4.3.2.5, the current Forest Service risk assessment defers to the toxicity values reported in the most recent ecological risk assessment from EPA (U.S. EPA/OPP/EFED 2014a).

Thus, based on the standard studies for toxicity to terrestrial plants, there is no indication that clethodim is likely to adversely affect dicots. Effects on monocots, however, could be variable ranging from little or no impact in tolerant monocots to serious damage to some sensitive species of monocots (i.e., Poaceae) at the maximum labeled application rate of 0.25 lb a.i./acre.

4.1.2.5.3. Field Studies/Observations

As discussed in Section 2.2, clethodim has been used as a grass herbicide since the later 1980s. While the open literature relating to toxicity in nontarget species is limited, there are a substantial number of published efficacy studies on clethodim. Efficacy studies are not reviewed in detail in Forest Service risk assessments except to the extent that they provide information on nontarget species. Because of the sparse open literature on clethodim and the limited detail available on the standard plant bioassays with clethodim (Section 4.5.2.5.3), particular attention is paid to efficacy studies in this risk assessment in an attempt to better characterize risks to nontarget vegetation.

An overview of the efficacy studies reviewed in the preparation of the current risk assessment is given in Appendix 4, Table A4-4. This table provides information on the target species (typically a grassy weed), the crop species, the application rate or range of application rates, observations on both efficacy and nontarget damage (if any), and the reference to the published study. Efficacy studies are often elaborate in detailing the relative efficacy of several different herbicides, herbicide mixtures, use of various adjuvants, and the impact of various treatment timings and/or field conditions. No attempt is made to cover these factors in the current risk assessment, although observations on some of these factors are given in Table A4-4. Application rates in the open literature publications are typically expressed in metric units such as kilogram

per hectare (kg/ha). In Table A4-4, the application rates are expressed as lb a.i./acre using the conversion of 1 kg/ha ≈ 0.982 lb/acre and rounded to 2 significant digits.

As summarized in Appendix 4 (Table A4-4), the application rates reported in the open literature range from 0.005 lb a.i./acre (5.6 g/ha in Reynolds et al. 1994) to 0.45 lb a.i./acre (0.5 kg/ha in Campbell et al. 1997). The high application rate reported in Campbell et al. (1997) is above the EPA's maximum labeled rate of 0.25 lb/acre. The Campbell et al. (1997) study was conducted in Australia, which presumably accounts for the high application rate. As discussed in in Section 2 (Program Description), clethodim is not labeled for forestry applications; accordingly almost all of the efficacy studies in the open literature involve agricultural applications.

As discussed in Section 4.1.2.5.1 and Section 4.1.2.5.2, clethodim is much more toxic to many species of monocots (i.e., true grasses of the family Poaceae) than to dicots (e.g., broadleaf plants), is clearly reflected in the field studies. Almost all of the crops listed in Table A4-4 are dicots, and all of the species of weeds listed in this table are monocots. Most of the efficacy studies summarized in Table A4-4 do not indicate whether or not crop injury was observed as a result of herbicide treatment, but typically report the impact of the herbicide on crop yield. Since an increase in crop yield is generally an important practical index of efficacy, in the current discussion, an increase in crop yield is considered equivalent to a lack of significant damage to the crop.

Almost all of the studies listed in Table A4-4 indicate that application rates of 0.025 lb/acre resulted in a substantial reduction in the monocot weed (typically expressed as either a reduction in weed biomass or weed cover) with no damage to the crop species, typically a dicot. Three publications (Braverrman 1996; Carey et al. 1992; Ferrero 1991) involved the application of clethodim to a Poaceae monocot crop—i.e., rice (*Oryza sativa*). All publications note that clethodim applications report effective control of the monocot weeds. The studies by Braverrman (1996) and Ferrero (1991), however, both involved treatments in which clethodim was applied to the drained rice bed prior to planting the rice. Thus, these studies, which are designed to investigate the efficacy of clethodim to control weeds in rice beds, are not designed to assess the tolerance of rice to clethodim treatment. At least some of the applications of clethodim in the study by Carey et al. (1992) involved applications to both the growing target species as well as growing rice. Carey et al. (1992) report that visible injury to rice (27%) was observed in one treatment year, but that the injury was transient and the crop recovered. This suggests that rice may be one of the more tolerant species of Poaceae monocots.

The field studies do not suggest that clethodim caused substantial damage to any dicot; furthermore, most of the field studies clearly indicate a lack of damage to dicots. McKinley et al. (1987) noted visual damage in 3-7% of soybean plants following applications of clethodim at rates in the range of 0.04 to 0.16 lb a.i./acre. It is not clear from the publication, however, that this damage was statistically significant. Across the range of application rates in the McKinley et al. (1987) study, there is no positive relationship between the application rate and decreased crop yield (Table 1, p. 32 of publication). Kurtz and Neil (1992) report a rate of 26% visual damage in kenaf (*Hibiscus cannabinus*, a dicot) on day 10 after treatment with clethodim at a rate of 0.1 lb a.i./acre in 1 of 2 years over which the study was conducted. This damage, however, appears to have been transient and did not affect plant height, relative to controls

(Table 1, p. 127 of study). Kurtz and Neil (1992, p. 126) provide the following statement on damage to the kenaf: *Phytotoxicity from treatments except MSMA, fluazifop-P, sethoxydim, quizalofop, and clethodim was manifested as reduced plant height and necrosis both years*. Because the visual damage following applications of clethodim occurred only during 1 of the 2 years of the study and did not affect plant height, Kurtz and Neil (1992) seem to suggest that the observations associated with clethodim were incidental.

The lack of damage to dicots reflected in the open literature on clethodim is consistent with observations from the U.S. EPA/OPP, which tracks pesticide incidents of damage to nontarget species. The only incident of damage involving clethodim, as it relates to the ecological risk assessment, is as follows:

> *Incident # 1002969-058*
> *In 1995 the use of Select 2EC (a.i. Clethodim) allegedly caused damage to cotton after direct application in Florida. The certainty that clethodim caused this damage was "possible"; however the legality of this application is undetermined. This is the only incident reported involving c1ethodim.*
>
> U.S. EPA/OPP/EFED 2008a, p. 8.

4.1.2.5.4. Resistance

Resistance is a common concern with many herbicides, including clethodim, particularly when attempts are made to use the lowest possible application rate (Bourgeois and Morrison 1997; Delye et al. 2006; Neve and Powles 2005). As would be expected, cross-resistance is a concern for other herbicides (e.g., sethoxydim) which also inhibit ACCase (Vangessel et al. 1997). Nonetheless, Stoltenberg and Wiederholt (1995) observed that a population of giant foxtail with a 134-fold resistance to sethoxydim had only a slight and inconsistent resistance to clethodim. Based on assays of ACCase inhibition, resistance factors for clethodim are reported to range from about 1.3 (Neve and Powles 2005) to 49 (Yu 2007). Several other studies report ACCase resistance factors within this range (Leach et al. 1995; Smeda et al. 1997; Shukla et al. 1997).

As discussed by Shukla et al. (1997), it is not clear that relatively low levels of resistance at the enzymatic level will necessarily confer a high level of resistance to target species in the field. Furthermore, relatively few measures of resistance based on *in vivo* bioassays are available. In greenhouse studies, Smeda et al. (1997) reports resistance factors for tolerant populations of Johnsongrass (*Sorghum halepense*) ranging from 1.5 to 4.8 based on plant growth.

4.1.2.6. Terrestrial Microorganisms

Studies on terrestrial microorganisms are not required for pesticide registration in the United States, and the EPA ecological risk assessments on clethodim (U.S. EPA/OPP/EFED 2007a,b, 2008a) do not address effects on terrestrial microorganisms. Microorganisms possess ACCase, and various ACCase inhibitors are proposed or are used as microbicides (e.g. Kurth et al. 2009; More et al. 2012). Studies regarding the toxicity of clethodim or other HRAC Class A herbicides to microorganisms are not included in the available literature. As discussed in Section 4.1.2.5.1, the differential sensitivity of clethodim in true grasses and dicots appears to be related to differences in ACCases in true grasses and dicots. As with mammalian ACCases, the ACCases in bacteria are structurally different from ACCases in plants (e.g., Tong 2005). Given the apparent relationship of differing ACCases to sensitivity to clethodim, it seems only modestly

speculative to suggest that clethodim is not likely to be highly toxic to terrestrial microorganisms.

4.1.3. Aquatic Organisms

4.1.3.1. Fish

4.1.3.1.1. Acute toxicity in fish

As summarized in Appendix 5 (Table A5-1), acute bioassays are available on technical grade clethodim in several species of fish, including bluegill sunfish, fathead minnows, rainbow trout, zebra fish, all of which are freshwater fish, and one species of marine fish, (i.e., sheepshead minnow). In addition, a single longer-term toxicity study is available in fathead minnows (Appendix 5, Table A5-2).

A full Data Evaluation Record (DER) is available only for the acute bioassay in bluegills (MRID 409745-29). Accordingly, all other toxicity data on fish are taken from the EPA ecological risk assessments (U.S. EPA/OPP/EFED 2007a,b, 2014a) or from ECOTOX, a database of toxicity studies maintained by the U.S. EPA (http://cfpub.epa.gov/ecotox/). As detailed in Appendix 5 (Table A5-1), the summaries of some studies differ in the different EPA documents – e.g., discrepancies in reported LC_{50} values or NOECs. As noted elsewhere in the current risk assessment, such discrepancies are common and reflect reassessments or reevaluations of registrant submitted studies by the EPA. In such cases, preference is given to the most recent EPA risk assessment associated with the registration review of clethodim (U.S. EPA/OPP/EFED 2014a).

The definite acute LC_{50} values for technical grade clethodim in fish range from 24.4 mg a.i./L (rainbow trout, MRID 409745-28) to 133 mg a.i./L (zebra fish, MRID 484170-03). Based on the standard classification system used by the U.S. EPA (see SERA 2014a, Table 16 with discussion in Section 4.1.2), these LC_{50} values would classify clethodim as being *Slightly Toxic* to *Practically Nontoxic* to fish. As with endpoints for other species, the Forest Service risk assessments are primarily concerned with NOAECs rather than LC_{50} values. As summarized in Appendix 5 and discussed further in Section 4.3.3.1, information is available on the NOAECs for clethodim in apparently tolerant and apparently sensitive fish species – i.e., an NOAEC of 7.8 mg a.i./L in rainbow trout (a sensitive species) and 33 mg a.i./L in bluegill sunfish (a tolerant species).

4.1.3.1.2. Longer-term toxicity in fish

As discussed in Section 1, the U.S. EPA/OPP is conducting a registration review for clethodim (U.S. EPA/OPP 2009a). As part of this process, the Environmental Fate and Effects Division of the U.S. EPA/OPP prepared a preliminary problem formulation for clethodim (U.S. EPA/OPP/EFED 2008a). This problem formulation indicates that the EPA requested an early life stage study in freshwater fish, and the rationale for the request is stated as:

> *The requested data would allow EPA to refine its chronic risk (growth and reproduction) estimates for freshwater fish, and allow it to define an action area for endangered species. Risk mitigation strategies (e.g., determining maximum clethodim application rate that results in an RQ below the LOC) cannot be evaluated without these data.*
>
> U.S. EPA/OPP/EFED 2008a, p. 18

As detailed in the recent ecological risk assessment in support of the registration review of clethodim (U.S. EPA/OPP/EFED 2014a, p. 77), an early life stage study in fathead minnows has been submitted to the EPA (Bidinotto 2003, MRID 481043-03) and a full DER for this study is available. As detailed in Appendix 5 (Table A5-2), this study reports an NOAEC of 0.01 mg a.i./L with a corresponding LOAEC of 0.031 mg a.i./L based on reduced survival.

As detailed in the DER for Bidinotto (2003, p. 3 of DER), the Agency notes a large number of deficiencies in this study including the amount of solvent used, the number of replicates, the use of de-chlorinated tap water, the failure to determine actual concentrations of clethodim in the test solutions, and the failure to evaluate hatching success and post-hatching survival. Because of these deficiencies, this study is classified by the U.S. EPA as "Supplemental" rather than "Acceptable".

While not specifically discussed in the DER from the EPA, the study by Bidinotto (2003) was conducted by BIOAGRI Laboratories Ltd., Piracicaba, Brazil and was sponsored by Agan Chemical Manufacturers Ltd., Ashdod, Israel. While these facts, in and of themselves, do not impact the assessment of the quality of the study, it is possible that some of the apparent issues with study quality may have been exacerbated by issues in translation.

Despite the reservations expressed by the EPA (as noted above) and as discussed further in Section 4.3.3.1, U.S. EPA/OPP/EFED (2014a) does use this study to assess the potential longer-term effects of clethodim to fish. The use of this study for risk assessment is a clear concern to the Agency:

> *It should be noted that there are major uncertainties associated with the chronic fish endpoint that is used in this risk assessment. First, the available fathead minnow toxicity study NOAEC endpoint is based on mortality, and not the typical sublethal (growth or reproduction) endpoints that are used for chronic exposures, and could be an underestimation of risk to fish. Second, the chronic toxicity value that is being used is based on an ACR which relies on an extrapolation among species. However, this is the best available information to evaluate chronic risk to fish in this risk assessment.*
>
> U.S. EPA/OPP/EFED 2014a, p. 37

As noted in the Valent (2014) review of the preliminary ecological risk assessment by U.S. EPA/OPP/EFED (2014a), the decision to use the study by Bidinotto (2003) quantitatively is unusual given the Agency's concerns with this study. To address the deficiencies in the Bidinotto (2003) study, Valent (2014) indicates that it is willing to conduct an early life stage

study in rainbow trout. This study, however, has not yet been initiated and it is unclear if the study will be conducted in the foreseeable future (Jones 2014c).

4.1.3.2. Amphibians

As with terrestrial phase amphibians, there are no data to characterize the toxicity of clethodim to aquatic-phase amphibians. The EPA risk assessments on clethodim do not cite any registrant-submitted studies on aquatic-phase amphibians (U.S. EPA/OPP/EFED 1990b, 2007a,b), which is not unusual, since toxicity data on aquatic-phase amphibians are not required for most pesticide registrations. The general lack of toxicity data on aquatic-phase amphibians extends to the open literature and the database maintained by Pauli et al. (2000).

As noted in the EPA problem formulation for clethodim (U.S. EPA/OPP/EFED 2008a), the Agency will generally use toxicity data on fish as a surrogate for aquatic-phase amphibians.

4.1.3.3. Aquatic Invertebrates

As with fish, the available data on the toxicity of clethodim to aquatic invertebrates (Appendix 6) is limited. Two acute bioassays are available in *Daphnia magna*, a standard test species of freshwater invertebrate (Forbis 1986, MRID 409745-30; Burgess et al., 1990, MRID 416851-01) and two acute bioassays are available on saltwater invertebrates – i.e., the Eastern oyster (Palmer et al. 2011a , MRID 485630-01) and a mysid shrimp (Palmer et al. 2011b, MRID 484170-01).

Of the two daphnid acute bioassays, only the study by Burgess et al. (1990, MRID 416851-01) is classified as acceptable. This study involved Select 2 EC, a 25.6 % a.i. formulation that is specifically considered in the current risk assessment (Table 4). Based on summaries of this study in U.S. EPA/OPP/EFED (2007a,b. 2008a) the EC_{50} from this study is 5.7 mg a.i./L. Based on the full DER, the EC_{50} is given as 20.2 mg formulation/L. Correcting for the percent active ingredient in this formulation, EC_{50} is about 5.2 mg a.i./L [20.2 mg formulation/L x $0.256_{a.i./formulation}$ = 5.1712 mg a.i./L]. The reason for the discrepancy between the 5.7 mg a.i./L value from the EPA risk assessments and the calculated value of 5.2 mg a.i./L is not apparent. The current Forest Service risk assessment will use the somewhat lower value of 5.2 mg a.i./L because this concentration can be directly linked to the full DER.

It should be noted that the most recent ecological risk assessment by U.S. EPA/OPP/EFED (2014a) in support of the registration review of clethodim specifies the EC_{50} from MRID 416851-01 as 20.2 mg a.i./L. This appears to be an error. In response to a query to the U.S. EPA/OPP concerning this discrepancy, Jones (2014b) indicated that the toxicity values are reported in the DER as measured concentrations rather than as formulation. While the summary in the DER (Burgess et al. 1990, p. 1) does indicate that the concentration of 20.2 mg/L is a measured concentration, the dosage section of the DER (Burgess et al. 1990, p. 3) states the following: *The concentrations made were based on total product*.

The bioassays on saltwater species reflect a substantial difference in sensitivity between arthropods and mollusks. The EC_{50} of 31.3 mg a.i./L for a mysid shrimp is higher than the EC_{50} of 5.3 mg a.i./L for the Eastern oyster by a factor of about 6 [31.3 mg a.i./L ÷ 5.3 mg a.i./L ≈ 5.906]. Nonetheless, the EC_{50} of 5.2 mg a.i. for *Daphnia magna* is below that for mysid shrimp albeit only modestly.

One chronic study conducted with technical grade clethodim in *Daphnia magna* reports a NOEC of 0.94 mg a.i./L with a corresponding LOEC of 3 mg a.i./L based on growth and reproduction. As summarized in Appendix 6 (Table A6-2), this study is reported in both ECOTOX and the most recent U.S. EPA/OPP/EFED (2014a) ecological risk assessment. This chronic study in daphnids is not discussed in the earlier EPA risk assessments on clethodim (U.S. EPA/OPP/EFED 2007a,b; 2008a) but this appears to have been an oversight corrected in the 2014 EFED risk assessment. Based on the summary in both ECOTOX and U.S. EPA/OPP/EFED (2014a, 37), no effects on reproduction were observed at a concentration of 0.94 mg a.i./L with a LOEC of 3 mg a.i./L based on a decrease in the number of offspring and the body length of offspring.

As summarized Appendix 6 (Table A6-3), Perschbacher et al. (1997) conducted a mesocosm study on a mixed plankton community in which clethodim was sprayed at application rates equivalent to 0.0007, 0.007 and 0.07 kg a.i./ha (≈0.000062, 0.00062, and 0.0062 lb a.i./acre) as a Select formulation, not otherwise specified. The only effect noted was a significant, not otherwise specified, increase in copepod nauplii at the lowest application rate. No quantitative information is provided on this response. Given the lack of a response at higher application rates, the increase in copepod numbers may have been incidental.

4.1.3.4. Aquatic Plants

4.1.3.4.1. Algae

Compared to the sparse data on the toxicity of clethodim to fish and aquatic invertebrates, the toxicity data on algae are robust. As summarized in Appendix 7 (Table A7-1), 10 algal bioassays are available on nine species. These include bioassays on the green alga *Pseudokirchneriella subcapitata* on both technical grade clethodim and the Select 2.0 EC formulation.

Unlike most other groups of nontarget organisms, some information on the toxicity of clethodim to algae is available in the open literature. Three open literature publications by Ma et al. (2002, 2004, 2006; Ma and Liang 2001) involve a 12% EC formulation that is not otherwise identified. As summarized in Table 4, several 12.6% formulations are explicitly considered in the current risk assessment. The publications from Ma and coworkers are from the Chinese literature. Ma and coworkers do not specify the name of the formulation tested, Chinese companies supply 12% EC formulations of clethodim (e.g., http://ruinaagro.en.alibaba.com /product/313995575-213076175/Sell_Clethodim_12_EC_CAS_99129_21_2_herbicide.html), and it seems reasonable that Ma and coworkers may have used a 12% formulation from China rather than any of the 12.6% formulations specified in Table 4.

The other study in the open literature is the publication by Schrader et al. (1998). This study is focused on the use of aquatic herbicides to control cyanobacteria in aquaculture. While clethodim is not labelled for aquatic applications, clethodim was assayed for differential toxicity to *Oscillatoria* cf. *chalybea*, an undesirable blue-green alga, and to *Pseudokirchneriella subcapitata*, a desirable green alga. The assays on clethodim were screening assays to determine whether clethodim is selectively toxic to *Oscillatoria* cf. *chalybea*. As summarized in Appendix 7 (Table A7-1), clethodim was not selectively toxic to this blue-green alga. Consequently, more refined bioassays were not conducted on clethodim. The screening assays by Schrader et al.

(1998) are noted only for the sake of completeness and are not otherwise considered in this risk assessment.

The bioassays on *Pseudokirchneriella subcapitata* with technical grade clethodim (MRID 416851-06) and Select 2.0 EC (MRID 420297-03) are registrant studies included in the recent EPA risk assessments on clethodim (U.S. EPA/OPP/EFED 2007a,b). The EC_{50} for Select 2.0 EC is 19.5 mg a.i./L. A definitive EC_{50} was not determined for technical grade clethodim, and the EC_{50} is reported as >11.4 mg a.i./L. While details of the study on technical grade clethodim are not available, it seems likely that 11.4 mg a.i./L was the highest concentration tested. Since the EC_{50} for Select 2.0 EC is higher than 11.4 mg a.i./L, these results are consistent with the supposition that the formulation is no more toxic and may be less toxic than the active ingredient. As discussed further in Section 4.1.3.4.2, the Select 2.0 EC formulation is clearly less toxic than technical grade clethodim to duckweed, an aquatic macrophyte.

Based on reported EC_{50} values, the most sensitive species is the marine diatom, *Skeletonema costatum*, with an EC_{50} of 8.6 mg a.i./L and an NOEC of 5.4 mg a.i./L. Based on reported NOECs, the most sensitive species is a freshwater diatom, *Navicula pelliculosa*, with a reported NOEC of 3.1 mg a.i./L and an EC_{50} of 11 mg a.i./L. Based on the lower EC_{50} value of 8.6 mg a.i./L, clethodim would be classified as *Moderately Toxic* to some species of algae. The highest EC_{50} value is about 90 mg a.i./L from the assay on *Chlorella pyrenoidosa* by Ma and Liang (2001). While the bioassays by Ma and coworkers are not discussed in the recent EPA risk assessments on clethodim (U.S. EPA/OPP/EFED 2007a,b), the 90 mg a.i./L LC_{50} could be used to classify *Chlorella pyrenoidosa* as *Slightly Toxic* to this species of algae.

As discussed in Section 4.1.2.5, clethodim inhibits ACCase in sensitive species of grass with IC_{50} values in the range of 0.02 to 1.1 µM (DiTomaso 1994; Rendina and Felts 1988) and in tolerant broadleaf plants with much higher IC_{50} values ranging from 53 to 1240 µM (Rendina and Felts 1988). Roessler (1990) determined an IC_{50} of 23 µM the brackish water diatom *Cyclotella cryptica*. This limited comparison is consistent with the available bioassay suggesting that algae do not appear to be remarkably sensitive to clethodim.

4.1.3.4.2. Aquatic Macrophytes

The only two available bioassays on an aquatic macrophyte both involve *Lemna gibba*. One bioassay used technical grade clethodim (MRID 42029701) and the other bioassay used Select 2.0 EC (MRID 42029702). These studies are summarized in ECOTOX and the recent EPA risk assessments on clethodim (U.S. EPA/OPP/EFED 2007a,b, 2014a).

As summarized in Appendix 7 (Table A7-2), these studies indicate that technical grade clethodim is more toxic than the Select 2.0 EC formulation. In terms of the EC_{50} values, technical grade clethodim (EC_{50}=1.1 mg a.i./L) is more toxic than Select 2.0 EC (EC_{50}=42.5 mg a.i./L) by a factor of about 40 [42.5÷1.1≈38.636]. In terms of the NOECs, however, the difference is only about a factor of about 4—i.e., an NOEC of 1.1 mg a.i./L for the formulation and an NOEC of 0.3 mg a.i./L for technical grade clethodim. This somewhat unusual relationship is due to the large difference between the EC_{50} of 42.5 mg a.i./L and the corresponding NOEC of 1.1 mg a.i./L for the bioassay on Select 2.0 EC. This 40-fold difference between the EC_{50} and NOEC suggests a very shallow underlying dose-response curve which in

turn suggests a high degree of the variability in the response threshold for the population of *Lemna gibba* assayed, which may be incidental.

4.1.3.5. Surfactants

As noted in Section 3.1.14.2, nonionic surfactants, methylated seed oils, or vegetable oil concentrates are recommended in both terrestrial and aquatic applications of clethodim formulations. It is beyond the scope of the current risk assessment to review the toxicity of all the adjuvants recommended for use with clethodim or the potential impact of these adjuvants on aquatic organisms.

As discussed above, clethodim is relatively nontoxic to aquatic animals. At least some of the recommended nonionic surfactants may be more toxic than clethodim to some aquatic animals. For example, the review by McLaren/Hart (1995) compiles LC_{50} values for fish and EC_{50} values for aquatic invertebrates in assays of several nonionic surfactants used with other herbicides. The acute toxicity values these surfactants cover a wide-range of LC_{50} values (i.e., about 1 to >1000 mg/L).

Based on the label instructions for some clethodim formulations, the recommended concentration for nonionic surfactants is 0.25% v/v. Assuming a surfactant density of 1 g/mL for illustration, 0.25% w/v corresponds to a concentration of 2500 mg/L. Given the low toxicity of clethodim to both fish and aquatic invertebrates—i.e., defined LC_{50} values ranging from 5.2 mg/L (*Daphnia magna*, MRID 416851-01) to 15 mg/L (rainbow trout, MRID 409745-28)—the use of a relatively toxic nonionic surfactant in an aquatic application of clethodim may be viewed as posing a greater risk to aquatic animals than would be anticipated from exposure to clethodim alone.

Notwithstanding the above discussion, there is no basis for asserting that the risks posed by the surfactants would be substantial. Two applications of clethodim at a rate of 0.25 lb a.i./acre with a 14-day application interval may be taken as a reasonable example. As detailed in Attachment 2 (Worksheet B04a), the peak expected concentration of clethodim in surface water would be about 0.275 mg a.i./L. If 0.25% surfactant is added to a representative formulation containing 12.6% clethodim (Table 4), the peak concentration of the surfactant in water would be about 0.0055 mg/L [0.275 mg a.i./L x 0.25% ÷ 12.6% a.i. ≈ 0.005456 mg/L].

As discussed in the EPA ecological risk assessments on clethodim (U.S. EPA/OPP 2007a, Appendix F), the standard criterion used by U.S. EPA/OPP is a level of concern for endangered species of 0.05, meaning that the ratio of the anticipated concentration in water to the acute LC_{50} should be no greater than 0.05. Using a very toxic surfactant with an acute LC_{50} of 1 mg/L, the ratio of the anticipated concentration of the surfactant in water (0.0055 mg/L) to the LC_{50} of 1 mg/L is 0.0055—i.e., below the 0.05 level of concern by a factor greater than 9 [0.05 ÷ 0.0055 ≈ 9.0909]. Thus, there is no apparent basis for asserting that the use of surfactants with clethodim applications is likely to pose an acute hazard to aquatic species. The use of a relatively nontoxic surfactant (e.g., an LC_{50} of 1000 mg/L) would result in a correspondingly lower ratio (e.g., 0.0000055), below the EPA level of concern (0.05) by a factor of over 9,000.

The above discussion applies only to potential acute risks. Since a useful compendium on the longer-term toxicity of nonionic surfactants to aquatic organisms is not available, the potential for longer-term risks cannot be assessed.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview

A standard set of exposure assessments for terrestrial and aquatic organisms is provided in the EXCEL workbooks for clethodim. Attachment 1 details the exposure assessments for a single application at the maximum single application rate of 0.25 lb a.i./acre. Attachment 2 details the exposure assessments for the maximum seasonal application rate of two applications at 0.25 lb a.i./acre with an application interval of 14 days. As in the human health risk assessment, three general types of exposure scenarios are considered: accidental, acute non-accidental, and longer-term.

Exposure assessments for mammals are detailed in Worksheet G01a for mammals and in Worksheet G01b for birds. For both mammals and birds, the highest exposure scenarios are associated with the consumption of contaminated vegetation. This is a common pattern for foliar applications of any pesticide. The highest exposures are associated with the consumption of contaminated short grass by a small mammal or bird. For acute exposure scenarios, the highest estimated dose for a small mammal is 208 mg/kg bw, the upper bound dose for the consumption of contaminated short grass following two applications of clethodim. The comparable dose for a small bird is 514 mg/kg bw. For longer-term exposure scenarios, the maximum doses are also associated with the consumption of short grass—i.e., 33.8 mg/kg bw/day for a small mammal and 83.5 mg/kg bw/day for a small bird.

For terrestrial plants, five exposure scenarios are considered quantitatively: direct spray, spray drift, runoff, wind erosion, and the use of contaminated irrigation water. The highest exposures for terrestrial plants are associated with direct spray and spray drift. Nonetheless, as discussed in the risk characterization, runoff and sediment losses are also significant sources of potential exposure for terrestrial plants in sites that may favor runoff, particularly sites with predominantly clay soils. For sensitive species, potential exposures involving the use of contaminated water for irrigation are also significant.

Exposures of aquatic plants and animals to clethodim are based on essentially the same information used to assess the exposure to terrestrial species from contaminated water.

4.2.2. Mammals and Birds

All exposure scenarios for terrestrial animals are summarized in Worksheet G01 in the EXCEL workbooks that accompany this risk assessment (Attachments 1 and 2). An overview of the mammalian and avian receptors considered in the current risk assessment is given in Table 22. These data are discussed in the following subsections. Because of the relationship of body weight to surface area as well as to the consumption of food and water, for any type of exposure, the dose for small animals is generally higher, in terms of mg/kg body weight, than the dose for large animals. The exposure assessment for mammals considers five nontarget mammals of varying sizes: small (20 g) and medium (400 g) sized omnivores, a 5 kg canid, a 70 kg herbivore, and a 70 kg carnivore. Four standard avian receptors are considered: a 10 g passerine, a 640 g predatory bird, a 2.4 kg piscivorous bird, and a 4 kg herbivorous bird. Because of presumed differences in diet, (i.e., the consumption of food items), all of the mammalian and avian receptors are not considered in all of the exposure scenarios (e.g., the 640 g predatory bird is not used in the exposure assessments for contaminated vegetation). Toxicity data are not available

on terrestrial-phase amphibians (Section 4.1.2.3); accordingly, exposure assessments for these terrestrial vertebrates are not developed.

4.2.2.1. Direct Spray

The unintentional direct spray of wildlife during broadcast applications of a pesticide is a credible 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. The first spray scenario (Worksheet F01a) concerns the direct spray of half of the body surface of a 20 g mammal during a pesticide application. This exposure assessment assumes first-order dermal absorption using the first-order dermal absorption rate coefficient (k_a) discussed in Section 3.1.3.2. As discussed in Section 3.1.3.2, the k_a used in this risk assessment is taken from a study in rats (MRID 410302-02). While there are concerns that using the k_a from the rat study may be extremely conservative in estimating dermal absorption in humans, this concern is not relevant to exposure assessments for mammalian wildlife.

The second exposure assessment (Worksheet F01b) assumes complete absorption over Day 1 of exposure. This assessment is included in an effort to encompass increased exposures due to grooming.

Exposure assessments for the direct spray of a large mammal are not developed. As discussed further in Section 4.4.2.1, the direct spray scenarios lead to HQs far below the level of concern, and an elaboration for body size would have no impact on the risk assessment.

4.2.2.2. Dermal Contact with Contaminated Vegetation

As discussed in the human health risk assessment (Section 3.2.3.3), the 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 as well as a transfer rate from the contaminated vegetation to the skin. Unlike the human health risk assessment for 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.

For clethodim, as well as most other herbicides and insecticides applied in broadcast applications, the failure to quantify exposures associated with dermal contact adds relatively little uncertainty to the risk assessment, because the dominant route of exposure will be the consumption of contaminated vegetation, as addressed in the following subsection.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey

In foliar applications of pesticides, the consumption of contaminated vegetation is an obvious concern. Except for the large carnivorous mammal and the predatory bird, exposure assessments for the consumption of contaminated vegetation are developed for all mammals and birds listed in Table 22.

The initial concentrations of clethodim on contaminated food items are based on the U.S. EPA/OPP (2001) adaptation of the residue rates from Fletcher et al. (1994), as summarized in Table 16. The methods of estimating the peak and time-weighted average concentrations of clethodim in vegetation are identical to those used in the human health risk assessment (Section 3.2.3.7). As summarized in Table 16, fruit and short grass comprise the food commodities with the lowest pesticide residue rates (fruit) and the highest pesticide residue rates (short grass). Tall grass and broadleaf forage plants are estimated to have intermediate residue rates. For each of these four types of vegetation, both acute and longer-term exposure scenarios are developed, as detailed in Attachment 1, Worksheet G01a for mammals and Worksheet G01b for birds.

The acute and chronic exposure scenarios are based on the assumption that 100% of the diet is contaminated, which may not be realistic for some acute exposures and seems an unlikely event in chronic exposures—i.e., animals may move in and out of the treated areas over a prolonged period of time. While estimates of the proportion of the diet contaminated could be incorporated into the exposure assessment, the estimates would be an essentially arbitrary set of adjustments. The proportion of the contaminated diet is linearly related to the resulting HQs, and its impact is discussed further in the risk characterization (Section 4.4.2.1).

The estimated food consumption rates by various species of mammals and birds are based on field metabolic rates (kcal/day), which, in turn, are based on the adaptation of estimates from Nagy (1987) by the U.S. EPA/ORD (1993). These allometric relationships account for much of the variability in food consumption among mammals and birds. There is, however, residual variability, which is remarkably constant among different groups of organisms (Table 3 in Nagy 1987). As discussed by Nagy (2005), the estimates from the allometric relationships may differ from actual field metabolic rates by about ±70%. Consequently, in all worksheets involving the use of the allometric equations for field metabolic rates, the lower bound is taken as 30% of the estimate and the upper bound is taken as 170% of the estimate.

The estimates of field metabolic rates are used to calculate food consumption based on the caloric value (kcal/day dry weight) of the food items considered in this risk assessment and estimates of the water content of the various foods. Estimates of caloric content are summarized in Table 23. Most of the specific values in Table 23 are taken from Nagy (1987) and U.S. EPA/ORD (1993).

Along with the exposure scenarios for the consumption of contaminated vegetation, similar sets of exposure scenarios are provided for the consumption of small mammals by either a predatory mammal (Worksheet F10a) or a predatory bird (Worksheet F10b) and the consumption of contaminated insects by a small mammal, a larger (400 g) mammal, and a small bird

(Worksheets F09a-c). The residue rates for insects are taken from the U.S. EPA/OPP (2001) adaptation of the residue rates in Fletcher et al. (1994), as summarized in Table 16.

4.2.2.4. Ingestion of Contaminated Water

The methods for estimating clethodim concentrations in water are identical to those used in the human health risk assessment (Section 3.2.3.4.6.1). The only major differences in the exposure estimates concern the body weight of and the quantity of water consumed by the mammal or bird. Like food consumption rates, water consumption rates, which are well characterized in terrestrial vertebrates, are based on allometric relationships in mammals and birds, as summarized in Table 22. The exposure assessments for mammals and birds are detailed in Worksheets F02a-f (accidental spill), Worksheets F08a-f (peak concentrations), and Worksheets F16a-f (longer-term concentrations) in Attachments 1 and 2, the EXCEL workbooks for one and two applications of clethodim.

Like food consumption, water consumption in birds and mammals varies substantially with diet, season, and many other factors; however, quantitative estimates regarding the variability of water consumption by birds and mammals is not well documented in the available literature and is not considered in the exposure assessments. Nevertheless, as summarized in Table 14, the upper and lower bound estimates of clethodim concentrations in surface water vary substantially (i.e., by a factor of over 36,000 for acute exposures and a factor of about 58,000 for chronic exposures). Given this degree of variability in the estimated concentrations of clethodim in surface water, it is unlikely that a quantitative consideration of the variability in water consumption rates of birds and mammals would have a substantial impact on the risk characterization. In addition and as discussed further in Section 4.4.2.1 (risk characterization for mammals) and Section 4.4.2.2 (risk characterization for birds), exposures associated with the consumption of contaminated surface water are far below the level of concern (HQ=1). Consequently, even extreme variations on the consumption of contaminated water by mammals and birds would have no impact on the risk characterization for mammals and birds.

4.2.2.5. Consumption of Contaminated Fish

In addition to the consumption of contaminated vegetation, insects, and other terrestrial prey (Section 4.2.2.3), the consumption of contaminated fish by piscivorous species is a potentially significant route of exposure to clethodim. Exposure scenarios are developed for the consumption of contaminated fish after an accidental spill (Worksheets F03a-c), expected peak exposures (Worksheets F011a-c), and estimated longer-term concentrations (Worksheets F17a-c). These exposure scenarios are applied to 5 and 70 kg carnivorous mammals as well as a 2.4 kg piscivorous bird. The 70 kg carnivorous mammal is representative of a small or immature brown bear (*Ursus arctos*), which is an endangered species that actively feeds on fish (Reid 2006). As summarized in Table 22, the 5 kg mammal is representative of a fox, and the 2.4 kg bird is representative of a heron.

Clethodim exposure levels associated with the consumption of contaminated fish depend on the clethodim concentration in water and the bioconcentration factor for clethodim in fish. The concentrations of clethodim in water are identical to those discussed in Section 4.2.2.4. As discussed in Section 3.2.3.5, clethodim does not bioconcentrate substantially in fish. As summarized in Table 2, bioconcentration factors of 2.3 and 3.6 for whole fish are reported in U.S. EPA/OPP/EFED (2007a). While these values do not differ substantially, the lower value is

used for acute exposure scenarios and the upper value is used for longer-term exposure scenarios.

4.2.3. Terrestrial Invertebrates

4.2.3.1. Direct Spray and Drift

Estimated levels of exposure associated with broadcast terrestrial applications of clethodim are detailed in Worksheet G09 of Attachments 1 and 2 (the EXCEL workbooks for clethodim). This is a custom worksheet which includes aerial, ground broadcast (high boom and low boom), and backpack applications.

Honeybees are typically used by the U.S. EPA as a surrogate for other terrestrial insects (e.g., U.S. EPA/OPP 2007a,b, 2014a). Honeybee exposure levels associated with broadcast applications are modeled in the current risk assessments as a simple physical process based on the application rate and surface area of the bee. The surface area of the honeybee (1.42 cm^2) is based on the algorithms suggested by Humphrey and Dykes (2008) for a bee with a body length of 1.44 cm.

The amount of a pesticide 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. The estimated proportions of the nominal application rate at various distances downwind given in G09 are based on Tier 1 estimates from AgDRIFT (Teske et al. 2002) for distances of 0 (direct spray) to 900 feet downwind of the treated site. Further details of the use of AgDRIFT are discussed in Section 4.2.4.2 (Off-Site Drift) with respect to nontarget vegetation.

In addition to drift, foliar interception of a pesticide may occur. The impact of foliar interception varies according to 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) report that deposition in the lower canopy, relative to the upper canopy, generally ranged from about 10% (90% foliar interception in the upper canopy) to 90% (10% foliar inception by the upper canopy). In Worksheet G09, 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.

4.2.3.2. Ingestion of Contaminated Vegetation or Prey

As discussed in Section 4.1.2.4, oral toxicity data are not available for clethodim in bees or other species of terrestrial invertebrates. Consequently, an exposure assessment involving the consumption of contaminated vegetation by terrestrial invertebrates is not developed.

4.2.3.3. Contaminated Soil

As with the oral exposure assessment for the consumption of contaminated vegetation or prey, the exposure assessment for contaminated soil is not included in the current risk assessment

because appropriate and corresponding toxicity data (e.g., soil bioassays in earthworms) are not available.

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 clethodim 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. These exposure assessments are detailed in Worksheet G04 (runoff), Worksheet G05 (direct spray and drift), Worksheet G06a (contaminated irrigation water), and Worksheet G06b (wind erosion) for directed or broadcast foliar applications. These worksheets are included in both Attachment 1 (a single application at a rate of 0.25 lb a.i./acre) and Attachment 2 (two applications with a 14 day application interval).

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 scenario is modeled in the worksheets that assess off-site drift (see Section 4.2.4.2 below).

4.2.4.2. Off-Site Drift

Estimates of off-site drift are modeled using AgDRIFT. These estimates are summarized in Worksheets G05a and G05b of the EXCEL workbooks for clethodim (Attachments 1 and 2). These are custom worksheets that include estimates of drift for aerial, ground broadcast, and backpack applications. The drift estimates used in the current risk assessment are based on AgDRIFT (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 which can be viewed as plausible upper limits of drift.

In Worksheet G05a, aerial drift estimates are based on Tier 1 analyses 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. The use of small droplet sizes in Worksheet G05a is intended to generate extremely conservative estimates of drift that would not be anticipated in typical Forest Service applications.

In Worksheet G05b, aerial drift estimates are based on Tier 1 analyses using ASAE Coarse to Very Coarse drop size distributions (VMD≈440 µm) and the ground broadcast applications are based on ASAE fine to Medium Coarse drop size distributions (VMD≈340 µm). The product labels for all formulations of clethodim explicitly considered in this risk assessment (Table 4) specifically note that coarse droplet sizes should be used in aerial or ground applications. Thus, the drift values given in Worksheet G05b are likely to reflect estimates of drift that would be

more typical of Forest Service applications rather than the extremely conservative estimates of drift given in Worksheet G05a.

Drift associated with backpack applications (directed foliar applications) is likely to be much less than drift from ground broadcast applications. Few studies are available for quantitatively assessing drift after backpack applications. For the current 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).

The values for drift used in the current risk assessment should be regarded as little more than generic estimates similar to the water concentrations modeled using GLEAMS (Section 3.2.3.4.3). Actual drift will vary according to a number of conditions—e.g., the topography, soils, weather, drop size distribution, carrier, and the pesticide formulation.

4.2.4.3. Runoff and Soil Mobility

Terrestrial plant exposures associated with runoff and sediment losses from the treated site to an adjacent untreated site are summarized in Worksheet G04 of the EXCEL workbooks for clethodim (Attachments 1 and 2).

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 (Section 3.2.3.4). 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 have an impact on non-target plants. Percolation, on the other hand, represents the amount of herbicide transported below the root zone, which may affect water quality but should not affect off-site vegetation, except if the contaminated water is used for irrigation, as discussed further in Section 4.2.4.3. As with the estimates of clethodim in surface water, estimates of runoff and sediment losses are modeled for clay, loam, and sand at nine sites that represent different temperatures and rainfall patterns as specified in Table 11.

The exposure scenario for runoff and sediment losses assumes that the pesticide is lost from the treated field and spread uniformly over an adjacent untreated field of the same size. This assumption is admittedly arbitrary. Much more severe exposures could occur if all of the runoff losses were distributed into a much smaller area. Conversely, lower exposures would occur if runoff losses were distributed from the treated field to a much larger area.

For clethodim, the results of the standard GLEAMS modeling of runoff and sediment losses are summarized in Appendix 8 for a single application and Appendix 9 for two applications. Note that amount of runoff and sediment loss will vary substantially with different types of climates—i.e., temperature and rainfall—as well as soils, with no runoff or sediment loss anticipated in predominantly sandy soils. The input parameters used to estimate runoff and sediment losses are identical to those used in the Gleams-Driver modeling for concentrations of clethodim in surface water as discussed in Section 3.2.3.4 and summarized in Table 12 (site characteristics) and Table 13 (chemical-specific input parameters).

For a single application, the runoff for clethodim as a proportion of the application rate is taken as 0.0058 (0.0001 to 0.15). The central estimate and upper bound are taken directly from the Gleams-Driver modeling—i.e., the median and empirical upper 95% bound, as detailed in Appendix 8 (Table A8-1)—rounding all values to two significant places. The lower bound is effectively zero—i.e., for sandy soils regardless of temperature and rainfall rates. The lower bound value of 0.000058 is simply the central estimate of 0.0058 divided by 100. Much lower loss rates are plausible—i.e., in areas with predominantly sandy soils, as discussed further in the risk characterization (Section 4.4.2.5.2).

For a two applications, the runoff for clethodim as a proportion of the application rate is taken as 0.013 (0.00013 to 0.20). As with the single application, the central estimate and upper bound are taken directly from the Gleams-Driver modeling—i.e., the average and empirical upper 95% bound, as detailed in Appendix 9 (Table A9-1)—rounding all values to two significant places. Also as with the single application, the lower bound is effectively zero and the lower bound value of 0.00013 is simply the central estimate divided by 100.

4.2.4.4. Contaminated Irrigation Water

Forest Service risk assessments include this standard scenario for the use of contaminated water for irrigation. The exposure levels associated with this scenario depend on the pesticide concentration in the ambient water used for irrigation and the amount of irrigation water used. Concentrations in ambient water are based on the peak concentrations modeled in the human health risk assessment, as discussed in Section 3.2.3.4.6.

While the labels and/or EPA documents for many herbicides specifically state that water potentially contaminated with herbicides should not be used for irrigation, no such language has been identified for clethodim.

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. In the absence of any general approach for determining and expressing the variability of irrigation rates, the application of 1 inch of irrigation water with a range of 0.25 to 2 inches is used in this risk assessment. Details of the calculations used to estimate the functional application rates based on irrigation using contaminated surface water are provided in Worksheet G06a of the EXCEL workbooks for clethodim (Attachments 1 and 2).

4.2.4.5. Wind Erosion

Wind erosion can be a major transport mechanism for soil (e.g., Winegardner 1996), and wind erosion is also associated with the environmental transport of herbicides (Buser 1990). Wind erosion leading to off-site movement of pesticides is likely to be highly site-specific. The amount of clethodim that might be transported by wind erosion depends on several factors, including application rate, 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 unlikely that a substantial amount of clethodim would be transported by wind.

For this risk assessment, the potential effects of wind erosion are estimated in Worksheet G06b in Attachments 1 and 2. In this worksheet, it is assumed that clethodim is incorporated into the top 1 cm of soil, which is identical to the depth of incorporation used in GLEAMS modeling (Table 12). Average soil losses are estimated to range from 1 to 10 tons/ha/year with a central estimate of 5 tons/ha/year. These estimates are based on the results of agricultural field studies which 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 G06b, offsite losses are estimated to reach as much as 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 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 G06b may be somewhat more realistic for forest or rangeland applications, because forestry applications of herbicides are rarely made to fallow areas. As noted by Patric (1976), total soil erosion from all sources in well-managed forests is typically in the range of about 0.12-0.24 tons/ha/year [0.05 to 0.10 ton/acre/year], substantially below the range from 1 to 10 tons/ha/year used in Worksheet G06b. Thus, losses due to wind erosions following pesticide applications under forest canopies or heavily vegetated areas may be much less than the estimates used in this risk assessment.

In any event, the higher offsite losses reported by Larney et al. (1999) are comparable to exposures associated with offsite drift at distances of about 50 feet from the application site following low boom and high boom ground broadcast applications (Worksheet G05). All of the estimates for wind erosion and offsite drift are likely to vary dramatically according to site conditions and weather conditions.

4.2.5. Aquatic Organisms

The concentrations of clethodim in surface water used to estimate exposures for aquatic species are identical to those used in the human health risk assessment, as discussed in Section 3.2.3.4.6.1 and summarized in Table 15.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

All toxicity values used in the ecological risk assessment are summarized in Table 24. The derivation of each of these values is discussed in the following subsections. 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 the nature of exposure and the way in which the toxicity data are expressed. To maintain consistency with the exposure assessment, which is necessary for the development of hazard quotients (HQs) in the risk characterization, all toxicity values given in Table 24 are expressed as active ingredient (a.i.).

For terrestrial mammals, the acute dose response assessment is based on the same data as the human health risk assessment (i.e., a NOEL of 100 mg/kg bw). For longer-term exposures, the dose-response assessment for mammals is elaborated to consider the potential sensitivity of canids (NOEL of 1 mg/kg bw/day) relative to other mammals (NOEL = 19 mg/kg bw/day). The acute NOEL for birds is 950 mg/kg bw, substantially higher than the corresponding NOEL of 100 mg/kg bw for mammals. The chronic NOEL for birds (i.e., 20 mg/kg bw/day) is virtually identical to the value for mammals (NOEL = 19 mg/kg bw/day). For terrestrial invertebrates, the dose response assessment is based on a study in honey bees in which a dose of 860 mg/kg bw is taken as an approximate NOEL. Because of the lack of detail in the available toxicity studies on both birds and terrestrial invertebrates, there are several uncertainties associated with the dose-response assessment for these groups.

Clethodim is used for the control of grass weed species. In general, monocots (grasses) are much more sensitive than dicots (e.g., broad-leaved plants) to clethodim. While dicots appear to be uniformly tolerant to clethodim, some monocots are also relatively tolerant. For exposures associated with direct sprays or drift, NOELs for sensitive and tolerant species are 0.003 lbs/acre and 0.25 lbs/acre, respectively. With respect to soil contamination, the NOEL for sensitive species is 0.004 lbs/acre and the NOEL for tolerant species is 0.25 lbs/acre.

Little information is available on the toxicity of clethodim to aquatic invertebrates. Based in the available studies, *Daphnia magna* is the most sensitive aquatic invertebrate with an acute NOAEC of 1.4 mg/L and a longer-term NOAEC of 0.94 mg/L. Based on acute studies, mysid shrimp are less sensitive than daphnids with an NOAEC of 12.4 mg/L. No longer-term studies are available on mysids.

The acute effects of clethodim on fish are reasonably well characterized, however, data on longer-term exposures are marginal. For acute exposures, NOECs are proposed for sensitive species (0.75 mg/L) and tolerant species (33 mg/L). One early life stage study is available in fathead minnows and is used by U.S. EPA/OPP/EFED (2014a) to derive an estimated longer-term NOAEC of 0.002 mg a.i./L for trout. The quality of the early life stage study, however, is marginal and this study is not used in the current Forest Service risk assessment. Alternate longer-term NOAECs of 0.1 mg a.i./L for sensitive species and 0.6 mg a.i./L for tolerant species

are derived in the current risk assessment based on acute to chronic ratios, *Daphnia* to minnow correlations for chronic toxicity, and quantitative structure activity relationships.

Acute NOECs for algae are not substantially different from acute NOECs in fish. An NOEC of 3.1 mg/L is used sensitive species of algae and an NOEC of 11.1 mg/L is used for tolerant species of algae. For aquatic macrophytes, data are available only for *Lemna gibba*, and an NOEC of 0.3 mg/L is used for risk characterization. Because *Lemna* are monocots, this NOEC is presumed to apply to sensitive species of aquatic macrophytes.

4.3.2. Toxicity to Terrestrial Organisms

4.3.2.1. Mammals

In characterizing risk to mammalian wildlife, Forest Service risk assessments generally use the NOAELs which serve as the basis for the acute and chronic RfDs from the human health risk assessment. A more elaborate approach is used if sufficient data are available to characterize variable sensitivities among subgroups of mammals.

As discussed in Section 4.1.2.1, the available toxicity data do not suggest substantial differences in sensitivity among rats, mice, rabbits, and dogs. Consequently, the acute and chronic NOAELs used in the human health risk assessments (Table 17) are adopted for mammalian wildlife – i.e., the acute NOAEL of 100 mg/kg bw/day and the chronic NOAEL of 30 mg/kg bw/day.

4.3.2.2. Birds

As discussed in Section 4.1.2.2, the available toxicity data on birds are limited to a single acute gavage study in quail and acute dietary and reproduction studies in quail and mallards (Appendix 2). Given this limited database, the dose-response assessment for birds is relatively simple.

The estimated acute NOAELs for birds span a very narrow range of 947.1 mg a.i./kg bw (acute dietary in mallards) to 1025 mg a.i./kg bw (acute gavage in quail). Given this very narrow range, the selection of the acute NOAEL has little impact on the risk assessment. The acute dietary NOAEL of 947.1 mg a.i./kg bw is rounded to 950 mg a.i./kg bw used to characterize risks associated with acute exposures.

The two reproduction studies (Appendix 2, Table A2-3) suggest that quail are somewhat more sensitive than mallards. At a dietary concentration of 833 ppm, no effects were observed in mallards; whereas, adverse effects on offspring were observed in quail. Consequently, the estimated NOAEL of 19.6 mg a.i./kg bw/day (corresponding to a dietary concentration of 250 ppm) is used for the risk characterization of longer-term exposures in quail (MRID 410302-06). Given the lack of information on the food consumption in all of the bird dietary studies (Section 4.1.2.2), the NOAEL is rounded to 20 mg a.i./kg bw/day. For quail, the LOAEL of 67.2 mg/kg bw/day is based on decreased survival in offspring and egg hatch.

4.3.2.3. Reptiles and Amphibians (Terrestrial Phase)

Since toxicity data are not available for terrestrial-phase reptiles or amphibians (Section 4.1.2.3), no dose-response assessment can be derived for this group of organisms.

4.3.2.4. Terrestrial Invertebrates

As discussed in Section 4.1.2.4 and summarized in Appendix 3, standard contact bioassays in honeybees are available for both technical grade clethodim (Atkins 1986, MRID 409745-32) and Select 2.0 EC (Hoxter and Smith 1990, MRID 416851-07). Both of these studies report indefinite LD_{50} values of >100 µg/bee. As also detailed in Section 4.1.2.4, the dose of 100 µg/bee is equivalent to 862.07 mg/kg bw. The DERs available on both of these studies do not report mortality rates or information/observations on sublethal effects.

It seems likely that the dose 100 µg/bee did not cause any significant increase in mortality or signs of sublethal toxicity. Treatment-related adverse effects noted in a study are usually reflected in a DER prepared by the EPA. Nonetheless, the absence of details in the DERs for the two bee studies is acknowledged. In Table 23, the dose of 862.07 mg/kg bw is rounded to 860 mg/kg bw and the effect is designated as a "NOAEL?" As discussed in Section 4.4.2.4, the minor uncertainties associated with this questionable NOAEL have no substantial impact on this risk assessment, because plausible levels of exposure to bees are far below this dose.

Forest Service risk assessments derive oral toxicity values for bees or other insects as well as toxicity values for soil invertebrates when adequate data are available. As also noted in Section 4.1.2.4, the available information on clethodim does not support these types of dose-response assessments.

4.3.2.5. Terrestrial Plants (Macrophytes)

As with most herbicides, there are adequate data for the development of 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 4.1.2.5 and summarized in Appendix 4. Studies on seedling emergence are used to assess risks associated with exposures to soil residues of clethodim. Studies on vegetative vigor are used to assess risks associated with the deposition of clethodim onto plants as a result of direct spray or spray drift.

While the dose-response assessment for terrestrial macrophytes is based directly on standard bioassays submitted to the U.S. EPA/OPP in support of the registration of clethodim (Section 4.1.2.5.2), this dose-response assessment is supported by the substantial body of open literature indicating that clethodim is highly toxic to many monocots but relatively nontoxic to dicots (Section 4.1.2.5.3).

4.3.2.5.1. Vegetative Vigor

Clethodim is an effective herbicide for the control of grassy weeds (monocots). As summarized in Appendix 4 (Table A4-1) and discussed in Section 4.1.2.5, clethodim was assayed in several species of monocots at application rates of 0.0023 to 0.25 lb a.i./acre (Chetram 1990a, MRID 416851-05). Based on EC_{05} and NOAEC values, the most sensitive is ryegrass (an EC_{05} of 0.0023 lb a.i./acre based on plant dry weight). Onions are highly tolerant with no effects observed at the maximum application rate of 0.25 lb a.i./acre. As discussed in Section 4.1.2.5.2, onions are members of the Liliaceae family and are not true grasses – i.e., members of the family Poaceae.

As also summarized in Appendix 4 (Table A4-1) and discussed in Section 4.1.2.5, clethodim was assayed in several species of dicots at the maximum application rate of 0.25 lb a.i./acre. No serious adverse effects were noted on any species of dicot. No effects were noted in soybean or cucumber and transient increases in plant weight were noted in lettuce and cabbage. Carrots evidenced transient signs of visual damage and tomatoes evidenced a slight but significant decrease in plant height. Because of the lack of toxicity to dicots, more elaborate testing at lower doses was not required by the U.S. EPA. Consequently, dicots are designated as a tolerant plant species and 0.25 lb a.i./acre is taken as a functional NOAEL. As noted above, some monocots (e.g., onions) may also be classified as tolerant species.

4.3.2.5.2. Seedling Emergence

Soil exposures to clethodim appear to be much more toxic than foliar exposure. Otherwise, the patterns of toxicity are similar: Dicots are uniformly tolerant, and most, but not all, monocots appear to be highly sensitive. Based on the studies evaluated and used by the U.S. EPA/OPP/EFED (2014a), the most sensitive species is oat with an EC_{05} of 0.0004 a.i./acre based on a reanalysis of Chetram (1990b, MRID 416851-04). As detailed in Appendix 4 (Table A4-2), summaries of this study in U.S. EPA/OPP/EFED (2007a,b) differ somewhat from the DER for this study reporting NOEC values for oats is 0.004 or 0.0063 lb a.i./acre. All of the reported NOAECs from earlier EPA risk assessments, however, are substantially below the EC_{05} of 0.0004 a.i./acre reported in U.S. EPA/OPP/EFED (2014a, p. 41, Table 19).

Also as with the assays for vegetative vigor, dicots are tolerant species with an NOEC equivalent to the maximum application rate of 0.25 lb a.i./acre.

4.3.2.6. Terrestrial Microorganisms

The toxicity of clethodim to terrestrial microorganisms (Section 4.1.2.6) is not addressed in the available literature. Consequently, no dose-response assessment can be proposed for soil microorganisms.

4.3.3. Aquatic Organisms

4.3.3.1. Fish

4.3.3.1.1. Acute Toxicity

As discussed in Section 4.1.3.1.1 and detailed in Appendix 5 (Table A5-1), the definitive acute LC_{50} values for clethodim span a relatively narrow range – i.e., 24.4 mg a.i./L (rainbow trout, MRID 409745-28) to 133 mg a.i./L (zebra fish, MRID 484170-03). As with other toxicity values considered in the current risk assessment, the Forest Service prefers to characterize risk based on NOEC rather than LC_{50} values. For trout, the most sensitive species, the NOEC of 7.8 mg a.i./L is taken directly from MRID 409745-28. As indicated in the DER for this study (Swigert 1986b), the NOEC is based on measured concentrations of clethodim.

For tolerant species, the NOAEC of 103 mg/L reported in ECOTOX for zebra fish (MRID 484170-03) is not used. As indicated in Appendix 5 (Table A5-1), the NOEC of 103 mg/L reported in ECOTOX is not verified in the most recent EPA risk assessment which specifically notes that …*sublethal effects were not reported* (U.S. EPA/OPP/EFED 2014a, p. 76). As an alternative, the NOAEC for tolerant species is taken as 33 mg a.i./L based on measured concentrations. This value is the NOEC for bluegills from Swigert (1986a, MRID 409745-29).

This value is given in the full DER and is verified in several EPA risk assessments (U.S. EPA/OPP 2007a,b, 2014a, p.76).

4.3.3.1.2. Longer-term Toxicity

4.3.3.1.2.1. EPA Assessment

As discussed in Section 4.1.3.1.2, the U.S. EPA/OPP/EFED (2014a) uses an atypical early life stage study in fathead minnows (Bidinotto 2003, MRID 481043-03) which reports an NOAEC of 0.010 mg a.i./L with a corresponding LOAEL 0.031 mg a.i./L based on survival. As discussed in Section 4.1.3.1.2, the U.S. EPA/OPP classifies the study by Bidinotto (2003) as *Supplemental* rather than *Acceptable*. It is unusual for the Agency to use an early life stage study which does not report information on reproductive parameters such as hatching success; moreover, it is also unusual for the Agency to base a quantitative risk assessment on a study that is classified as *Supplemental*.

As detailed in Appendix 5 (Table A5-2), the U.S. EPA/OPP/ EFED (2014a) used an acute-to-chronic ratio approach to estimate a longer-term NOAEC for sensitive species of fish, taking trout as the sensitive species based on acute LC_{50} values. Specifically, the NOAEC of 0.010 mg a.i./L is multiplied by the ratio of the LC_{50} value in trout (24.4 mg a.i./L from MRID 409745-28) to the corresponding value in fathead minnows (110 mg a.i./L from MRID 484170-02) to estimate an approximate longer-term NOAEC of 0.002 mg a.i./L for sensitive species of fish [0.010 mg a.i./L x (24.4 mg a.i./L ÷ 110 mg a.i./L = 0.002218 mg a.i./L ≈ 0.002 mg a.i./L]. Given the serious reservations with the longer-term NOAEC in fathead minnows, confidence in the estimated NOAEC for trout is low.

As detailed in Section 4.1.3.1.2, the U.S. EPA/OPP/EFED (2014a, p. 37) expresses serious reservations with this dose-response assessment in fish.

Forest Service risk assessments generally defer to the U.S. EPA in matters of study selection for dose-response assessments. This deference is based on the fact that the U.S. EPA has the legislative mandate for the regulation of pesticides and also because the U.S. EPA has access to the full studies as well as the resources to review these studies in substantial detail. Forest Service risk assessments may differ from U.S. EPA in study selection if there is a compelling reason to do so; however, the rationale for taking this action is generally based on the availability of studies that the U.S. EPA has not addressed.

In the case of longer-term exposures of fish to clethodim, the current Forest Service risk assessment differs from U.S. EPA/OPP/EFED (2014a) in the dose-response assessment for longer-term exposures of fish to clethodim. As discussed in the following sections, this alternate dose-response assessment is based on a several factors not considered by the U.S. EPA – i.e., a substantial body of information on acute to chronic toxicity ratios in fish (Section 4.3.3.1.2.2), a quantitative assessment of the relationship of chronic toxicity in *Daphnia* to chronic toxicity in fathead minnows (Section 4.3.3.1.2.3), and quantitative structure activity relationships for toxicity to fish and other aquatic organisms (Section 4.3.3.1.2.4). Based on a weight of evidence determination (Section 4.3.3.1.2.5), alternative dose-response assessments are derived for tolerant and sensitive species of fish (Section 4.3.3.1.2.6).

4.3.3.1.2.2. Acute to Chronic Ratios (ACRs)

Acute to chronic ratios are defined as a ratio of an acute toxicity value to a chronic toxicity value. In the context of the current discussion on the longer-term toxicity of clethodim to fish, the ACR is more specifically defined as the ratio of the 96-hour LC_{50} to the NOAEC from the early life stage study by Bidinotto (2003). ACRs can be used to estimate longer-term toxicity values from acute values and to assess data quality issues with experimental studies. The justification for the use of ACRs is addressed in detail by the U.S. EPA (Hoff et al. 2010) in an Agency position paper. Furthermore, the use of ACRs is included in the National Academy of Sciences recent recommendations on the assessment of risks to threatened and endangered species (NAS 2013, p. 121, Eq. 1). The U.S. EPA/OPP/EFED (2014a) ecological risk assessment on clethodim does not specifically discuss the relationship of the acute toxicity data in fish to the reported NOAEC from the early life stage study by Bidinotto (2003).

As summarized in Appendix 5, Table A5-1, the study by Bidinotto (2003) reported an acute LC_{50} of 71.91 mg a.i./L for fathead minnow embryos. As discussed above, the NOAEC from the early life stage assay by Bidinotto (2003) is 0.01 mg a.i./L. Thus, the ACR from this study is greater than 7000 [71.91 mg a.i./L ÷ 0.010 mg a.i./L = 7191]. Most ACRs involve LC_{50} values for fry. As also summarized in Appendix 5, Table A5-1, the LC_{50} value for fathead minnow fry is 110 mg a.i./L (MRID 484170-02). Based on this LC_{50} and the chronic NOAEC from Bidinotto (2003), the ACR for clethodim is 11,000 [110 mg a.i./L ÷ 0.010 mg a.i./L].

A reasonably extensive literature is available on the relationship of acute to chronic toxicity values in fish and other aquatic organisms (e.g., Ahlers et al. 2006; Hoff et al. 2010; Kenaga 1982; Lange et al. 1998; Raimondo et al. 2007; Roex et al. 2000). These studies are summarized in Table 25.

The analysis most directly relevant to the assessment of the study by Bidinotto (2003) is the comparison of fathead minnow acute LC_{50} values to NOAECs from early life stage studies in fathead minnows by Ahlers et al. (2006). As indicated in Table 25, Ahlers et al. (2006) report a mean ACR of 11.5, a 90th percentile ACR of 66.4, and a maximum ACR of 1370 for this dataset. Kenaga (1982) also provides a comparison of LC_{50} values to chronic NOAECs in fathead minnows. This early compilation does not report mean ACRs with analyses of the percentile distribution of ACRs but does note that 96% of the ACRs are below 1000 and 98% of the ACRs are below 9999. Other analyses of ACRs in mixed species of fish are consistent with the analysis by Ahlers et al. (2006) indicating mean ACRs of about 10 and 90th percentile ACRs in the range of about 70 to 200.

Two of the analyses summarized in Table 25, are from the U.S. EPA – i.e., Hoff et al. (2010) and Raimondo et al. (2007). The paper by Hoff et al. (2010, Table 7, p. 46) recommends 90th percentile ACRs of up to 188.5 for different classes of compounds. Based on an analysis of studies submitted to EPA on various species of fish, Raimondo et al. (2007) reports a median ACR of 9.3 with a 90th percentile of 90 and a maximum of 2121. As discussed above, the ACR for clethodim is 11,000, which is higher than the maximum value from the recent analysis by Ahlers et al. (2006) by a factor of about 8 [11,000 ÷ 1370 ≈ 8.029] and higher than maximum value from the recent EPA analysis by Raimondo et al. (2007) by a factor of about 5 [11,000 ÷ 2121 ≈ 5.186].

Based on the estimate of the median ACR of 9.49 from Raimondo et al. (2007) and the acute LC_{50} of 110 mg a.i./L in fathead minnow (MRID 484170-02), the estimated chronic NOAEC of clethodim would be estimated at about 12 mg a.i./L [110 mg a.i./L ÷ 9.49 ≈ 11.591 mg a.i./L]. Based on the 90th percentile ACR of 66.4 from Ahlers et al. (2006), the estimated chronic NOAEC of clethodim would be estimated at about 1.7 mg a.i./L [110 mg a.i./L ÷ 66.4 ≈ 1.657 mg a.i./L]. Taking the maximum 90th percentile ACR of 188.5 from Hoff et al. (2010), the estimated chronic NOAEC of clethodim would be estimated at about 0.58 mg a.i./L [110 mg a.i./L ÷ 188.5 ≈ 0.5836 mg a.i./L].

While the analyses of ACRs cannot demonstrate that the study by Bidinotto (2003) is invalid, the ACR analysis reinforces concern with the conduct of this study (Section 4.1.3.1.2) and utility of this study as the basis for a dose-response assessment in fish.

4.3.3.1.2.3. Daphnid to Minnow Correlations

Another approach to evaluating the study by Bidinotto (2003) involves comparisons of the toxicity data on clethodim for *Daphnia magna* and fathead minnows. As with acute to chronic ratios, correlations between the toxicity of chemicals among aquatic species have been extensively studied for acute toxic endpoints (e.g., Mayer and Ellersieck 1986; Raimondo et al. 2010; Zhang et al. 2010). In the case of clethodim, the acute LC_{50} in fathead minnows is 110 mg a.i./L (MRID 484170-02) and the acute EC_{50} in *Daphnia magna* is 20.2 mg a.i./L (MRID 416851-01). This comparison is somewhat confounded in that the toxicity data for minnows involve technical grade clethodim whereas the toxicity data for daphnids involve a clethodim formulation. Nonetheless, the differences in acute toxicity are not remarkable and indicate that daphnids may be more sensitive than minnows to clethodim by about a factor of 5 [110 mg/L ÷ 20.2 mg/L ≈5.446].

As discussed above, the NOAEC for minnows from the early life stage study by Bidinotto (2003) is 0.01 mg a.i./L. As discussed in Section 4.1.3.3 and detailed in Appendix 6, Table A6-2, the NOEC for *Daphnia magna* from a standard chronic reproduction study is 0.94 mg a.i./L (MRID 481043-05). Thus, based on two chronic NOAECs, minnows would be classified as more sensitive than daphnids by a factor of nearly 100 [0.94 mg a.i./L ÷ 0.01 mg a.i./L].

Interspecies correlations for chronic toxicity are not as well documented as those for acute toxicity. Nonetheless, Maki (1979) examined the relationship of NOAECs from chronic studies in *Daphnia magna* to 1-year full chronic NOAECs in fathead minnows for 35 compounds, including 15 pesticides. The correlation across all compounds was statistically significant ($p<0.01$) and fit the following equation:

$$\ln(\textit{Fathead NOAEC}) = 1.407 + 0.727\ln(\textit{Daphnia NOAEC}) \qquad (7)$$

where NOECs are in units of mg/L. Based on this relationship and the NOAEC of 0.94 mg a.i./L in *Daphnia magna* (MRID 481043-05), the expected NOAEC in minnows would be about 3.9 mg/L [1.407 + 0.727 ln(0.94) = 1.36; $e^{1.36} \approx 3.89619$]. The estimated NOAEC of 3.9 mg a.i./L is greater than the reported NOAEC of 0.01 mg a.i./L from Bidinotto (2003) by a factor of nearly 400 [3.9 ÷ 0.1 = 390].

While interspecies correlations are not a substitute for properly conducted experiments, the inherent problems with the study by Bidinotto (2003) combined with the interspecies correlations from Maki (1979) add further weight to concerns with using the study by Bidinotto (2003) as the basis for the risk characterization of chronic exposures in fish.

4.3.3.1.2.4. Quantitative Structure Activity Relationships (QSAR)

A final approach to further evaluating the utility of the study by Bidinotto (2003) involves quantitative structure activity relationships (QSAR). QSAR methods are used extensively in toxicology, and the U.S. EPA has specifically developed a methodology for estimating the acute and chronic toxicity of chemicals to aquatic organisms (U.S. EPA/OPPTS 2012). This methodology is implemented as part of the U.S. EPA's Estimation Program Interface (EPI) Suite program, and the QSAR estimates for clethodim given in EPI Suite (2013) are summarized in Table 26.

EPI Suite (2013) provides QSAR estimates based on analyses of five chemicals to which clethodim can be related – i.e., aliphatic amines, vinyl/allyl ketones, vinyl/allyl halides, vinyl/allyl alcohols, and neutral organics. Each of these classes is indicated in the first column of Table 26 and different algorithms are used in the QSAR estimates for each class. In Table 26, QSAR estimates are given for *Daphnia* 48-hour EC_{50} values, *Daphnia* chronic values, fish 96-hour LC_{50} values, and fish chronic values. These estimates are given in the third column of Table 26. The term *chronic value* as used in EPI Suite is the geometric mean of the NOAEC and LOAEC (U.S. EPA/OPPTS 2012, p. 3).

The fourth column in the table gives the experimental values for clethodim. The acute toxicity values are taken directly from studies submitted to U.S. EPA – i.e., the 48-hour EC_{50} of 20.2 mg a.i./L for *Daphnia magna* (MRID 416851-01) and the 96-hour LC_{50} of 110 mg a.i. for fathead minnows (MRID 484170-02). The experimental chronic value for *Daphnia magna* of 1.68 mg a.i./L is the geometric mean of the NOAEC of 0.94 mg a.i./L and LOAEC of 3.0 mg a.i./L from MRID 481043-05 [$(0.94 \times 3.0)^{0.5} \approx 1.6793$]. The chronic value for fathead minnows of 0.018 mg a.i./L is the approximate geometric mean of the NOAEC of 0.01 mg a.i./L and LOAEC of 0.031 mg a.i./L from Bidinotto (2003) [$(0.01 \times 0.031)^{0.5} \approx 0.01761$]. These experimental values are repeated in the fourth column of Table 26 for each of the chemical classes.

The fifth column in Table 26 gives the ratio of the experimental to the predicted values – i.e., a ratio of >1 indicates that QSAR algorithm underestimates the experimental toxicity value – and the sixth column in Table 26 is the average ratio for daphnid acute and chronic values as well as the fish LC_{50}. Only these three groups are considered in the averaging because confidence in the experimental values for these endpoints is high relative to the fish chronic value, the early life stage study by Bidinotto (2003).

As indicated in Table 26, the QSAR estimate for the fish chronic value based on the algorithm for vinyl/allyl alcohols is 0.013 mg/L. This estimate is virtually identical to the corresponding experimental value – i.e., the geometric mean of 0.018 mg/L for the NOAEC and LOAEC from Bidinotto (2003). While this concordance could be viewed as supportive of the Bidinotto (2003) study, this conclusion would ignore the substantial and consistent bias in the QSAR estimates of

the chronic value for daphnids as well as the acute values for fish and daphnids. As indicated in Table 26, these experimental values are overestimated by factors of 2.63 (daphnid chronic value based on vinyl/allyl ketones) to over 186 (daphnid chronic value based on vinyl/allyl alcohols).

Based on averages of the ratios of experimental to predicted chronic values for daphnids as well as the acute values for fish and daphnids (i.e., column six in Table 26), the magnitude of the overestimates range from factors of about 7 to 80. The least bias is evident for the QSAR algorithm based on vinyl/allyl ketones – i.e., an average overestimate of a factor of 7.43. Using this average as an estimate in the bias in the QSAR estimate of the chronic value for fish (i.e., 0.835 mg/L), an adjusted estimate of the chronic value for fish is about 6.21 mg/L [7.43 x 0.835 mg/L]. As summarized in the last column of Table 26, the estimates of the corrected chronic values for fish (i.e., corrected for apparent bias) range from 1.04 to 6.21 mg a.i./L.

4.3.3.1.2.5. Weight of Evidence Assessment

Table 27 provides a summary of the estimated fish chronic toxicity values for clethodim based on the various lines of evidence discussed in previous sections. These estimates include the NOAEC of 0.01 mg/L from the study by Bidinotto (2003) as well as estimates based on the acute to chronic ratio method, the estimate from the Maki (1979) regression based on daphnid NOAECs, and the QSAR estimates from EPI Suite.

Typically, estimation methods for toxicity values are not considered in Forest Service risk assessments. In the case of chronic fish toxicity for clethodim, however, a consideration of estimation methods is appropriate because of serious concerns with the single early life stage study by Bidinotto (2003). These concerns are expressed both in the current risk assessment (Section 4.1.3.1.2) as well as the EPA Data Evaluation Record for the study by Bidinotto (2003).

As summarized in Table 27, all of the alternative estimation methods for the NOAEC in fathead minnows are higher than the NOAEC from Bidinotto (2003) by factors of 100 to 620. In addition, the estimation methods are reasonably consistent with each other. The range of NOAECs based on three different estimation methods is from 0.58 to 6.2 mg a.i./L, spanning a factor of about 11 [$6.2 \div 0.58 \approx 10.69$].

Given concerns with the conduct of the study by Bidinotto (2003), the inconsistency of the NOAEC from Bidinotto (2003) with alternative estimates of the NOAEC, and the concordance of estimated NOAECs using alternative methods (Table 27), the study by Bidinotto (2003) is not used in the current risk Forest Service assessment to characterize risks associated with longer-term exposures of fish to clethodim.

4.3.3.1.2.6. Alternative Dose-Response Assessment

For the current Forest Service risk assessment, the chronic NOAEC for tolerant species of fish is taken as 0.6 mg a.i./L. As discussed in Section 4.3.3.1.2.2, this NOAEC is based on the maximum 90th percentile acute to chronic ratio (i.e., 188.5) from the U.S. EPA review of default acute to chronic ratios (i.e., Hoff et al. 2010, Section 4.4.5, pp. 45-46) which is in turn taken from the open literature publication by Raimondo et al. (2007).

Specifically, the NOAEC of 0.6 mg a.i./L is based on the LC_{50} of 110 mg a.i./L in fathead minnows (MRID 484170-02) divided by the ARC of 188.5 and then rounded to one significant digit [110 mg a.i./L ÷ 188.5 ≈ 0.5836 mg a.i./L]. As summarized in Table 27, this NOAEC is supported by seven somewhat higher NOAECs (i.e., 1.0 to 6.2 mg a.i./L) estimated using other acute to chronic ratios, correlations with daphnid chronic NOAECs, and QSAR estimates. While an argument could be made for selecting a higher NOAEC (e.g., a central estimate of NOAECs from Table 27), the lowest NOAEC is selected has a conservative but still plausible value. The NOAEC of 0.6 mg a.i./L is based on data from fathead minnows and is applied to presumably tolerant species.

The NOAEC for presumably sensitive species is estimated using the method in the most recent U.S. EPA/OPP/EFED (2014a) ecological risk assessment. The estimated NOAEC of 0.6 mg a.i./L for fathead minnows is multiplied by the ratio of the acute LC_{50} in trout of 24.4 mg a.i./L (MRID 409745-28 from U.S. EPA/OPP/EFED 2014a) to the acute LC_{50} in fathead minnows of 110 mg a.i./L and then rounded to one significant digit. Thus, the calculated longer-term NOAEC for sensitive species is estimated as 0.1 mg a.i./L [0.6 mg a.i./L x 24.4 mg a.i./L ÷ 110 mg a.i./L ≈ 0.1331 mg a.i./L].

4.3.3.2. Amphibians (Aquatic-Phase)

As noted in Section 4.1.3.2, no information is available on the toxicity of clethodim to aquatic-phase amphibians. Consequently, no dose-response assessment is proposed for this group of organisms.

4.3.3.3. Aquatic Invertebrates

As discussed in Section 4.1.3.3 and detailed in Appendix 6 (Table A6-1), acute toxicity data are available on only three species of aquatic invertebrates: *Daphnia magna* (Burgess et al., 1990, MRID 416851-01), the Eastern oyster (Palmer et al. 2011a, MRID 485630-01), and a mysid shrimp (Palmer et al. 2011a, MRID 484170-01). Based on these studies, the most sensitive species is *Daphnia magna* with an acute LC_{50} of 5.17 mg a.i./L and a corresponding NOEC of 1.41 mg a.i./L. Following standard practice in Forest Service risk assessments, the NOEC for *Daphnia magna* is used to characterize acute risks in potentially sensitive species. The most tolerant aquatic invertebrate is the mysid shrimp with an acute LC_{50} of 33 mg a.i./L and an NOEC of 12.4 mg a.i./L. The NOEC of 12.4 mg a.i./L is used to characterize acute risks in tolerant species of aquatic invertebrates.

Only one chronic toxicity study is available – i.e., the standard reproduction study in *Daphnia magna* (MRID 481043-05). The NOEC of 0.94 mg a.i./L from this study is used to characterize risks associated with longer-term exposures in sensitive species of aquatic invertebrates. As discussed in Section 4.3.3.1, the acute-to-chronic ratio approach is used to estimate a longer-term NOEC for potentially sensitive species of fish. This method could be applied to estimating a longer-term NOEC in potentially tolerant species of aquatic invertebrates. The approach is not taken in the current risk assessment or in the most recent U.S. EPA/OPP/EFED (2014a) risk assessment.

While not explicitly discussed in the EPA risk assessment, the use of approximations such as the acute-to-chronic ratio approach may be justified in approximating risks to potentially sensitive species but the converse (i.e., approximating risks to potentially tolerant species) is not generally

used because the uncertainties in doing so are not justified for a downward adjustment of potential risk. As discussed further in Section 4.4.3.4, this admittedly biased conservative approach does not have a substantial impact on the current risk assessment because sensitive species of aquatic invertebrates do not appear to be at risk due to longer-term exposures to clethodim.

4.3.3.4. Aquatic Plants

4.3.3.4.1. Algae

Unlike the limited amount of data for most other groups of nontarget organisms, several toxicity studies in algae are available from the open literature (Ma and Liang 2001, Ma et al. 2001, 2002, 2004, 2006). All of these studies, however, were published in China and appear to have used a Chinese formulation (12% a.i.) of clethodim (Section 4.1.3.4.1). As summarized in Appendix 7 (Table A7-1), the EC_{50} values reported in the studies by Ma and coworkers range from about 23 mg a.i./L (*Raphidocelis subcapitata* from Ma et al. 2006) to 90 mg a.i./L (*Chlorella pyrenoidosa* from Ma et al. 2006). These EC_{50} values are somewhat higher than the toxicity values reported in the EPA ecological risk assessments on clethodim (U.S. EPA/OPP/EFED 2007a,b).

Another issue with the studies by Ma and coworkers involves the units in which the EC_{50} values are reported. The papers by Ma and coworkers do not explicitly state that the results are expressed in units of a.i as opposed to units of formulation. The papers, however, report all EC_{50} values in both mg/L and in molar concentrations. Molar concentrations, of course, apply only to clethodim and not the formulation. For example, Ma et al. 2002 report the EC50 for clethodim as 38.7047mg/L and 1.08×10^{-4} mol/L. Taking the molecular weight of clethodim as 359.91 g/L, the molar concentration corresponds to 38.87 mg/L [1.08×10^{-4} mol/L x 359.91 g/L = 0.03887 g/L = 38.87 mg/L]. The U.S. EPA/OPP/EFED (2014a, p. 78) appears to inappropriately correct the EC_{50} values reported in Ma et al. (2002) and Ma et al. (2006) for the proportion of a.i. in the formulation (0.12). Continuing with the example from Ma et al. (2002), the U.S. EPA/OPP/EFED (2014a, p. 78) reports the EC_{50} as 4.6 mg a.i./L [38.7047mg/L x 0.12 = 4.6446 mg/L]. This correction for the proportion of clethodim in the formulation appears to be an error.

While there is no reason to question the results from the Ma publications, they are not used quantitatively in the current risk assessment because their applicability to formulations used in the United States cannot be determined.

The EPA ecological risk assessments on clethodim (U.S. EPA/OPP/EFED 2007a,b) provide information on both NOEC values and EC_{50} values. Following standard practice in Forest Service risk assessments (SERA 2014a), only NOEC values are used for risk characterization. The most sensitive species is *Navicula pelliculosa* with an NOEC of 3.1 mg/L (MRID 420297-06).

The least sensitive species reported in the EPA risk assessments is *Pseudokirchneriella subcapitata*. Two bioassays are available in this species, one using technical grade clethodim (MRID 416851-06) and the other using Select 2.0 EC (MRID 420297-03). As detailed in Appendix 7 (Table A7-1), the NOEC values for the formulation assay are reported differently in ECOTOX—i.e., 8 mg/L—and U.S. EPA/OPP/ EFED (2007a,b)—i.e., >11.1 mg a.i./L. The reason for this discrepancy is unclear. Both ECOTOX and the EPA risk assessments report the

NOEC from the formulation study as 11.1 mg a.i./L. Thus, the minor inconsistency between ECOTOX and the EPA risk assessments is inconsequential. For tolerant species, the NOAEL of 11.1 mg a.i./L is used.

4.3.3.4.2. Aquatic Macrophytes

The only bioassays available for clethodim were conducted with *Lemna gibba* (duckweed). *Lemna* species are monocots. By analogy to the data on terrestrial plants, *Lemna* are assumed to be sensitive species. One bioassay is available on technical grade clethodim (MRID 420297-01) and another bioassay is available on Select 2.0 EC (MRID 420297-02). The bioassay with technical grade clethodim reports an NOEC of about 0.3 mg a.i./L, and the bioassay with the Select formulation reports an NOEC of 1.1 mg a.i./L. For the current risk assessment, the somewhat lower NOEC of 0.3 mg a.i./L is used. As discussed further in Section 4.4.3.4.2, the selection of the lower value has no impact on the risk characterization for clethodim because the NOEC is not exceeded at the upper bounds of expected exposures. For accidental exposures, the NOECs for both technical grade clethodim and the formulation are exceeded substantially.

4.4. RISK CHARACTERIZATION

4.4.1. Overview

Clethodim is an effective herbicide for the control of many grass weeds (i.e., monocots of the family Poaceae). Clethodim, however, is relatively nontoxic to dicots and non- Poaceae species of monocots. Consequently, applications of clethodim do not appear to pose a substantial risk to dicots or tolerant species of monocots – i.e., non-Poaceae monocots. Risks to sensitive nontarget monocots could occur due to drift, runoff, or the use of contaminated surface water for irrigation. The risks to nontarget plants from the wind erosion of contaminated soil appear to be low. Risks to sensitive species of monocots will be highly dependent on site-specific conditions as well as specific application methods. In directed foliar applications, the potential for damage to nontarget plants species appears to be low. Risks to sensitive species of monocots could be substantial, however, from drift following aerial applications and/or in applications at sites with high runoff potential (i.e., high rates of rainfall and clay soils).

While risks to grasses are to be expected given the labelled uses of clethodim (i.e., the control of grasses), the limited data also suggest that longer-term exposures associated with applications of clethodim may adversely impact sensitive species of fish. Confidence in the risk characterization for longer-term exposures of fish to clethodim is low, however, due to limitations in the toxicity data. Confidence in the risk characterization for fish would be enhanced substantially by a confirming early life stage study in fathead minnows and by early life stage studies in other potentially more sensitive species of fish such as trout. Risks to other groups of aquatic organisms appear to be minimal.

While risks to mammals can be well characterized, it is more difficult to characterize risks to other groups of terrestrial animals because of limitations in the available data on birds and terrestrial insects and the lack of data on amphibians. Some acute exposure scenarios for a small (20 g) mammal modestly exceed the level of concern at the upper bound of plausible exposures but serious effects on mammals do not seem likely. Similarly, the potential for direct effects on birds associated with acute exposures appears to be low. Longer-term exposures for a small (10 g) bird, however, exceed the level of concern by factors of about 2 to 4 for two applications of clethodim. While the magnitude of these HQs is not substantial, serious adverse effects on offspring (i.e., mortality and decreased hatching) cannot be ruled out.

The risk characterization for clethodim focuses on the potential for direct toxic effects. Nonetheless, there is a potential for secondary effects in virtually all groups of nontarget organisms. Terrestrial applications of any effective herbicide, including clethodim, are likely to alter vegetation within the treatment area. This alteration could have secondary effects on terrestrial or aquatic animals, including changes in food availability and habitat quality. These secondary effects may be beneficial to some species and detrimental to others; moreover, the magnitude of secondary effects is likely to vary over time. While these concerns are acknowledged, they are not specific to clethodim or herbicide applications in general. Any effective method for vegetation management, including mechanical methods which do not involve clethodim or any other herbicide, could be associated with secondary effects on both nontarget animals and vegetation.

Another limitation with the risk assessment on clethodim involves the small number of species on which toxicity data are available relative to the large number of species that may be exposed during and following applications of clethodim. While this limitation is common to virtually all ecological risk assessments, concern with this limitation is exacerbated by the lack of field studies relevant to the assessment of the effects of clethodim applications on most groups of nontarget species.

4.4.2. Terrestrial Organisms

4.4.2.1. Mammals

The risk characterization for mammals is summarized in Worksheet G02a of the attachments that accompany this risk assessment—i.e., Attachment 1 for a single application at the maximum rate of 0.25 lb a.i./acre and Attachment 2 for two applications at the same rate with the minimum 14-day application interval (Section 2.4).

Based on the central estimates of expected exposures, none of the HQs for mammals exceed the level of concern following either one or two applications. The highest central estimate of the HQ is 0.4 for the acute consumption of contaminated short grass by a small (20g) mammal. Notice that the HQ of 0.4 applies to both a single application and two applications, although the underlying exposures (Worksheet G01a) are different—i.e., 36 mg/kg bw following one application and 42.6 mg/kg bw following two applications. When these exposures are divided by the acute NOAEL of 100 mg/kg bw and rounded to one significant digit, the HQs are identical. This pattern holds for many of the HQs for the consumption of contaminated vegetation. Because the estimated half-lives for clethodim on vegetation are relatively short—i.e., 5.75 (5.4-6.1) days—an application interval of 14 days leads to a substantial reduction in residues associated with the first application, and the impact of the second application results in only modestly higher residues—e.g., a factor of about 1.2 for both the central and upper estimates of exposure.

For one application, the upper bound HQs for acute non-accidental exposures lead to modest excursions (maximum upper bound HQ=1.7 for the consumption of contaminated grass) above the level of concern (HQ=1) for a small (20g) mammal. For two applications, the HQs for a small mammal reach or exceed the level of concern for the acute consumption of broadleaf foliage (HQ=1.2), tall grass (HQ=1), and short grass (HQ=2) as well as the longer-term consumption of broadleaf foliage (HQ=1) and short grass (HQ=1.8). For the longer-term exposure scenarios, the time-weighted average concentrations on vegetation are about a factor of 2 higher following two applications, relative to one application; hence, the HQs for two applications are about twice as high as those for a single application.

As discussed in Section 4.3.2.1, the acute HQs are based on a developmental study in rats for which the NOAEL was 100 mg/kg bw/day and the LOAEL was 350 mg/kg bw/day based on reduced body weight and salivation in at least some of test animals. The LOAEL of 350 mg/kg bw/day would correspond to an HQ of 3.5. As noted above, the highest HQ for the small (20g) mammal is 2. It should also be noted that the LD_{50} for mice, a small mammal with a body weight of about 20 g, is about 2500 mg/kg bw (MRID 409745-08 as summarized in Appendix 1, Table A1-1), which would correspond to an HQ of 25. Thus, it is not clear that any overt

adverse effects would be detectable in small mammals at an HQ of 2. Sublethal effects could include decreased body weight gain.

For larger mammals with body weights in the range of 400 g to 70 kg, all of the HQs associated with expected levels of exposure are below the level of concern even at the upper bounds of exposures.

The potential for a modest risk to small mammals but no substantial risks to larger mammals is consistent with the risk characterization for mammals given in the most recent EPA risk assessment on clethodim (i.e., U.S. EPA/OPP/EFED 2014a, Table 23, p. 47).

None of the accidental exposure scenarios for mammals approach a level of concern. While this may not be intuitive, it reflects the fact that the accidental exposure scenarios primarily involve spills into water and the consequent consumption of contaminated water. As discussed in Section 4.2, the consumption of contaminated vegetation leads to much higher exposures than the consumption of contaminated water even for exposures following an accidental spill.

4.4.2.2. Birds

None of the acute exposure scenarios for birds approach a level of concern. This difference from the risk characterization for mammals is due primarily to differences in the toxicity values for these two groups of animals. As summarized in Table 23 and discussed in Section 4.3.2.2, the acute NOAEL for birds (950 mg/kg bw) is about a factor of 10 higher than the corresponding value for mammals (100 mg/kg bw/day).

The estimated longer-term NOAEL for birds (20 mg/kg bw/day) is almost identical to the NOAEL for mammals (19 mg/kg bw/day); consequently, the risk characterization for longer-term exposures of birds to clethodim is very similar to that for mammals. None of the central estimates of exposure result in HQs that exceed the level of concern (HQ=1). At the upper bounds of the exposure the level of concern is exceeded only for the small (10 g) bird. Following one application, the level of concern is exceeded for the consumption of broadleaf vegetation (HQ=1.2) and the consumption of short grass (HQ=2). For two applications, the level of concern is exceeded for the consumption of broadleaf vegetation (HQ=2), the consumption of tall grass (HQ=1.9), and the consumption of short grass (HQ=4).

As discussed in Section 4.3.2.2, the study used to define the NOAEL of 20 mg/kg bw/day (MRID 410302-06) noted a LOAEL of 67.2 mg/kg bw/day based on decrease survival in offspring and egg hatch. This LOAEL corresponds to an HQ of about 3 [67.2 mg/kg bw/day ÷ 20 mg/kg bw/day ≈ 3.36]. Consequently, the longer-term scenario for the consumption of short grass (HQ=4) may be viewed as a clear concern for potential effects on the populations of small birds. Two factors reduce this concern. First, most small birds will consume insects and fruits rather than short grass. As summarized in Table 16, the residue rates for small insects are taken as those for broadleaf vegetation. The second factor reducing concern with the high HQ for the longer term consumption of short grass is that clethodim will effectively control grasses, and the longer-term consumption of short grasses following applications of clethodim may not be a reasonable scenario.

Notwithstanding these mitigating factors, the LOAEL for birds is only a factor of 3 above the NOAEL. Given the large number of bird species and the small number of species on which data are available, a concern for species that may be more sensitive than standard test species seems reasonable. In addition, the nature of the LOAEL (decreased survival in offspring and decreased egg hatch) for birds represents a serious adverse effect that could impact populations of sensitive species of birds. Given the limited data on the effects of clethodim on birds, these concerns cannot be characterized further.

4.4.2.3. Reptiles and Amphibians (Terrestrial Phase)

Risks to reptiles and terrestrial phase amphibians cannot be characterized directly because of the lack of data on the toxicity of clethodim to this group of organisms.

4.4.2.4. Terrestrial Invertebrates

As summarized in Worksheet G09, the direct spray of a honeybee with clethodim leads to an HQ of 0.02—i.e., below the level of concern by a factor of 50. While Worksheet G09 considers both foliar interception and exposures associated with drift, these standard elaborations are not necessary. Albeit limited, the available information on the toxicity of clethodim to honeybees, offers no evidence that honeybees will be adversely affected by the direct spray or drift from applications of clethodim.

4.4.2.5. Terrestrial Plants

4.4.2.5.1. Direct Spray and Spray Drift

The HQs for sensitive and tolerant species of terrestrial plants are summarized in Worksheet G05a (fine droplets) and Worksheet G05b (coarse droplets). These worksheets are customized to reflect the use of three sets of values for drift: aerial application, ground high-boom broadcast application, and ground low-boom broadcast application. As detailed in Section 4.2.4.2, all estimates of drift are based on AgDRIFT (Teske et al. 2002). As detailed in Section 4.3.2.5 and summarized in Table 24, all HQs are based on NOAELs from studies on vegetative vigor (foliar applications)—i.e., an EC_{05} of 0.0023 lb a.i./acre for sensitive species of monocots and a NOAEL of 0.25 lb a.i./acre for dicots and tolerant species of monocots.

Clethodim is an effective herbicide for the control of grassy weeds. If sensitive species of monocots are directly sprayed with clethodim at the maximum application rate of 0.25 lb a.i./acre, the impact will be severe (HQ=109). Following a direct spray, the HQs for tolerant species (i.e., dicots and some tolerant species of monocots) are 1. An HQ of 1 is defined as the level of concern. As discussed in Section 4.3.2.5, clethodim has been assayed for toxicity to dicots only at the maximum labeled application rate of 0.25 lb a.i./acre. Consequently, the HQ of 1 for dicots and tolerant species of monocots does not imply that the exposures border on a true level of concern.

Based on estimates of drift using AgDRIFT, risks to sensitive monocots remain above the level of concern downwind from the application site. As summarized in Worksheet G05a for the application of fine droplets, the risks will be greatest with aerial applications (e.g., HQ=3 at 300 feet down wind). The HQs for fine droplet applications, however, should be viewed as essentially accidental exposures and misapplications of clethodim. For coarse droplet applications, which would be the norm in actual applications in Forest Service programs, the

risks to sensitive species of nontarget vegetation fall below the level of concern at a distance of 300 feet downwind (HQ=1) for aerial applications. Ground boom applications result in only modest exceedances of the level of concern at a distance of 25 feet downwind (i.e., HQs of 1.4 to 1.8). For backpack applications, the HQ does not exceed the level of concern at 25 feet downwind (HQ=0.9).

To put it simply, directed spray applications using coarse droplets, which are most likely to be used by the Forest Service, are not likely to damage nontarget vegetation at distances of greater than 25 feet from the application site based on the Tier 1 estimates of drift used in the current risk assessment. As detailed in the documentation for WorksheetMaker (SERA 2011a, Section 3.2.2), a large number of application-specific practices are available which could decrease drift and these practices can be reflected in elaborated AgDrift modeling.

4.4.2.5.2. Soil Exposures by Runoff

Risks to nontarget vegetation associated with runoff and sediment losses to a field adjacent to the treated site are estimated in Worksheet G04 (Attachment 1 for a single application and Attachment 2 for two applications). For tolerant species of plants, including dicots and tolerant species of monocots, the upper bound HQs are below the level of concern—i.e., an HQ of 0.2.

For sensitive species of plants (i.e., grasses of the family Poaceae), the upper bound HQs substantially exceed the level of concern following both a single application (HQ=94) and two applications (HQ=125). The exposure components of these HQs are based on the Gleams-Driver modeling. As with the estimates of the concentrations of clethodim in water (Section 3.2.3.4.3), Gleams-Driver simulations are conducted for nine different locations encompassing extremes of temperature and rainfall. For each of these nine sites, three separate sets of simulations are conducted for soils that consist predominantly of clay, loam, and sand. As detailed in Section 4.2.4.3, with respect to runoff, the estimated exposures of nontarget plants adjacent to the application site are taken as a composite (i.e., a central estimate and a range) for all of the simulations combined. Consequently, the range of HQs for sensitive species does not apply to any specific location but is a composite of HQs that might be seen nationally.

Table 1 of Appendix 8 (one application) and Appendix 9 (two applications) should be consulted in any consideration of the consequences of potential risks to sensitive species of nontarget vegetation in a site-specific application. In areas with predominantly sandy soils, the runoff of clethodim following foliar applications should be negligible and risks to nontarget plants should also be negligible. Conversely, risks will be greatest in areas with predominantly clay soils and moderate to high rates of rainfall. Risks may also be relatively high in cool locations with predominantly loam soils. Further generalizations do not appear to be warranted, because the modeling conducted for the current risk assessment is inherently conservative and a number of site-specific conditions could reduce, and perhaps substantially reduce, estimates of risks to nontarget vegetation.

4.4.2.5.3. Contaminated Irrigation Water

The HQs for nontarget plants associated with using clethodim contaminated surface water for irrigation are summarized in Worksheet G06a. For a single application (Attachment 1), the HQs are 1.2 (0.003 to 37) for sensitive species and 0.01 (0.00005 to 0.3) for tolerant species of

terrestrial plants. For two applications (Attachment 2), the HQs are 2 (0.006 to 68) for sensitive species and 0.02 (0.00005 to 0.5) for tolerant species of terrestrial plants.

As with the HQs for runoff, the HQs associated with irrigation water for tolerant species of plants do not require further characterization. The key variables in this exposure scenario are the expected concentrations in ambient water (Section 3.2.3.4.6.1) and the amount of irrigation water applied, which is assumed to be 1 (0.25 to 2) inches. Taking into account reasonable variations that might be made in the exposure scenario, there is little basis for asserting that tolerant species of plants will be at risk. Risks to sensitive species of plants, however, could be substantial at the upper bounds of exposures.

As with the estimates of risks from runoff (Section 4.4.2.5.2), the exposure components of the HQs are based on the Gleams-Driver simulations. Consequently, the upper bound risks will be most commonly associated with site conditions, including high rates of rainfall and soils conducive to runoff and/or percolation losses. As with the assessment of risks due to runoff, Table 1 of Appendix 8 (one application) and Appendix 9 (two applications) should be consulted in any consideration of the consequences of potential risks to sensitive species of nontarget vegetation in a site-specific application.

4.4.2.5.4. Wind Erosion

Risks to nontarget vegetation associated with wind erosion of contaminated soils are insubstantial. The upper bound HQ for sensitive species is 0.02, below the level of concern by a factor of 50. As detailed in Section 4.2.4.5, substantial uncertainties are associated with this exposure scenario, and the expected loss rates for soil are intended to represent forestry applications. Much higher loss rates could occur if clethodim were to be applied inadvertently to fallow soil. Within this limitation, the HQs for both sensitive and tolerant species indicate that wind erosion is not a substantial concern relative to other routes of exposure.

4.4.2.6. Terrestrial Microorganisms

The toxicity of clethodim to terrestrial microorganisms is not addressed in the available literature (Section 4.3.2.6). Consequently, no risk characterization for this group of organisms is developed.

4.4.3. Aquatic Organisms

The risk characterization for aquatic organisms is summarized in Worksheet G03 of the attachments that accompany this risk assessment.

4.4.3.1. Fish

4.4.3.1.1. Acute Exposures

As discussed in Section 4.3.3.1.1, the acute toxicity data on clethodim in fish are limited to a few standard test species. In terms of the quality of the available toxicity data, the risk characterization relies on recent EPA ecological risk assessments (U.S. EPA/OPP/EFED 2007a,b; 2014a). Based on the limited information on the acute toxicity of clethodim to fish, there is no basis for asserting that clethodim in surface water will directly impact fish. Following two applications, the highest HQ is 0.04 (the upper bound acute HQ for sensitive species of fish following two applications of clethodim), which is below the level of concern by a factor of 20.

Following an accidental spill, the upper bound HQ for sensitive species of fish reaches but does not exceed the level of the concern (HQ=1).

4.4.3.1.2. Longer-term Exposures

While acute exposures do not appear to pose risks to fish, the risk characterization for longer-term exposures is more nuanced and far less certain.

The uncertainty with the risk characterization is based on the limited longer-term toxicity data in fish, specifically the single early life stage study in fathead minnows (Bidinotto 2003, MRID 481043-03). As discussed in Section 4.1.3.1.2, this study is used by the U.S. EPA/OPP (2014a); however, the EPA also expresses serious reservations with this study and these reservations are shared in the current Forest Service risk assessment. In the dose-response assessment for longer-term exposures in fish (Section 4.3.3.1.2), the current Forest Service risk assessment derives alternative dose-response assessments for fish that are substantially higher than those used by the U.S. EPA/OPP (2014a). Specifically, U.S. EPA/OPP (2014a) derives an NOAEC of 0.002 mg a.i./L for presumably sensitive species of fish (trout) from the study in fathead minnows by Bidinotto (2003). The current Forest Service risk assessment uses estimated NOAECs of 0.6 mg a.i./L for tolerant species of fish and 0.1 mg a.i./L for sensitive species of fish based on a weight-of-evidence evaluation considering acute to chronic ratios, *Daphnia* to minnow correlations for chronic toxicity, and quantitative structure activity relationships (Section 4.3.3.1.2).

The hazard quotients associated with longer-term exposures of fish to clethodim are summarized in Table 28 for 1, 2, 4, and 18 applications. These HQs are taken from Worksheet G03 in Attachment 1 (1 application), Attachment 2 (2 applications), Attachment 3 (4 applications), and Attachment 4 (18 applications). Based on central estimates and lower bounds of the HQs, there is no basis for asserting that longer-term exposures would lead to adverse effects in fish. The highest central estimate of the HQ is 0.7 which is associated with 18 applications at a rate of 0.25 lb a.i./acre and an application interval of 14 days. As discussed in Section 2.4, 18 applications are not anticipated in Forest Service programs. More typically, Forest Service programs would involve only one or two applications of 0.25 lb a.i./acre and an application interval of 14 days.

While the central estimates of the HQs do not exceed the level of concern (HQ=1), exceedances in the level of concern are noted in some upper bound HQs, particularly for sensitive species of fish – i.e., HQs of 1.1, 2.0, 4, and 14 following 1, 2, 4, and 18 applications, respectively. For tolerant species of fish, the only exceedance in Table 28 involves an HQ of 2 following 18 applications. As discussed above, 18 applications are not anticipated in Forest Service programs.

While the current Forest Service risk assessment differs from the most recent ecological risk assessment from the EPA (i.e., U.S. EPA/OPP/EFED 2014a) in the dose-response assessment for longer-term exposures in fish, the qualitative risk characterizations in the current risk assessment and the U.S. EPA risk assessment are essentially identical. As noted by U.S. EPA/OPP/EFED (2014a, p. 9): *There is the potential for chronic direct effects to fish for all uses of clethodim*.

Confidence in the risk characterization for fish would be enhanced substantially by a confirming early life stage or full life cycle study in fathead minnows and by an early life stage study in rainbow trout. In the absence of such studies, confidence in the risk characterization for fish is low.

4.4.3.2. Amphibians

As noted in Section 4.1.3.2, no information is available on the toxicity of clethodim to aquatic-phase amphibians. Consequently, no risk characterization is developed for this group of organisms.

4.4.3.4. Aquatic Invertebrates

As discussed in Section 4.3.3.3, several acute toxicity studies and one longer-term study are available in aquatic invertebrates. As noted above in the discussion of the risk characterization for fish (Section 4.4.3.1), the available toxicity data in aquatic invertebrates does not suggest a remarkable difference in acute and chronic NOEC values for sensitive species – i.e., acute and chronic NOECs in *Daphnia magna* of 1.4 mg/L and 0.94 mg/L, respectively. Based on these NOECs, none of HQs for aquatic invertebrates associated with expected peak or longer-term concentration of clethodim in surface water approach a level of concern following one or two applications of clethodim – i.e., the upper bound of the HQ following two applications is 0.2. The lack of apparent risk to aquatic invertebrates associated with expected concentrations of clethodim in surface water is consistent with the risk characterization for aquatic invertebrates given in the most recent ecological risk assessment from U.S. EPA/OPP/EFED (2014a, p. 2).

An accidental spill of clethodim could be associated with adverse effects in sensitive species for which the upper bound HQ is 5. This HQ is associated with a concentration of 7.57 mg a.i./L which is above the LC_{50}s of 5.17 to 5.3 mg a.i./L in sensitive species of aquatic invertebrates (Appendix 6, Table A6-1). Thus, in the event of a severe accidental spill, mortality in sensitive species of aquatic invertebrates would be expected.

4.4.3.4. Aquatic Plants

4.4.3.4.1. Algae

There are no substantial concerns with risk characterization for algae. Based on a standard set of bioassays reviewed and used in the EPA risk assessments on clethodim (U.S. EPA/OPP/EFED 2007a,b; 2014a), there is no indication that algae will be adversely affected by anticipated levels of clethodim in surface water. Following two applications of clethodim, the upper bound HQ for sensitive species of algae is only 0.7.

Even in the case of an accidental spill, the upper bound HQ of 2 is only modestly above the level of concern. While some growth inhibition of algae might be seen following an accidental spill, it seems equally likely that hormetic responses might induce a slight stimulation of growth. Thus, it does not seem likely that an accidental spill of clethodim would have a substantial or even grossly observable impact on algal populations.

4.4.3.4.2. Macrophytes

The risk characterization for aquatic macrophytes is based on bioassays in a single species, *Lemna gibba* (Section 4.3.3.4.2). Because *Lemna* species are monocots, the risk characterization is nominally applied to presumably sensitive species. While this seems reasonable by analogy to the toxicity data on terrestrial plants, the limitations in the data are obvious.

Within the above limitations, the risk characterization for aquatic plants is essentially identical to the risk characterization for algae for anticipated concentrations of clethodim in surface water.

The upper bound HQ associated with two applications of clethodim is 0.9, which approaches but does not exceed the level of concern.

For the accidental spill scenarios, however, the upper bound HQ is 25. This upper bound HQ is based on a concentration of clethodim in water of about 7.6 mg a.i./L. As detailed in Appendix 9 (Table A9-2), this concentration exceeds the EC_{50} of technical grade clethodim (1.1 mg a.i./L) by a factor of about 7 but is below the LC_{50} of the Select 2.0 EC formulation (42.5 mg a.i./L) by a factor of about 5. For the accidental spill scenario, it seems most reasonable to base the risk characterization on the formulation data. Using this approach, the HQ of 25 might not be associated with substantial mortality in macrophytes. A reservation with this interpretation, however, is that the applicability of the formulation toxicity data on Select 2.0 EC to the many other available formulations of clethodim is not known. In the absence of such data, the potential for substantial mortality in aquatic macrophytes following an accidental spill of formulations other than Select 2.0 EC cannot be ruled out. If substantial mortality in macrophytes were to occur in a densely vegetated pond, adverse effects in other aquatic species could occur secondary to oxygen depletion.

5. REFERENCES

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

DERs	**Data Evaluation Records from various EPA documents. Source document is identified in the individual citation to each study.**
E-Docket	**Docket IDs: EPA-HQ-OPP-2008-0658, EPA-HQ-OPP-2009-0307 at www.regulations.gov.**
EPA01	**Data from several EPA web sites – root www.epa.gov.**
EPA02	**Data from EPA's Office of Pesticide Programs' Science Reviews on Clethodim** [http://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:7:16721629090140::NO:1,3,31,7,12,25:P3_XCHEMICAL_ID:1847]
EPARegRv	**EPA documents associated with U.S. EPA/OPP's Registration Review of clethodim.**
FOIA01	**Added in response to FOIA EPA-HQ-2013-009201.**
FS01	**Comments from the Forest Service on preliminary program description.**
FS02	**Comments from the Forest Service on initial draft.**
Internet	**References obtained from various sites on the Internet.**
PeerRev	**Documents added during or after peer review.**
SET00	**Papers from preliminary scoping.**
SET01	**TOXLINE, ECOTOX, and limited tree search of reviews.**
SET02	**Sundry references found during prog. desc. preparation.**
SET03	**Supplemental references for the hazard identification.**
SET03	**Supplemental references for ERA.**
Std	**Standard references used in most Forest Service risk assessments.**

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{Valent 2013} Valent (Valent Profession Products). 2013. Company History. Available at: http://www.valent.com/aboutvalent/companyhistory. Downloaded on September 6, 2013. [Set00]

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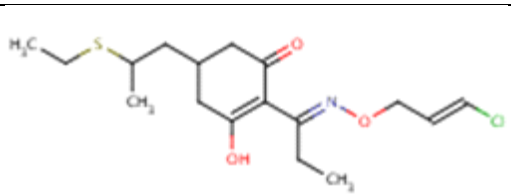
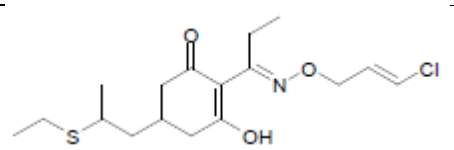
Table 1: Key Reviews and Related Documents on Clethodim

Reference[1]	Comment
ESFA 2011	Large (95 pp.) review of studies relevant to environmental fate, human health, and ecological effects. Most studies are not summarized in detail and the studies are cited to other EU documents/reviews and the primary studies (which appear to be registrant submitted studies) are not identified.
FAO/WHO 1994	Modest (40 pp.) review of information relevant to environmental fate and human health effects. Very good summary of studies, all of which appear to be registrant submitted. References to studies are abbreviated but full titles are given.
IPCS 1994	Brief (14 pp.) review of mammalian studies by registrants. Study summaries are relatively detailed and full citations are given.
U.S. EPA/OPP/EFED 2007a	Substantial (58 pp.) ecological risk assessment. Reasonably detailed studies on environmental fate and ecotoxicity. References to MRIDs are provided.
U.S. EPA/OPP/EFED 2007b	Substantial (97 pp.) ecological risk assessment. Reasonably detailed studies on environmental fate and ecotoxicity. References to MRIDs are provided.
U.S. EPA/OPP/EFED 2014a	Substantial (137 pp.) and most recent (1/13/2015) EPA ecological risk assessment. This is the preliminary ecological risk assessment for the Registration Review of clethodim.
U.S. EPA/OPP/HED 1990a	Large (436 pp) and detailed summary of studies related to HHRA. Essentially a compendium of DERs. For the scoping level risk assessment, this document is used to obtain details of key studies.
U.S. EPA/OPP/HED 2007a	Substantial (33 pp.) summary of registrant studies and HHRA.
U.S. EPA/OPP/HED 2008a	Substantial (34 pp.) summary of registrant studies relating to human health effects.
U.S. EPA/OPP/HED 2010a	Substantial (56 pp.) summary of registrant studies relating to human health effects.
U.S. EPA/OPP/HED 2014a	Substantial (41 pp.) review and reevaluation of registrant studies and the most recent human health risk assessment identified (1/30/2014). This is the preliminary human health risk assessment for the Registration Review of clethodim.

[1] The most relevant reviews designated by bold font. Some U.S. EPA/OPP tolerances and specifically focused documents – e.g., exposure assessments, registration status, use applications, etc. – are not summarized above but are discussed in the text as appropriate.

See Section 1.1 for discussion.

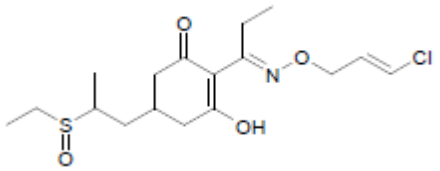
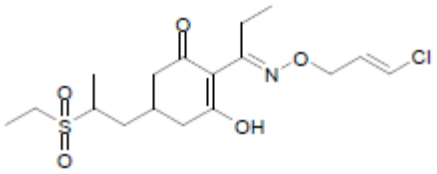
Table 2: Chemical and Physical Properties of Clethodim and Selected Metabolites

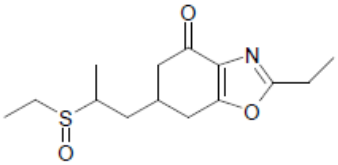
Item	Value	Reference[1]
	Identifiers	
CAS No.	99129-21-2	HSDB 2012; Tomlin 2004 and others
Chemical group	Cyclohexanedione oxime graminicide	Tomlin 2004
	Cyclohexanedione	Mallory-Smith and Retzinger 2003
	Cyclohexenone	U.S. EPA/OPP 2010a
	Cyclohexene oxime herbicide	Wood 2013
Commercialization	Chevron, Patent GB 2090246, 1987	Tomlin 2004
Common name	Clethodim	
CAS Name [2]	(E,E)-(±)-2-[1-[[(3-chloro-2-propenyl)oxy] imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one	Tomlin 2004
IUPAC Name [2]	(±)-2-[(E)-1-[(E)-3-chloroallyloxyimino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxycyclohex-2-enone	Tomlin 2004
Systematic Name	2-Cyclohexen-1-one, 2-(1-(((3-chloro-2-propenyl)oxy)imino)propyl)-5-(2-(ethylthio)propyl)-3-hydroxy-	ChemIDplus
Development code(s)	RE-45601 (Chevron)	Kincade et al. 1987 Tomlin 2004; U.S. EPA/OPP/HED 2010a,b
Mechanism	Fatty acid synthesis inhibitor, by inhibition of acetyl CoA carboxylase (ACCase).	Tomlin 2004
	WWSA Class 1/HRAC Class A: Inhibitors of acetyl CoA carboxylase (ACCase)	Mallory-Smith and Retzinger 2003
Initial Year of Registration	1991	CalEPA 2010
Molecular formula	$C_{17}H_{26}ClNO_3S$	HSDB 2012, Tomlin 2004
Smiles Code	`CCSC(C)CC1CC(=C(C(=NOC/C=C/Cl)CC)C(=O)C1)O`	Tomlin 2004
	`O=C1CC(CC(C)SCC)CC(O)=C1C(CC)=NOCC=CCL`	EPI-Suite 2013
Structure `Working Note: The two structures are identical. Just different rotational perspectives.`		ChemIDplus 2013
		U.S. EPA/OPP 2014a
Use	Post-emergence control of annual and perennial grasses	Labels
	Chemical Properties	
Aqueous photolysis	**DT_{50} (days)** / **pH at 25°C** 1.6 / 5 5.45 / 7 7.79 / 9	HSDB 2012
	DT_{50} (days) / **pH at 25°C** 1.39 / 5 4.05 / 7 5.43 / 9	U.S. EPA/OPP/EFED 2007a, MRID 410301-33

Item	Value	Reference[1]
	DT_{50} (days) / **pH at 25°C** 1.5 / 5 6.4 / 7 9.3 / 9	U.S. EPA/OPP/EFED 2007a, MRID 410301-34
	DT_{50} (days) / **pH at 25°C** 1.5-1.7 / 5 2.5-6.8 / 7 6.0-9.6 / 9	U.S. EPA/OPP/EFED 2014a, MRID 410301-33 and MRID 410301-34
	DT_{50} (days) / **pH at 25°C** 2.4 / 5 2.6 / 6 3.2 / 7	Falb et al. 1990
Boiling point	Decomposes below boiling point.	HSDB 2012; Tomlin 2004; Dynamac 1989
Density	1.1395 g/cm^3 (TGAI) 0.9446 g/cm^3 (26.6% EC formulation)	Dynamac 1989
Form	Clear amber liquid	HSDB 2012, Tomlin 2004
	Viscous amber to green-yellow colored liquid depending upon purity	PPDB/UK 2012
	Amber viscous liquid with light aromatic odor	Dynamac 1989
Henry's Law Constant	2.68 x 10^{-10} at 20°C	PPDB/UK 2012
	1.16 x 10^{-11} at 25°C (Calculated)	EPI-Suite 2013
Hydrolysis	**DT_{50} (days)** / **pH** 28 / 5 300 / 7 310 / 9	U.S. EPA/OPP/EFED 2007a, MRID 409745-20; Tomlin 2004
	DT_{50} (days) / **pH** 28 / 5 289 / 7 305 / 9	U.S. EPA/OPP/EFED 2014a, MRID 409745-20
	Stable	PPDB/UK 2012
Hydrolysis (**Residues of Concern**)	**DT_{50} (days)** / **pH** 414 / 5 3,660 / 7 45,000 / 9 **These used in EFED 2014 modelling.**	U.S. EPA/OPP/EFED 2014a, MRID 409745-20
Kow	≈39.8 [log Kow 1.6]	PPDB/UK 2012. Also cited in U.S. EPA/OPP/EFED 2007a
	≈31,600 [log Kow = 4.51 at 21°C] Cited to: S.T. Ha (1994) Determinations of Octanol/Water Partition Coefficients of Clethodim … By Reversed-Phase High Performance Liquid Chromatography, Valent U.S.A Corporation. Project No. 10768.	U.S. EPA/OPP/HED 2010a,b, cited to Valent Corp. study. U.S. EPA/OPP/HED 2014a, MRID 48881405.
	≈64,565 [log Kow = 4.81]	U.S. EPA/OPP/EFED 2014a, MRID 48881405.
	13,800 (calculated, NOS)	PPDB/UK 2012

Item	Value	Reference[1]
	15,000	Dynamac 1989; CalEPA 2010 referenced to PPDB/UK 2010
	≈15,800 [log Kow 4.2]	EPI-Suite 2013
	3000 at pH 5 40 at pH7 0.49 at pH 9	EXTOXNET 1995
Molecular weight (g/mole)	359.9154	ChemIDplus 2013
	359.91	HSDB 2012; U.S. EPA/OPP/HED 2014a
	359.92	PPDB/UK 2012.
Melting point	-80 °C	PPDB/UK 2012
	177.5 (156.1-220.5) Calculated	EPI-Suite 2013
pKa	4.47 at 25°C	Dynamac 1989, PPDB/UK 2012
	4.51 at 21°C	U.S. EPA/OPP/HED 2014a, MRID 48881405
	4.62	U.S. EPA/OPP/EFED 2014a, MRID 48881405
Specific gravity	1.14 g/mL (20 °C)	Tomlin 2004 U.S. EPA/OPP/HED 2010a,b, MRID 461241-03
	1.16 g/mL	PPDB/UK 2012
Thermal decomposition		
Vapor pressure	$<1x10^{-2}$ mPa (20 °C)	U.S. EPA/OPP/HED 2014a, MRID 48881405; Tomlin 2004
	1.4×10^{-7} Pa m^3/mol	PPDB/UK 2012
	$<1x10^{-2}$ mPa (20 °C)	U.S. EPA/OPP/HED 2010a,b, MRID 461241-03
Water solubility	49.9 mg/L	U.S. EPA/OPP/EFED 2007a, MRID 409745-20
	29 mg/L	U.S. EPA/OPP/EFED 2014a, MRID 488814-05
	5,400 mg/L (reported as 0.54 g/100 mL)	U.S. EPA/OPP/HED 2010a,b, 2014a; MRID 461241-03, Dynamac 1989
	5450 mg/L at 20°C	PPDB/UK 2012
	1.36 mg/L [calculated from estimated Kow]	EPI-Suite 2013
	Environmental Properties	
Bioconcentration	2.1 (whole fish)	PPDB/UK 2012
	Bluegill sunfish: 0.71 edible tissue; 3 non-edible tissue; 2.3 whole fish	U.S. EPA/OPP/EFED 2007a, MRID 409745-31
	0.7-2.1 (edible), 3.0-4.0 (inedible), 2.3-3.6 (whole fish)	U.S. EPA/OPP/EFED 2014a, MRID 409745-31
	Bluegill sunfish: 2.1 edible tissue; 4 non-edible tissue; 3.6 whole fish	U.S. EPA/OPP/EFED 2007a, MRID 409745-24

Item	Value	Reference[1]
Bioconcentration (*continued*)	0.7-2.1 (edible), 3.0-4.0 (inedible), 2.3-3.6 (whole fish); >70% depuration in 3-14 days	U.S. EPA/OPP/EFED 2014a, MRIDs 409745-24 and 409745-31
	279.9 L/kg (calculated)	EPI-Suite 2013
Foliar washoff fraction	0.7 by analogy to sethoxydim.	Section 3.2.3.4.3
Foliar half-life	5.75 (5.4-6.1) days **The method of Juraske et al. (2008) dividing the soil half-lives of 92 (86.4-97.6) days for total toxic residues by 16.**	Section 3.2.3.4.3
Soil half-life (NOS)	0.55 – 2.61 days (lab at 20°C)	PPDB/UK 2012
Soil adsorption, Freundlich	Freundlich coefficients: Kf = 0.39, Kfoc = 22.7, 1/n = 1.01	PPDB/UK 2012
Soil Adsorption Linear (L/kg oc):	K_{oc}: 5-270 **Working Note: U.S. EPA/OPP/EFED 2007a used 5 for FIRST modeling.**	U.S. EPA/OPP/EFED 2007a, MRID 409745-23
	4.9, 65, 68, 132, 271 L/kg (presumably for different soils)	U.S. EPA/OPP/EFED 2014a, MRID 409745-23
	K_{oc}: 1091 (calculated)	EPI-Suite 2013
Residues of concern	12, 27, 38, 57, 86 L/kg oc	U.S. EPA/OPP/EFED 2014a, MRID 409745-23
Soil half-life, aerobic	1.6 (1.06-2.6) days (parent) 35.4 (30.1-38.6) days (total toxic metabolites)	U.S. EPA/OPP/EFED 2006a, p. 4. MRID 440667-01 MRID 413768-01
	1.2 days (MRID 413768-01) 2.5 days (MRID 409745-22)	U.S. EPA/OPP/EFED 2014a, Table 4, p. 16
Soil half-life, aerobic **(Residues of Concern)**	44 days (MRID 413768-01) 87 days (MRID 409745-22)	U.S. EPA/OPP/EFED 2014a
Soil half-life, anaerobic	No acceptable study.	U.S. EPA/OPP/EFED 2007a, p. 39-40
	92 (86.4-97.6) days for total toxic residues. **Note: These are the most recent values from EFED and are used in modeling to account for the formation of potentially toxic metabolites.**	U.S. EPA/OPP/EFED 2009a, p. 4. MRID 409745-21 MRID 413768-01
Soil photolysis	Could not be measured due to rapid biodegradation.	U.S. EPA/OPP/EFED 2007a, MRID 410301-35
	7 days	U.S. EPA/OPP/HED 2014a and U.S. EPA/OPP/EFED 2014a, MRID 410301-35
Sediment half-life	16.7 days (water and sediment) 7 days (water only phase)	PPDB/UK 2012
Field dissipation half-life	3 days	PPDB/UK 2012
	2.5 to 3.7 days Indicates that off-site movement is an important component of apparent dissipation rates – i.e., these values are much less than degradation rates for total toxic metabolites.	U.S. EPA/OPP 2009a, p. 3

Item	Value	Reference[1]
Water, aqueous photolysis (**Residues of Concern**)	**Half-life (days)** / **pH** 2.1-8.1 / 5 4.1-24 / 7 7.5-27 / 9 **These used in EFED 2014 modelling.**	U.S. EPA/OPP/EFED 2014a, MRIDs 410301-33 and 410301-34
Water, aerobic metabolism	184 (172.8-195.2) days No experimental values. Use aerobic soil values x 2.	U.S. EPA/OPP/EFED 2009a, p. 4.
Water, anaerobic metabolism	233 days	U.S. EPA/OPP/EFED 2014a, MRID 416523-01
Water, anaerobic metabolism (**Residues of Concern**)	1217 days **Used in EFED 2014 modelling.**	U.S. EPA/OPP/EFED 2014a, MRID 416523-01
	Sulfoxide Metabolite	
Structure		U.S. EPA/OPP/EFED 2014a
Molecular weight	368	U.S. EPA/OPP/EFED 2007a
Soil adsorption Koc	44	U.S. EPA/OPP/EFED 2007a
Aerobic metabolism	30-35 days	U.S. EPA/OPP/EFED 2007a, estimated from MRID 409745-22
	Sulfone Metabolite	
Structure		U.S. EPA/OPP/EFED 2014a
Molecular weight	376	U.S. EPA/OPP/EFED 2007a
Soil adsorption Koc	22	U.S. EPA/OPP/EFED 2007a
	6, 13, 19, 29, 43 L/kg oc (presumably for different soils)	U.S. EPA/OPP/EFED 2014a, MRID 409745-23
Aerobic metabolism	30-90	U.S. EPA/OPP/EFED 2007a, estimated from MRID 409745-22

Item	Value	Reference[1]
	Oxazole Sulfoxide Metabolite	
Structure		U.S. EPA/OPP/EFED 2014a
Soil adsorption Koc	50, 135, 429, 460, 771 L/kg oc	U.S. EPA/OPP/EFED 2014a, MRID 409745-23

[1] There a many sources of information on the standard values for clethodim – e.g., molecular weight. In general, only two sources are cited for each value. More than two sources are cited only to highlight apparent discrepancies.
[2] See Section 2.2 for a discussion of the (±) designation of the racemic mixture of enantiomers.

Table 3: Clethodim Formulations Listed on Greenbook.net

Source: www.Greeenbook.net unless otherwise specified.

Formulation[1]	Supplier	EPA Registration Number
Arrow 2EC	MANA Crop Protection	66222-60
Clethodim	CropSmart	42750-72-72693
Clethodim 2E	Albaugh	42750-72
Clethodim 2EC	Albaugh	42750-72[2]
Clethodim 2EC	Micro Flo	51036-416
Clethodim 2EC	Tacamo Ag.	83520-22
Clethodim 2EC	AmTide LLC	83851-18
Clethodim 2EC	Willowood USA	87290-11
Dakota	Rotam NA	9468-37-83979
Envoy	Valent	59639-78
Envoy Plus	Valent	59639-132
HM-0714	Helena	5905-578
Intensity	Loveland	34704-864
Intensity One	Loveland	34704-976
Prism	Valent	59639-78
Quali-Pro	MANA Arrow 2 EC	66222-60
Section 2EC	WinField	1381-204
Select	WinField	59639-3-1381
Select 2 EC	Valent	59639-3
Select Max	Valent	59639-132
Shadow	Arysta LifeScinece	66330-353
Shadow	Micro Flow	66330-353
Shadow	Arvesta	66330-353
Shadow Herbicide	Arysta LifeScinece	66330-353
Tapout [2]	Helena	5905-578
Tide Clethodim 2EC	Tide International	84229-21
Volunteer (Tenkoz-Arysta)	Tenkoz	66330-353-55467
Volunteer (Tenkoz-Valent)	Tenkoz	59639-3-55467
Volunteer CA (Tenkoz-Valent)	Tenkoz	59639-3-55467

[1]Formulations in bold font are included in Table 4 (detailed summary).
[2] Added at the request of Forest Service Region 5.

Many other formulations of clethodim are available. See Section 2.2 for discussion.

Table 4: Representative Clethodim Formulations

Source: www.Greeenbook.net unless otherwise specified.

This table is based on product labels available at the time that this risk assessment was completed. See Section 2.4 for a discussion of the anticipated increase in the maximum annual application rate and anticipated Forest Service maximum annual rates.

Formulation, Supplier, EPA Registration Number	Composition/ Characteristics	Application Information, Methods and Rates[2]
Arrow 2 EC MANA (Makhteshim Agan of North America) EPA Reg. No. 66222-60	26.4% a.i. on label and MSDS. 73.6% inerts [1] 2 lbs a.i./gallon Density: 0.967 g/mL at 20°C pH: 4.44	Control of grasses in tree farms, conifer nurseries, and conifer plantations but not in forests. Also labeled for applications to rights-of-way, utility lines, fence lines, and several other non-crop sites. Application rates: 6-16 oz/acre [≈0.094-0.25 lb a.i./acre] for applications to conifers. Maximum Seasonal Rate: 0.5 lb a.i./acre/season. Minimum Application Interval: 14-days (crops). Adjuvants for conifers: COC containing a minimum of 15% emulsifiers at 1% v/v (but not less than 1 pt./acre). Application Volumes Ground Application: 5-40 gallons/acre. Aerial Application: 3-10 gallons/acre.
Clethodim 2E Albaugh, Inc. EPA Reg. No. 42750-72	26.4% a.i. on label, 25-27% on MSDS. 73.6% inerts [1] 2 lbs a.i./gallon Specific Gravity (approximate but varies by batch): 0.93-0.98 g/mL at 20 °C 7.8-8.2 lb/gal. pH: 4.3	Control of grasses in tree farms, conifer nurseries, and conifer plantations but not in forests. Also labeled for applications to rights-of-way, utility lines, fence lines, and several other non-crop sites. Application rates: 8-16 oz/acre [0.125-0.25 lb a.i./acre] for perennial grasses. Maximum Seasonal Rate: 0.5 lb a.i./acre/season. Minimum Application Interval: 14-days (crops). Adjuvants for conifers: COC containing a minimum of 80% oils and 15% emulsifiers. Application Volumes Ground Application: 5-40 gallons/acre. Aerial Application: 3-10 gallons/acre.

Formulation, Supplier, EPA Registration Number	Composition/ Characteristics	Application Information, Methods and Rates[2]
Clethodim 2EC Tacoma Ag, LLC EPA Reg. No. 83520-22	26.4% a.i. on label and MSDS 73.6% inerts [1] 2 lbs a.i./gallon Specific Gravity 0.961 g/mL pH: 4.0-4.5	Control of grasses in tree farms, conifer nurseries, and conifer plantations but not in forests. Also labeled for applications to rights-of-way, utility lines, fence lines, and several other non-crop sites. Adjuvants for conifers: COC with at least 15% emulsifier at 1% v/v but not less than 1 pint/acre. Application rates: 8-16 oz/acre [0.125-0.25 lb a.i./acre] for perennial grasses. Maximum Seasonal Rate: 0.5 lb a.i./acre/season. Minimum Application Interval: 14-days (crops). Application Volumes Ground Application: 5-40 gallons/acre. Aerial Application: 3-10 gallons/acre.
Dakota Rotam NA, Inc. EPA Reg. No. 9468-37-83979	26.4% a.i. on label 73.6% inerts [1] 2 lbs a.i./gallon Specific Gravity 0.93-0.98 g/mL at 20 °C 7.8-8.2 lb/gal. pH: 4.0-4.5	Control of grasses in tree farms, conifer nurseries, and conifer plantations but not in forests. Also labeled for applications to rights-of-way, utility lines, and fence lines. Adjuvants for conifers: COC with at least 15% emulsifier at 1% v/v but not less than 1 pint/acre. Application rates: 8-16 oz/acre [0.125-0.25 lb a.i./acre] for perennial grasses. Maximum Seasonal Rate: 0.5 lb a.i./acre/season. Minimum Application Interval: 14-days (crops). Application Volumes Ground Application: 5-40 gallons/acre. Aerial Application: 3-10 gallons/acre.
Envoy Valent Professional Products EPA Reg. No. 59639-78	12.6% a.i. on label, 12-13% on MSDS 0.94 lbs./gallon Density: 0.93 g/ml @ 20° C (7.76 lb/gal) pH: 4–5 as 1% emulsion in distilled water	Control of grasses in tree farms, conifer nurseries, and conifer plantations but not in forests. Also labeled for applications to rights-of-way, utility lines, and fence lines. Adjuvants for conifers: COC with at least 15% emulsifiers at 1% v/v but not less than 1 pt./acre. Application rates: 13-34 oz/acre [≈0.095-≈0.25 lb a.i./acre] Maximum Seasonal Rate: 0.5 lb a.i./acre/season. Minimum Application Interval: Not specified. Application Volumes Ground Application: 5-40 gallons/acre. Aerial Application: 3-10 gallons/acre.

Formulation, Supplier, EPA Registration Number	Composition/ Characteristics	Application Information, Methods and Rates[2]
Envoy Plus Valent Professional Products EPA Reg. No. 59639-132	12.6% a.i. on label, 12-14% on MSDS 0.97 lbs. a.i./gallon Density: 0.921 g/mL (7.69 lbs/gal.) at 20°C pH: 4.5 @ 25°C (1% emulsion)	Control of grasses in tree farms, conifer nurseries, and conifer plantations but not in forests. Also labeled for applications to rights-of-way, utility lines, and fence lines. Adjuvants for conifers: NIS at 0.25% v/v or COC/MSO at 1 qt/acre or 1% v/v. Application rates: Application rates: 12-32 oz/acre [≈0.091-≈0.24 lb a.i./acre] for perennial grasses. Maximum Seasonal Rate: 0.5 lb a.i./acre/season. Minimum Application Interval: 14 days (non-crop). Application Volumes Ground Application: 5-40 gallons/acre. Aerial Application: 3-10 gallons/acre.
Intensity Loveland Products EPA Reg. No. 34704-864	26.4% a.i. on label 73.6% inerts [1] 2 lbs a.i./gallon Specific Gravity 0.961 g/mL pH: 3.6 (5% emulsion)	Control of grasses in tree farms, conifer nurseries, and conifer plantations but not in forests. Also labeled for applications to rights-of-way, utility lines, and fence lines. Adjuvants for conifers: COC with at least 15% emulsifier at 1% v/v but not less than 1 pint/acre. Application rates: 8-16 oz/acre [0.125-0.25 lb a.i./acre] for perennial grasses. Maximum Seasonal Rate: 0.5 lb a.i./acre/season. Minimum Application Interval: 14 days (crops). Application Volumes Ground Application: 5-40 gallons/acre. Aerial Application: 3-10 gallons/acre.
Intensity One Loveland Products EPA Reg. No. 34704-976	12.6% a.i. on label and MSDS 87.4% inerts [1] 0.97 lbs. a.i./gallon Specific Gravity 0.941 g/mL pH: 4-5 (1% emulsion)	Control of grasses in tree farms, conifer nurseries, and conifer plantations but not in forests. Also labeled for applications to rights-of-way, utility lines, and fence lines. Application rates: 8-32 oz/acre [≈0.061-≈0.24 lb a.i./acre] for perennial grasses. Maximum Seasonal Rate: 0.5 lb a.i./acre/season (includes conifers). Minimum Application Interval: 14 days (crops). Adjuvants for conifers: NIS at 0.25% v/v or COC/MSO at 1 qt./acre or 1% v/v. Application Volumes Ground Application: 5-40 gallons/acre. Aerial Application: 3-10 gallons/acre.

Formulation, Supplier, EPA Registration Number	Composition/ Characteristics	Application Information, Methods and Rates[2]
Section 2EC Winfield Solutions EPA Reg. No. 1381-204	26.4% a.i. on product label, 25-27% a.i. on MSDS. 73.6% inerts [1] 2 lbs a.i./gallon Specific Gravity 0.97 g/mL pH: 4.1 (5% emulsion)	Control of grasses in tree farms, conifer nurseries, and conifer plantations but not in forests. Also labeled for applications to rights-of-way, utility lines, and fence lines. Application rates: 6-16 oz/acre [≈0.094-≈0.25 lb a.i./acre] for perennial grasses. Maximum Seasonal Rate: 0.5 lb a.i./acre/season. Minimum Application Interval: 14 days (crops). Adjuvants for conifers: COC with at least 15% emulsifier at 1% v/v but not less than 1 pt/acre. Application Volumes Ground Application: 5-40 gallons/acre. Aerial Application: 3-10 gallons/acre.
Select 2 EC Valent EPA Reg. No. 59639-3	26.4% a.i. on product label, 25-27% a.i. on MSDS [3]. 73.6% inerts [1] 2 lbs a.i./gallon Specific Gravity 0.95 g/mL @ 20°C pH: 3.6 (5% emulsion)	Not specifically labeled for applications to conifers or for other forestry uses. This formulation is included in this detail table because toxicity data on this formulation are available as discussed in Section 3 (Human Health) and Section 4 (Ecological Risk).
Shadow Arysta LifeScinece NA EPA Reg. No. 66330-353	26.4% on label and MSDS 2 lbs. a.i./gallon Specific Gravity 0.96 g/mL 8.0 lbs./gal. pH: 4.6 (1% emulsion)	Control of grasses in tree farms, conifer nurseries, and conifer plantations but not in forests. Also labeled for applications to rights-of-way, utility lines, and fence lines. Application rates: 6-16 oz/acre [≈0.094-≈0.25 lb a.i./acre] for perennial grasses. Maximum Seasonal Rate: 0.5 lb a.i./acre/season. Minimum Application Interval: 14 days (crops). Adjuvants for conifers: COC with at least 15% emulsifier at 1% v/v but not less than 1 pt/acre. Application Volumes Ground Application: 10-20 gallons/acre. Aerial Application: 3-15 gallons/acre.

Formulation, Supplier, EPA Registration Number	Composition/ Characteristics	Application Information, Methods and Rates[2]
Tapout Helena Holding Company 5905-578	12.6% on product label and MSDS. 87.4% inerts 0.97 lb a.i./gallon Specific Gravity 0.915-0.935 g/mL pH: N.S.	Control of grasses in tree farms, conifer nurseries, and conifer plantations but not in forests. Also labeled for applications to rights-of-way, utility lines, and fence lines. Application rates: 9-32 oz/acre [≈0.068-0.24 lb a.i./acre] for perennial grasses. Maximum Seasonal Rate: 0.5 lb a.i./acre/season. Minimum Application Interval: 14 days (crops and trees). Adjuvants for conifers: NIS at 0.25% v/v or COC/MSO at 1 qt./acre or 1% v/v. Application Volumes Ground Application: 5-40 gallons/acre. Aerial Application: 3-10 gallons/acre.

[1] The % inerts is taken from product label. See Table 5 for additional details on inerts from MSDSs.
[2] Unless otherwise noted, application rates are for the control of grasses on conifers.
[3] MSDS taken from http://www.msdsonline.com/.
KEY: NA = North America; COC=crop oil concentrate; MSO=methylated seed oil; NIS = nonionic surfactant.

Note: Individuals involved in field applications must consult the relevant product label for details. More specific directions for or limitations on applications may exist in some specific locations. Summaries in this table are limited to forestry and other relevant nonagricultural applications.

See Section 2 for discussion.

Table 5: Disclosed Inerts in Clethodim Formulations

Sources: Material Safety Data Sheets from www.greenbook.net.

Formulation (Supplier, EPA Reg. No.) [1]	Inert[2]	CAS No.	% w/w from MSDS
Arrow 2 EC (MANA, 66222-60)	Heavy aromatic petroleum	64742-94-5	22.1%
	*Naphthalene	91-20-3	2.2%
Clethodim 2E (Albaugh, 42750-72)	Petroleum distillates	99129-21-2	25-27%
	*Trimethylbenzene	N.S.	2-3%
	*Naphthalene	91-20-3	5-7%
Clethodim 2EC (Tacamo, 83520-22)	Solvent Naphtha, heavy aromatic	64742-94-5	58-62%%
	Naphthalene	91-20-3	<6%
Dakota (Rotam, 9468-37-83979)	Solvent Naphtha, heavy aromatic	64742-94-5	58-62%%
	Naphthalene	91-20-3	<6%
	1,2,4-trimethylbenzene	95-63-6	<1%
Envoy (Valent, 59639-78)	Total hydrocarbons	64742-94-5	70-80%
	*Naphthalene	91-20-3	5-9%
	Other	N.S.	1-15%%
Envoy Plus (Valent, 59639-132)	Total hydrocarbons	64742-94-5	45-48%
	*Naphthalene	91-20-3	<5%
	Other	N.S.	39-42%%
Intensity (Loveland, 34704-864)	Xylene range aromatic solvent	64742-94-5	73.6% total inerts
	*Naphthalene	91-20-3	
Intensity One (Loveland, 34704-976)	Xylene range aromatic solvent	64742-94-5	87.4% total inerts
	*Naphthalene	91-20-3	
Section 2EC (WinField, 1381-204)	Not specified on MSDS. Label indicates petroleum distillates		73-75%
Select 2 EC (Valent, 59639-3)	Total Hydrocarbons	64742-94-5	65-71%
	*Naphthalene	91-20-3	5-7%
	*Trimethylbenzene	N.S.	2-3%
	Other	N.S.	1-10%
Shadow (Arysta, 66330-353)	Aromatic hydrocarbons	64742-94-5	61%
	*Naphthalene	91-20-3	5-7%
Tapout (Helena, 5905-578)	Surfactants and methylated soybean oil.[3]	N.S.	87.4%

[1] See Table 4 for details.
[2] Chemical names as indicated on MSDS.
[3] The product label for Tapout indicates that the formulation contains petroleum distillates.
* An asterisk in an indented line indicates that the inert is part of the previous non-indented inert.

See Section 2.2 for initial discussion.

Table 6: Toxicity Data on formulations from MSDSs

Formulation	% a.i.	Oral LD_{50}	Dermal LD_{50}	Inhalation LC_{50}	Skin Irritation	Eye Irritation	Skin Sens.
Arrow 2EC	26.4	2,000 – 5,000	>5,000	2.09	Moderate	Moderate	No
Clethodim 2E	26.4	5,000 (F)	>5,000	>2.0	Moderate	Moderate	No
Clethodim 2EC	26.4	>5,000	>5,000	>2.0	Moderate	Moderate	No
Dakota	26.4	>5,000	>5,000	>2.0	Moderate	Moderate	No
Envoy	12.6	4,800 (F) >5,000 (M) [III]	>5,000 [IV]	>5.4 [2] [IV]	II	II	May be
Envoy Plus	12.6	>5,000 [IV]	>5,000 [IV]	>2.11 [IV]	II	III	Yes
Intensity	26.4	N/A	N/A	N/A	Minimal	Signif-icant	No
Intensity One	12.6	>5,000 (F)	>5,000	>2.11	Moderate	Moderate	Yes
Section 2EC	26.4	N/A	N/A	N/A	N/A	N/A	N/A
Select 2 EC	26.4	Slight	Minimal	Irritation	Yes	Yes	May
Shadow	26.4	1,630	>5,000	>3.9	Moderate	Moderate	No
Tapout	26.4	Minimal	Minimal	Minimal	Mild	Mild	N.S.

[1] Toxicity values specified on MSDS for formulation in units of mg/kg for oral and dermal and mg/L for inhalation. EPA Toxicity Categories given in brackets [] following the LD_{50}s and LC_{50}.

[2] No product specific toxicology data available. The 4-hour LC_{50} in rats for a similar formulation Select 2 EC Herbicide was greater than 5.4 mg/l. (Toxicity Category IV). This product is also expected to be a respiratory irritant.

See Section 2.3 for initial discussion.
This table is also discussed in several parts of
Section 3.1 (Hazard Identification for human health)

Table 7: Target Species for Clethodim Identified by the Forest Service

Scientific Name	Common Name(s)	Forest Service Region(s)
Bromus tectorum	Cheat grass	R5
Bromus diandrus	Ripgut brome	R5
Bromus madritensis	Compact brome	R5
Bromus rubens	Red brome	R5
Vulpia myuros	Rat's tail fescue	R5
Schismus barbatus	Mediterranean grass	R5
Bromus hoardeaceus	Soft brome	R5
Bromus subvelutinus	Hoary brome	R5
Poa bulbosa	Bulbous bluegrass	R5
Hordeum murinum	Wall barley/ False barley	R5
Piptatherum milaceum	Smilo grass	R5
Taeniatherum canput-medusae	Medusahead rye	R5

See Section 2.3 for discussion.

Table 8: Dermal Absorption of Clethodim by Male Rats

Experimental Data (proportion absorbed)

Time (hours)	0.05 mg Dose Group	0.5 mg Dose Group	5 mg Dose Group
2	0.085	0.044	0.02
10	0.284	0.144	0.067
24	0.428	0.341	0.297

Analysis of First-order dermal absorption coefficient (k_a in $hours^{-1}$)

Dose Group (mg/rat)	Central Estimate	Lower 95% bound	Upper 95% bound	*p*-value for k_a
0.05	0.025	0.013	0.037	0.011
0.5	0.017	0.015	0.019	0.0010
5.0	0.014	0.005	0.022	0.020

Source: MRID 410302-02 summarized in U.S. EPA/OPP/HED (1990, p. 15)
See Section 3.1.3.2.1 for discussion.

Table 9: Excretion of clethodim by rats

Sex	Dose (mg/kg bw)	Hour	% Urine	% Feces	Proportion Remaining
Females	450	24	53.1	3.2	0.437
		48	88.4	7.7	0.039
		168	93.1	9.4	-0.025
	4.5[1]	24	83.9	8.5	0.076
		48	83.9	10.7	0.054
	4.5[2]	24	79.8	13.9	0.063
		48	85.5	16.3	-0.018
Males	450	24	59.3	4.9	0.358
		48	83.6	10.8	0.056
		168	87.9	13.1	-0.01
	4.5[1]	24	86.2	10.9	0.029
		48	91.9	14.5	-0.064
	4.5[2]	24	82.9	11.9	0.052
		48	88.8	15.2	-0.04

[1] Single dose
[2] Multiple doses

Source: Rose and Griffis 1988, Table 3
See Section 3.1.3.3 for discussion.

Table 10: Worker Exposure Rates

Absorbed Dose Rates (mg/kg bw/day per lb applied)

Worker Group	Central Estimate	Lower C.I.	Upper C.I.	Lower P.I.	Upper P.I.
Directed foliar	0.08	0.02	0.06	0.1	0.5
Broadcast foliar	0.0001	0.00004	0.0002	0.000002	0.005
Aerial	0.00002	0.000006	0.00007	0.0000005	0.0008

CI: Confidence Interval.
PI: Prediction Interval.

Treatment Rates: Acres Treated per Day

Worker Group	Central	Lower	Upper
Directed foliar	4.4	1.5	8.0
Broadcast foliar	112	66	168
Aerial	490	240	800

Source: SERA (2013).
See Section 3.2.2.1 for discussion.

Table 11: 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.

Table 12: Input Parameters for Fields and Waterbodies Used in Gleams-Driver Modeling

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

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

Application, Field, and Soil Specific Factors [1]	Code[3]	Clay	Loam	Sand
Percent clay (w/w/):	CLAY	50%	20%	5%
Percent silt (w/w/):	SILT	30%	35%	5%
Percent sand (w/w/):	SAND	20%	45%	90%
Percent Organic Matter:	OM	3.7%	2.9%	1.2%
Bulk density of soil (g/cc):	BD	1.4	1.6	1.6
Soil porosity (cc/cc):	POR	0.47	0.4	0.4
Soil erodibility factor (tons/acre):	KSOIL	0.24	0.3	0.02
SCS Runoff Curve Number [2]:	CN2	82	70	59
Evaporation constant (mm/d):	CONA	3.5	4.5	3.3
Saturated conductivity below root zone (in/hr):	RC	0.087	0.212	0.387
Saturated conductivity in root zone (in/hr)	SATK	0.087	0.212	0.387
Wilting point (cm/cm):	BR15	0.28	0.11	0.03
Field capacity (cm/cm):	FC	0.39	0.26	0.16

[1] The qualitative descriptors are those used in the QuickRun window of Gleams-Driver. Detailed input values for the soil types are given in the sub-table below which is adapted from SERA (2007b, Tables 2 and 3). All fields are run for about 6 months before the pesticide is applied in early summer.

[2] From Knisel and Davis (Table H-4), *Clay*: Group D, Dirt, upper bound; *Loam*: Group C, woods, fair condition, central estimate; *Sand*: Group A, meadow, good condition, central estimate.

[3]Codes used in documentation for GLEAMS (Knisel and Davis 2000) and Gleams-Driver (SERA 2007a)

Table 13: Chemical parameters used in Gleams-Driver modeling

Parameter	Values	Note/Reference
Halftimes (days)		
Aquatic Sediment	1217-3650 days	Note 1
Foliar	5.75 (5.4-6.1) days	Note 2
Soil	92 (86.4-132) days	Note 3
Water	184 (172.8-264) days	Note 4
Soil $K_{o/c}$, mL/g	44 (5–270)	Note 5
Sediment K_d, mL/g	Clay: 0.11 – 5.67 Loam: 0.085 – 4.6 Sand: 0.035 – 1.86	Note 6
Water Solubility, mg/L	29 mg/L	Note 7
Foliar wash-off fraction	0.7	Note 8
Fraction applied to foliage	0.5	Standard assumption
Depth of Soil Incorporation	1 cm	Standard assumption
Irrigation after application	none	
Initial Application Date	March 15	U.S. EPA/OPP/EFED 2014a

Notes

Number	Text
1	Lower bound based on single available anaerobic aquatic metabolism study for all residues of concern (MRID 416523-01, Table 7, p. 24, U.S. EPA/OPP/EFED 2014a). The upper bound is based on 3x of this value and used as modeling input by U.S. EPA/OPP/EFED (2014a, Table 8, p. 25).
2	The method of Juraske et al. (2008) dividing the soil half-lives of 92 (86.4-97.6) days for total toxic residues by 16. These estimates are close to the foliar half-life of 3 days for sethoxydim given by Knisel and Davis (2000).
3	Central estimate and lower bound based on half-lives for total toxic residues taken from U.S. EPA/OPP/EFED 2009a, p. 4. (MRIDs 409745-21 and MRID 413768-01). Upper bound based on 90th percentile for total residues in two soils from U.S. EPA/OPP/EFED (2014a, Table 8, p. 25)
4	No experimental values. Central estimate and lower bound based on aerobic soil values x 2 (U.S. EPA/OPP/EFED 2009a, p. 4). Upper bound based on 2x soil metabolism input value from U.S. EPA/OPP/EFED (2014a, Table 8, p. 25).
5	Central estimated from U.S. EPA/OPP/EFED (2014a, MRID 409745-23) for clethodim sulfoxide. Upper and lower bounds based on range of values from U.S. EPA/OPP/EFED 2009a. In FIRST modeling (Tier 1), EPA used only the lowers bound.
6	The Kd values are taken as Koc x OM, where OM is the proportion of organic carbon in the soil. Based on the soils used in Gleams-Driver modeling (Table 12), the organic matter is 3.7% in clay, 2.9% in loam, and 1.2% in sand. Taking OC = OM/1.724 (Knisel and Davis 2000), the organic carbon is 2.1% in clay, 1.7% in loam, and 0.69% in sand.
7	As summarized in Table 2, a wide range of values have been reported. Value used is taken from most recent EPA risk assessment (U.S. EPA/OPP/EFED 2014a, MRID 488814-05). This is not a sensitive parameter for GLEAMS.
8	No information located for clethodim. The value of 0.7 is based on analogy to sethoxydim.

Table 14: Summary of Modeled Concentrations in Surface Water

Scenario/Source	Peak Concentrations (ppb or µg/L per lb/acre)	Long-Term Average Concentrations (ppb or µg/L per lb/acre)
Direct Spray and Spray Drift (coarse droplets)		
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]	0.9 to 16	N/A
Stream, Direct Spray (Section 3.2.3.4.2) [a]	91.4	N/A
Stream, drift at 25 feet (Section 3.2.3.4.2) [a]	0.8-13	N/A
Pond Concentration due to Wind Erosion	1.39 (0.069-34.7)	N/A
Single Application (Appendix 8)		
Pond, Section 3.2.3.4.4	43.5 (0 - 650)	21.6 (0 - 420)
Stream, Section 3.2.3.4.4	13.4 (0 - 132)	0.85 (0 - 6.1)
Two Applications with 14-day Interval (Appendix 9)		
Pond, Section 3.2.3.4.4	86.8 (0.0-1,160)	41.8 (0.0-790)
Stream, Section 3.2.3.4.4	25.9 (0.0-270)	1.63 (0.0-13)
Four Applications with 14-day Intervals (Appendix 10)		
Pond, Section 3.2.3.4.4	172 (0 - 2210)	86.4 (0 - 1440)
Stream, Section 3.2.3.4.4	46.6 (0 - 440)	3.38 (0 - 24.4)
18 Applications with 14-day Intervals (Appendix 10)		
Pond, Section 3.2.3.4.4	619 (0 - 8270)	138 (0 - 1500)
Stream, Section 3.2.3.4.4	292 (0 - 5370)	12.6 (0 - 97)
EPA Tier 1 Models		
GENEEC	No modeling located	No modeling located
FIRST (Reservoir model), 2 applications [b]	155.8	30.5
FIRST (Reservoir model), 2 applications [c]	149.2	52
SCIGROW (Ground water), 2 applications [d]	5.56	Not modeled
SCIGROW (Ground water), 2 applications [e]	39.2	Not modeled
PRZM-GW (Ground water), 18 applications [f]	635.6	511.1
EPA PRZM Tier 2[h]		
Mississippi cotton, 2 applications	26	24 (60 day mean)
North Carolina Peanut, 2 applications	16	16 (60 day mean)

[a] Section 3.2.3.4.2 discusses expected concentrations in terms of the nominal application rate of 1 lb a.i./acre. The values for direct spray and drift are taken from Worksheet B04c2 (direct spray and drift as 25 feet for a pond suing coarse droplets) and Worksheet B04d2 (direct spray and drift at 25 feet for a stream) adjusted to WRC values based on the application rate of 0.25 lbs/acre.

[b] Taken from U.S. EPA/OPP/EFED (2006a, p. 2) and normalized for application rate of 0.25 lb/acre – i.e., peak 38.953 µg/L ÷ 0.25 lb a.i./acre = 155.8 µg/L per lb/acre; annual average 7.631 µg/L ÷ 0.25 lb/acre = 30.524 µg/L per lb/acre .

[c] Taken from U.S. EPA/OPP/EFED (2009a, p. 2) and normalized for application rate of 0.25 lb/acre – i.e., peak 37.3 µg/L ÷ 0.25 lb a.i./acre = 149.2 µg/L per lb/acre; annual average13 µg/L ÷ 0.25 lb a.i./acre = 52 µg/L per lb/acre.

[d] Taken from U.S. EPA/OPP/EFED (2006a, p. 8) and normalized for application rate of 0.25 lb/acre – i.e., peak 1.39 µg/L ÷ 0.25 lb a.i./acre = 5.56 µg/L per lb/acre.

[e] Taken from U.S. EPA/OPP/EFED (2009a, p. 2) and normalized for application rate of 0.25 lb/acre – i.e., peak 9.8 µg/L ÷ 0.25 lb a.i./acre = 39.2 µg/L.

[f] Taken from U.S. EPA/OPP/EFED (2013a, p. 2). The EPA modeling is based on 18 applications at 0.25 lb a.i./acre. Normalized for 2 applications at 0.25 lb a.i./acre – i.e., peak (1,430 µg/L ÷ 0.25 lb a.i./acre) ÷ (18 ÷ 2) = 635.6 µg/L ; chronic (1,150 µg/L ÷ 0.25 lb a.i./acre) ÷ (18 ÷ 2) = 511.1 µg/L per lb/acre.

[h] Taken from U.S. EPA/OPP/EFED (2014, Tables 9 and 10). Includes only runs based on 2 applications at 0.25 lb a.i./acre with a 7 day application interval.

Table 15: Concentrations in surface water used in this risk assessment

Foliar Broadcast, one application	**Peak WCR[1]**	**Longer-term WCR[1]**
Central	0.044 Pond central	0.022 Pond central
Lower	0.00044 Central ÷ 100	0.00022 Central ÷ 100
Upper	0.65 Pond upper	0.42 Pond upper
Foliar Broadcast, two applications	**Peak WCR[1]**	**Longer-term WCR[1]**
Central	0.087 Pond central	0.042 Pond central
Lower	0.00087 Central ÷ 100	0.00042 Central ÷ 100
Upper	1.2 Pond upper	0.79 Pond upper
Foliar Broadcast, four applications	**Peak WCR[1]**	**Longer-term WCR[1]**
Central	0.17 Pond central	0.086 Pond central
Lower	0.0017 Central ÷ 100	0.00086 Central ÷ 100
Upper	2.2 Pond upper	1.4 Pond upper

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

See Section 3.2.3.4.6 for discussion

Table 16: Estimated residues in food items per lb a.i. applied

Food Item	Central [a]	Lower [b]	Upper [a]
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

All concentration given in units of ppm (mg agent/kg food) per lb a.i./acre.

[a] U.S. EPA/EFED 2001, p. 44 as adopted from Fletcher et al. (1994).
[b] Central values × (Central Value ÷ Upper Value).

Table 17: Summary of toxicity values used in human health risk assessment

Acute – single exposure

Element	Derivation of RfD
EPA Document	U.S. EPA/OPP/ HED 2014a, p. 31
Study	MRID 487885-02 (2012) and MRID 481418-01 (2006)
NOAEL Dose	100 mg/kg bw/day
LOAEL Dose	1000 mg/kg bw/day
LOAEL Endpoint(s)	Decreased spontaneous activity, ruffled fur, head tilt, and hunched posture
Species, sex	Rats
Uncertainty Factor/MOE	100
Acute RfD	1 mg/kg bw/day

Note: The EPA risk assessments use these values for short-term (1-30 days) dermal and inhalation exposures.

Chronic – lifetime exposure

Element	Derivation of RfD
EPA Document	U.S. EPA/OPP/ HED 2014a, p. 15, Table 4.3
Study	MRID 410301-12
NOAEL Dose	30 mg/kg bw/day
LOAEL Dose	150 mg/kg bw/day
LOAEL Endpoint(s)	Mice
Species, sex	*…reduced survival, decreased red cell mass and increased incidences of bile duct hyperplasia, of pigmentation of the liver and of foci of amphophilic macrophages in the lung* (U.S. EPA/OPP 2014a, p. 31)
Uncertainty Factor/MOE	100
Chronic RfD	0.3 mg/kg bw/day

Occupational – 1 to 6 month exposure periods

Element	Derivation of RfD
EPA Document	U.S. EPA/OPP/ HED 2010a, p. 16
Study	MRID 410301-06
NOAEL Dose	75 mg/kg bw/day
LOAEL Dose	125 mg/kg bw/day
LOAEL Endpoint(s)	Increased liver weights with pathology.
Species, sex	Dog
Uncertainty Factor/MOE	100
Equivalent RfD	0.75 mg/kg bw/day

This NOAEL with an MOE of 100 is use by U.S. EPA/OPP/HED (2010a, pp. 16-17) for intermediate (1-6 months) dermal and inhalation exposures.

Table 18: Risk Characterization for Workers

Hazard Quotients for Accidental/Incidental Exposures

Scenario	Central	Lower CI	Upper CI
Contaminated Gloves, 1 min.	1E-02	1E-03	7E-02
Contaminated Gloves, 1 hour	0.6	7E-02	**4**
Spill on Hands, 1 hour	5E-03	1E-03	2E-02
Spill on lower legs, 1 hour	1E-02	3E-03	4E-02

Hazard Quotients for General Exposures

Receptor	Central	Lower PI	Lower CI	Upper CI	Upper PI
Backpack Applications:	0.1	1E-02	3E-02	0.3	**1.3**
Ground Broadcast Applications:	4E-03	4E-05	9E-04	1E-02	0.3
Aerial Applications:	3E-03	4E-05	5E-04	2E-02	0.2

PI=Prediction Interval; CI=Confidence Interval.

Source: Worksheet E02 in Attachment 1 and Attachment 2.
See Section 3.4.2 for discussion.

Table 19: Risk Characterization for the General Public – One Application

HQs for Accidental Acute Exposures

Scenario	Receptor	Central	Lower	Upper
Direct Spray of Child, whole body	Child	0.2	4E-02	0.7
Direct Spray of Woman, feet and lower legs	Adult Female	2E-02	4E-03	7E-02
Water consumption (spill)	Child	9E-02	3E-03	0.9
Fish consumption (spill)	Adult Male	2E-03	9E-05	1E-02
Fish consumption (spill)	Subsistence Populations	9E-03	4E-04	6E-02

HQs for Non-Accidental Acute Exposures

Scenario	Receptor	Central	Lower	Upper
Vegetation Contact, shorts and T-shirt	Adult Female	8E-03	7E-03	9E-03
Contaminated Fruit	Adult Female	3E-03	1E-03	5E-02
Contaminated Vegetation	Adult Female	4E-02	3E-03	0.3
Swimming, one hour	Adult Female	3E-05	8E-09	1E-03
Water consumption	Child	5E-04	2E-07	1E-02
Fish consumption	Adult Male	1E-05	6E-09	2E-04
Fish consumption	Subsistence Populations	5E-05	3E-08	1E-03

HQs for Chronic/Longer Term Exposures

Scenario	Receptor	Central	Lower	Upper
Contaminated Fruit	Adult Female	9E-04	4E-04	2E-02
Contaminated Vegetation	Adult Female	1E-02	8E-04	0.1
Water consumption	Adult Male	3E-04	8E-08	9E-03
Fish consumption	Adult Male	3E-06	1E-09	8E-05
Fish consumption	Subsistence Populations	2E-05	1E-08	6E-04

Source: Attachment 1, Worksheet E04.
See Section 3.4.3 for discussion.

Table 20: Risk Characterization for the General Public – Two Applications

HQs for Accidental Acute Exposures

Scenario	Receptor	Central	Lower	Upper
Direct Spray of Child, whole body	Child	0.2	4E-02	0.7
Direct Spray of Woman, feet and lower legs	Adult Female	2E-02	4E-03	7E-02
Water consumption (spill)	Child	9E-02	3E-03	0.9
Fish consumption (spill)	Adult Male	2E-03	9E-05	1E-02
Fish consumption (spill)	Subsistence Populations	9E-03	4E-04	6E-02

HQs for Non-Accidental Acute Exposures

Scenario	Receptor	Central	Lower	Upper
Vegetation Contact, shorts and T-shirt	Adult Female	8E-03	7E-03	9E-03
Contaminated Fruit	Adult Female	3E-03	2E-03	6E-02
Contaminated Vegetation	Adult Female	5E-02	3E-03	0.4
Swimming, one hour	Adult Female	6E-05	2E-08	3E-03
Water consumption	Child	1E-03	3E-07	3E-02
Fish consumption	Adult Male	2E-05	1E-08	4E-04
Fish consumption	Subsistence Populations	1E-04	6E-08	2E-03

HQs for Chronic/Longer Term Exposures

Scenario	Receptor	Central	Lower	Upper
Contaminated Fruit	Adult Female	2E-03	8E-04	3E-02
Contaminated Vegetation	Adult Female	2E-02	2E-03	0.2
Water consumption	Adult Male	5E-04	2E-07	2E-02
Fish consumption	Adult Male	6E-06	3E-09	1E-04
Fish consumption	Subsistence Populations	4E-05	2E-08	1E-03

Source: Attachment 2, Worksheet E04.
See Section 3.4.3 for discussion.

Table 21: Comparison of Toxicity Values in Mammals

Subchronic Toxicity Values

Species	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Duration (Days)	Reference
Mice	600 (28 d)	N/A	28	MRID 410301-03
Rats	≈145 (90 d)	≈180	90	MRID 410301-07
Rabbits	100 (12 d)	300	12	MRID 410301-15
Dogs	75 (90 d)	125	90	MRID 410301-06

Chronic Toxicity Values

Species	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Duration (Months)	Reference
Mice	30	150	18	MRID 410301-12
Rats	21	113	24	MRID 410301-21
Dogs	75	150	12	MRID 410301-11

See Appendix 1, Tables A1-2 and A1-3 for details.
See Section 4.1.2.1 for discussion.

Table 22: Terrestrial Nontarget Animals Used in Ecological Risk Assessment

MAMMALS [1]

Animal	Representative Species	W[4]	Food Consumption[5]	Water Consumption
Small mammal	Mice	20	$2.514\ W^{0.507}$ [Eq 3-48]	$0.099\ W^{0.9}$ [Eq 3-17]
Larger mammal	Squirrels	400	$2.514\ W^{0.507}$ [Eq 3-48]	$0.099\ W^{0.9}$ [Eq 3-17]
Canid	Fox	5,000	$0.6167\ W^{0.862}$ [Eq 3-47]	$0.099\ W^{0.9}$ [Eq 3-17]
Large Herbivorous Mammal	Deer	70,000	$1.518\ W^{0.73}$ [Eq 3-46]	$0.099\ W^{0.9}$ [Eq 3-17]
Large Carnivorous Mammal	Bear	70,000	$0.6167\ W^{0.862}$ [Eq 3-47]	$0.099\ W^{0.9}$ [Eq 3-17]

BIRDS [2]

Animal	Representative Species	W[4]	Food Consumption[5]	Water Consumption
Small bird	Passerines	10	$2.123\ W^{0.749}$ [Eq 3-36]	$0.059\ W^{0.67}$ [Eq 3-15]
Predatory bird	Owls	640	$1.146\ W^{0.749}$ [Eq 3-37]	$0.059\ W^{0.67}$ [Eq 3-15]
Piscivorous bird	Herons	2,400	$1.916\ W^{0.704}$ [Eq 3-38]	$0.059\ W^{0.67}$ [Eq 3-15]
Large herbivorous bird	Geese	4,000	$1.146\ W^{0.749}$ [Eq 3-37]	$0.059\ W^{0.67}$ [Eq 3-15]

INVERTEBRATES [3]

Animal	Representative Species	W[4]	Food Consumption[5]
Honey bee [7]	*Apis mellifera*	0.000116	≈2 (1.2 to 4)[6]
Herbivorous Insects	Various	Not used	1.3 (0.6 to 2.2)

[1] Sources: Reid 2006; U.S. EPA/ORD 1993.
[2] Sources: Sibley 2000; Dunning 1993; U.S. EPA/ORD 1993.
[3] Sources: Humphrey and Dykes 2008; Reichle et al. 1973; Winston 1987
[4] Body weight in grams.
[5] For vertebrates, based on allometric relationships estimating field metabolic rates in kcal/day for rodents (omnivores), herbivores, and non-herbivores. For mammals and birds, the estimates are based on Nagy (1987) as adapted by U.S. EPA/ORD (1993). The equation numbers refer to U.S. EPA/ORD (1993). See the following table for estimates of caloric content of food items. For herbivorous insects, consumption estimates are based on fractions of body weight (g food consumed/g bw) from the references in Note 3.
[6] For honeybees, food consumption based on activity and caloric requirements. Used only when estimates of concentrations in nectar and/or pollen can be made, which is not the case in the current risk assessment.
[7] A surface area of 1.42 cm2 is used for the direct spray scenario of the honey bee. This value is based on the algorithms suggested by Humphrey and Dykes (2008) for a bee with a body length of 1.44 cm.

See data on food commodities in following table.
See Sections 4.2.2 and 4.2.3.2 for discussion.

Table 23: Diets: Metabolizable Energy of Various Food Commodities

Food Item	Animal Group	Caloric Value [1] (kcal/g bw)	Water Content [2]	Comment/Source(s)
Fruit	Mammals	1.1	0.77	See Footnote 3
	Birds	1.1	0.77	See Footnote 4
Fish	Mammals	4.47	0.70	Water content from Ali et al. (2005).
	Birds	3.87	0.70	Water content from Ali et al. (2005).
Insects	Mammals	4.47	0.70	Water contents from Chapman 1998 (p. 491). Typical ranges of 60-80%.
	Birds	4.30	0.70	Water contents from Chapman 1998 (p. 491). Typical ranges of 60-80%.
Vegetation (NOS)	Mammals	2.26	0.85	See Footnote 5
	Birds	2.0	0.85	See Footnote 5

[1] Metabolizable energy. Unless otherwise specified, the values are taken from U.S. EPA/ORD (1993), Table 3-1, p. 3-5 as adopted from Nagy 1987.

[2] From U.S. EPA/ORD (1993), Table 4-2, p. 4-14 unless otherwise specified.

[3] Based on a gross caloric value of 2.2 kcal/g bw (U.S. EPA/ORD 1993, Table 4-2). An assimilation factor for mammals eating fruit not identified. Use estimate for birds (see below).

[4] Based on a gross caloric value of 2.2 kcal/g bw (U.S. EPA/ORD 1993, Table 4-2) and an assimilation factor for the consumption of fruit by birds of 51% [2.2 kcal/g bw x 0.51 ≈ 1.1 kcal/g bw]

[5] Based on a gross caloric value of 4.2 kcal/g bw for dicot leaves (U.S. EPA/ORD 1993, Table 4-2). For birds, the value is corrected by an assimilation factor for the consumption leaves by birds of 47% [4.2 kcal/g bw x 0.47 = 1.974 kcal/g bw]

See Sections 4.2.2.3 for discussion.

Table 24: Summary of toxicity values used in ecological risk assessment

Group/Duration	Organism	Endpoint	Toxicity Value (a.i.)	Reference
Terrestrial Animals				
Acute				
Mammals (including canids)		NOAEL, rats	100 mg/kg bw	Section 4.3.2.1.
Birds		Mallard dietary NOEL	950 mg/kg bw	Section 4.3.2.2
Honey Bee (oral)		No studies available.	N/A	Section 4.3.2.4.1
Honey Bee (contact)		NOAEL?	860 mg/kg bw	Section 4.3.2.4.2
Longer-term				
Mammals		NOAEL, mice	30 mg/kg bw/day	Section 4.3.2.1
Bird		Mallard NOEL.	20 mg/kg bw/day	Section 4.3.2.2.
Terrestrial Plants				
Soil	Sensitive	NOEL in most sensitive monocot	0.0004 lb/acre	Section 4.3.2.5.2
	Tolerant	NOEL in dicots and tolerant monocots	0.25 lb/acre	
Foliar	Sensitive	NOEL in most sensitive monocot from EPA	0.0023 lb/acre	Section 4.3.2.5.2
	Tolerant	NOEL in all dicots and tolerant monocot (corn)	0.25 lb/acre	
Aquatic Animals				
Acute				
Amphibians	Sensitive	No studies available.	N/A	Section 4.3.3.2
	Tolerant	No studies available.	N/A	
Fish	Sensitive	Trout, NOAEC	7.8 mg/L	Section 4.3.3.1
	Tolerant	Bluegill, NOEC	33 mg/L	
Invertebrates	Sensitive	*Daphnia magna*, NOAEC	1.4 mg/L	Section 4.3.3.3
	Tolerant	Mysid shrimp, NOAEC	12.4 mg/L	
Longer-term				
Amphibians	Sensitive	No studies available.	N/A	Section 4.3.3.2
	Tolerant	No studies available.	N/A	
Fish	Sensitive	ACR and Relative Acute Toxicity	0.1 mg/L	Section 4.3.3.1.2
	Tolerant	Acute to Chronic Ratio (ACR)	0.6 mg/L	
Invertebrates	Sensitive	*Daphnia magna*, NOEC	0.94 mg/L	Section 4.3.3.3
	Tolerant	No studies available.	N/A	
Aquatic Plants				
Algae	Sensitive	Diatom NOEC	3.1 mg/L	Section 4.3.3.4
	Tolerant	Green alga NOEC	11.1 mg/L	Section 4.3.3.4
Macrophytes	Sensitive	*Lemna* NOEC (monocot)	0.3 mg/L	Section 4.3.3.4
	Tolerant	No adequate studies available.	N/A	Section 4.3.3.4

Table 25: Acute to Chronic Ratios in Fish

Species/Number of Data Points	Data Source(s)	Acute-Chronic Ratios	Study
Mixed species of fish (n=39)	System Chemicals Safety database (German Federal Environ. Agency),all data	Median: 10.5 90th Percentile: 198.2 Maximum: 2,250	Ahlers et al. 2006
Fathead minnow early life stage (n=18)	As above	Median: 11.5 90th Percentile: 66.4 Maximum: 1,370	Ahlers et al. 2006
Mixed species of fish	Not explicitly discussed. Cites open literature. See Table 7 of paper.	Median: Default ACRs of 3.6 to 17.2 90th percentile: Default ACRs of 5.1 to 188.5	Hoff et al. 2010 [EPA white paper]
Fathead minnow (n=135 for all species) [2]	Open literature and some unpublished reports.	ACR / Cumulative Percent 1-9 / 36% 1-99 / 86% 1-999 / 96% 1-9,999 / 98% Above from Table 3, p. 351 of paper.	Kenaga 1982
Mixed species of fish (n=62) [3]	All substances, ECETOC Aquatic Toxicity (EAT) database [4]	Median: 9.48 90th Percentile: 72.9 Maximum: 1,290	Lange et al. 1998
Mixed species of fish (n=261) [5]	Various sources within U.S. EPA. Data limited to flow-through studies.	Median: 9.3 90th Percentile: 90.0 Maximum: 2,121	Raimondo et al. 2007
Mixed fish and invertebrates	Open literature, excluding some atypically high ACRs.	Average: 14.38 ±24.92 [6]	Roex et al. 2000

[1] Table 2 of publication provides additional analyses of other subsets of data. Clethodim does not contain structural groups identified in Table 5 of publication that may be associated with high acute to chronic ratios in fish.
[2] Full data set for all species included 135 ACRs for 84 chemicals in 9 species of fish and 2 species of aquatic invertebrates).
[3] Table 3 of publication provides additional analyses of other subsets of data.
[4] European Centre for Ecotoxicology and Toxicology of Chemicals (http://www.ecetoc.org/)
[5] Table 1 of Raimondo et al. (2007) provides additional analyses of other subsets of data. While not providing details, the paper notes no significant differences between species of fish including fathead minnows with the median ACR for fathead minnows of 9.6 (p. 2020 of paper).
[6] This is average over all classes of compounds. Analysis focused on deriving log/log transformed correlations of acute LC_{50} to longer-term LOAEC values. Not comparable to other analyses.

See Section 4.3.3.1.2.2. for discussion.

Table 26: QSAR Estimates of Toxicity from EPI Suite

EcoSAR Class	Group	Predicted (mg/L)	Experimental (mg/L)	Ratio of Experimental /Predicted Values	Average Ratio[1]	Adjusted Estimate of Fish Chronic Value (mg/L) [2]
Aliphatic Amines	*Daphnia*, 48-h EC_{50}	0.469	20.2	43.07	48.34	
	Daphnia chronic	0.026	1.68	64.62		
	Fish,96-h LC_{50}	2.946	110	37.34		
	Fish chronic	0.061	0.018	0.30		2.95
Vinyl/Allyl Ketones	*Daphnia*, 48-h EC_{50}	3.124	20.2	6.47	7.43	
	Daphnia chronic	0.64	1.68	2.63		
	Fish,96-h LC_{50}	8.327	110	13.21		
	Fish chronic	0.835	0.018	0.02		6.21
Vinyl/Allyl Halides	*Daphnia*, 48-h EC_{50}	0.917	20.2	22.03	45.33	
	Daphnia chronic	0.265	1.68	6.34		
	Fish,96-h LC_{50}	1.022	110	107.63		
	Fish chronic	0.13	0.018	0.14		5.89
Vinyl/Allyl Alcohols	*Daphnia*, 48-h EC_{50}	0.769	20.2	26.27	80.15	
	Daphnia chronic	0.009	1.68	186.67		
	Fish,96-h LC_{50}	3.998	110	27.51		
	Fish chronic	0.013	0.018	1.38		1.04
Neutral Organics	*Daphnia*, 48-h EC_{50}	2.801	20.2	7.21	13.74	
	Daphnia chronic	0.383	1.68	4.39		
	Fish,96-h LC_{50}	3.714	110	29.62		
	Fish chronic	0.383	0.018	0.05		5.26

[1] The average of the ratios includes on the *Daphnia* 48-h EC_{50}, the Daphnia chronic, and Fish 96-h LC_{50}. As discussed in Section 4.3.3.1.2.4, this average is used as an estimate of bias for the fish chronic value. Using Aliphatic Amines as an example the average ratio is calculated as (43.07 + 64.62 + 37.34)/3 = 48.3415 which is round to 48.34.

[2] Calculated as the Average Ratio (Column 5) multiplied by the estimate of the chronic value for fish (Column 4). Using Aliphatic Amines as an example, 0.061 mg/L x 48.34 = 2.94874 mg/L. This value is rounded to 2.95 mg/L as the Adjusted Estimate of Fish Chronic Value.

See Section 4.3.3.1.2.4 for discussion.
Data from EPI Suite 2013

Table 27: Summary of Weight of Evidence for Chronic NOAEC in Fish

Source	Estimated NOAEC (mg a.i./L)	Reference
Bidinotto 2003	0.01	Section 4.1.3.1.2.
Acute to Chronic Ratio Method, 90th percentile		Section 4.3.3.1.2.2.
Ahlers et al. 2006	1.7	
Hoff et al. 2010	0.58	
Daphnid chronic correlation (Maki 1979)	3.9	Section 4.3.3.1.2.3.
QSAR (EPI Suite 2014)		Section 4.3.3.1.2.4.
Vinyl/allyl ketones	6.2[1]	
Vinyl/allyl halides	5.9	
Neutral organics	5.3	
Aliphatic amines	3.0	
Vinyl/allyl alcohols	1.0	

[1] The QSAR estimate for vinyl/allyl ketones may be viewed as the best QSAR estimate because this estimate has lowest apparent bias for studies on daphnids (acute and chronic) and fathead minnows (acute). See Table 26 for details.

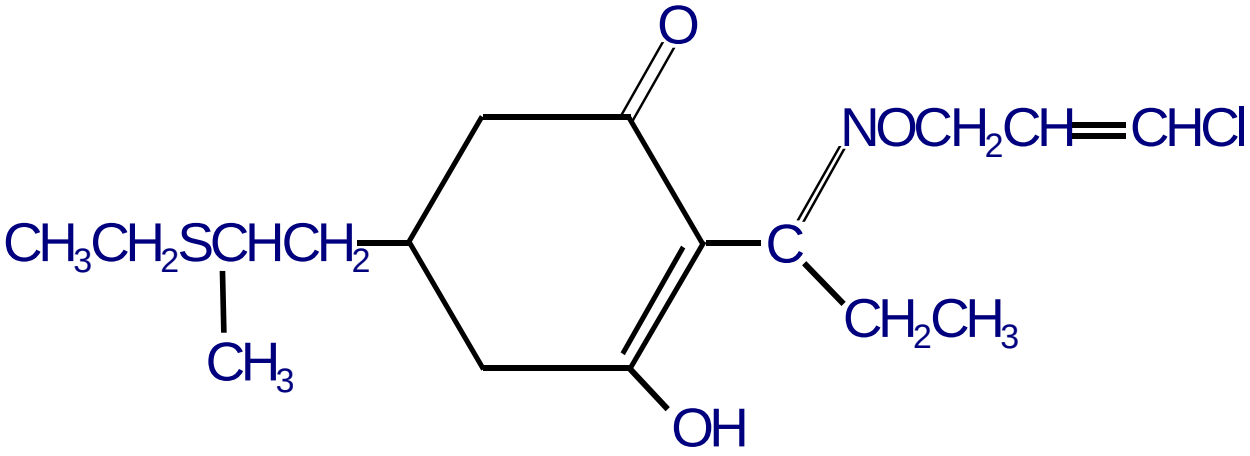
See Section 4.3.3.1.2.5 for discussion.

Table 28: Summary of Hazard Quotients for Longer-term Exposures of Fish

Number of Applications	Fish Group	Central Estimate of HQ	Lower Bound of HQ	Upper Bound of HQ
1	Sensitive	0.06	0.0006	**1.1**
	Tolerant	0.009	0.00009	0.2
2	Sensitive	0.1	0.001	**2.0**
	Tolerant	0.02	0.0002	0.3
4	Sensitive	0.2	0.002	**4**
	Tolerant	0.04	0.0004	0.6
18	Sensitive	0.7	0.007	**14**
	Tolerant	0.1	0.001	**2**

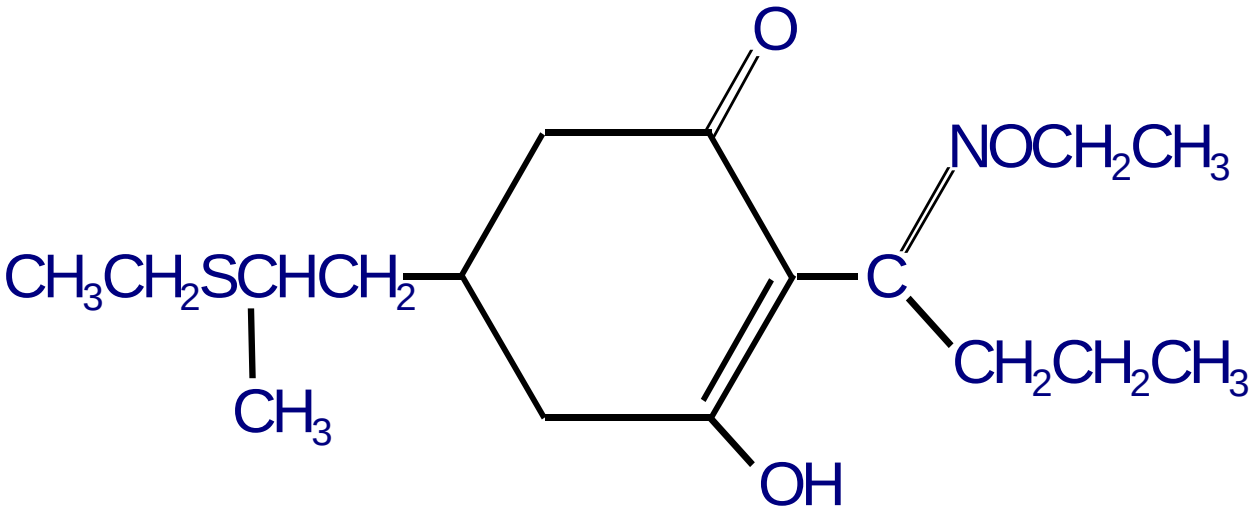
Data taken from Worksheet G03 in Attachment 1 (1 application),
Attachment 2 (2 applications),
Attachment 3 (4 applications),
and Attachment 4 (18 applications)

See Section 4.4.3.1.2 for discussion.



Clethodim

Systematic Name[1]: 2-Cyclohexen-1-one, 2-(1-(((3-chloro-2-propenyl)oxy)imino)propyl)-5-(2-(ethylthio)propyl)-3-hydroxy-



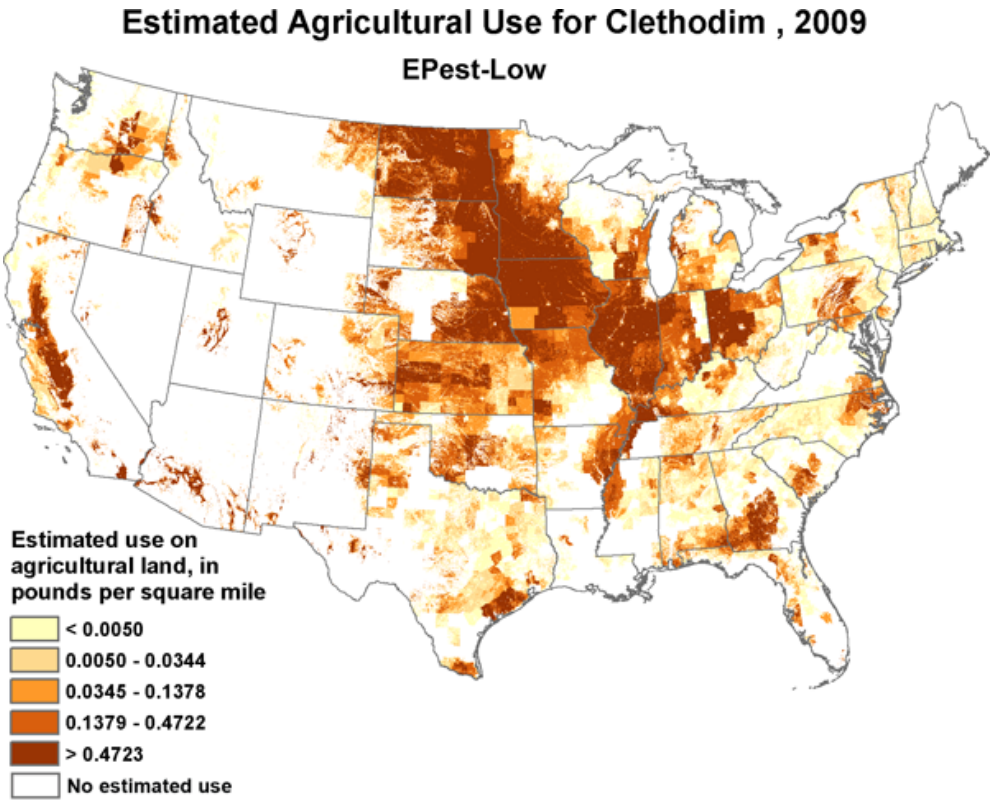
Sethoxydim

Systematic Name[1]: 2-Cyclohexen-1-one, 2-(1-(ethoxyimino)butyl)-5-(2-(ethylthio)propyl)-3-hydroxy-

[1] ChemIDplus (2013)

Figure 1: Structures of Clethodim and Sethoxydim

See Section 2.2 for discussion.



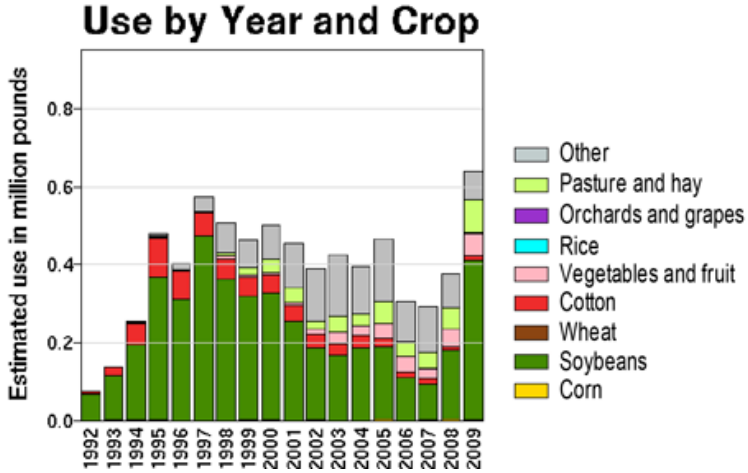
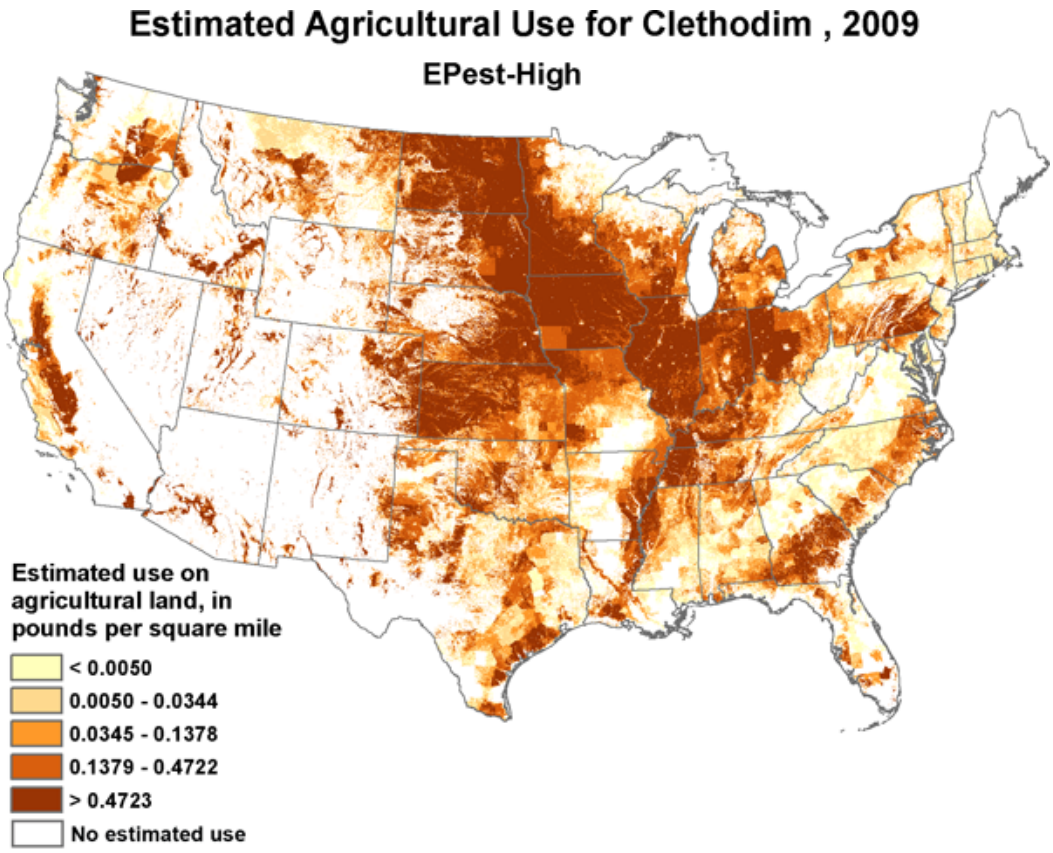


Figure 2: Lower Bound Estimated Agricultural Use in the United States for 2009

Source: USGS (2013)
See Section 2.5 for discussion.



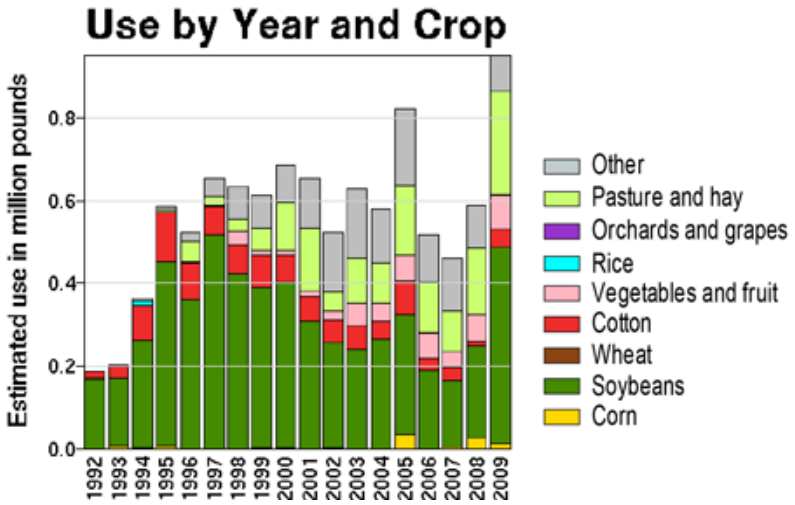


Figure 3: Upper Bound Estimated Agricultural Use in the United States for 2009

Source: USGS (2013)
See Section 2.5 for discussion.

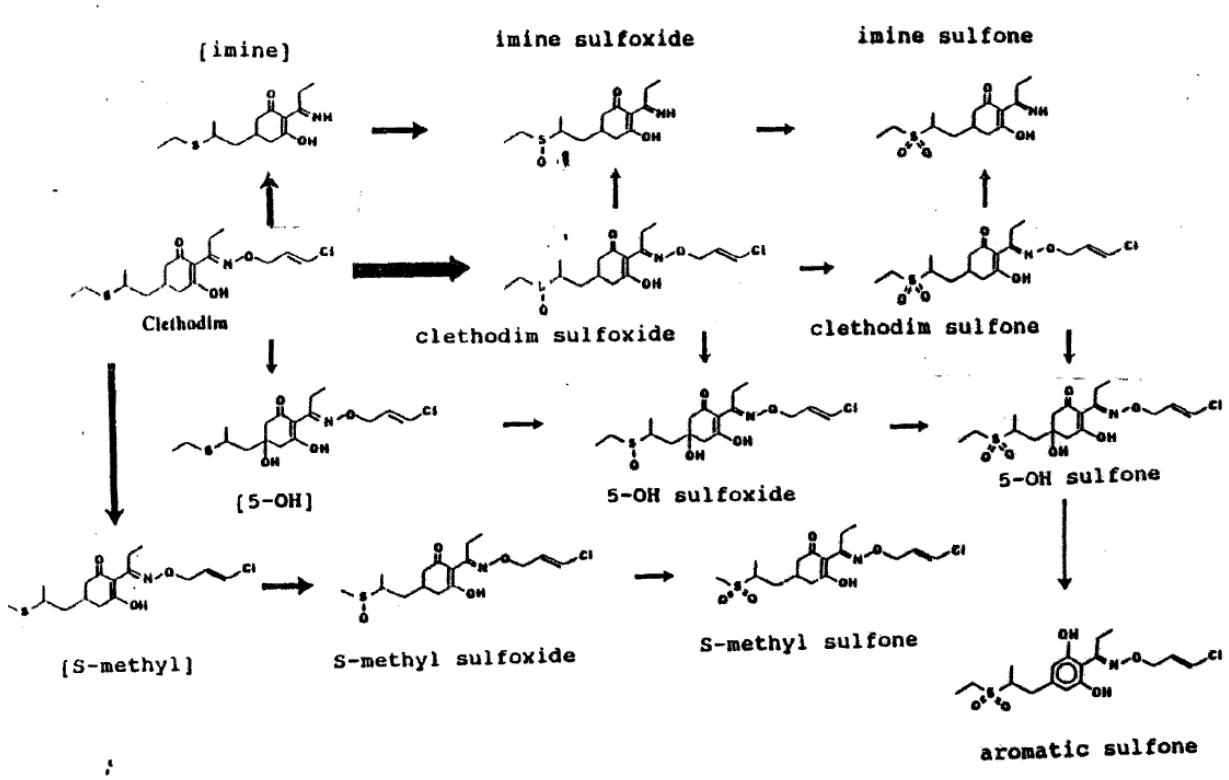


Figure 4: Proposed metabolic pathway for clethodim in rats.

Source: Rose and Griffis 1988.
See Section 3.1.3.1 for discussion.

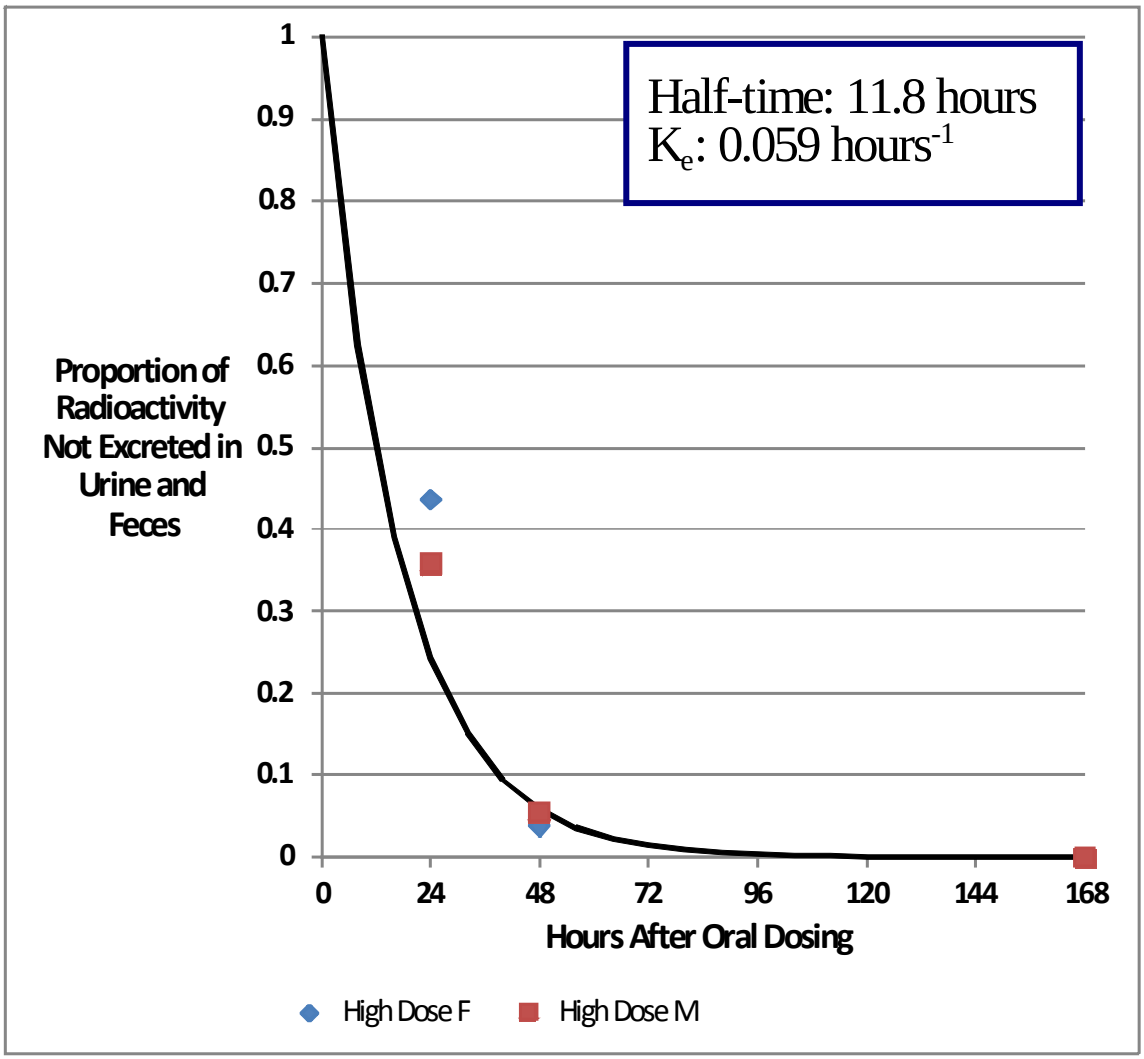


Figure 5: Whole body excretion of clethodim by rats

Source: Rose and Griffis 1988, Table 3
See Section 3.1.3.3 for discussion.

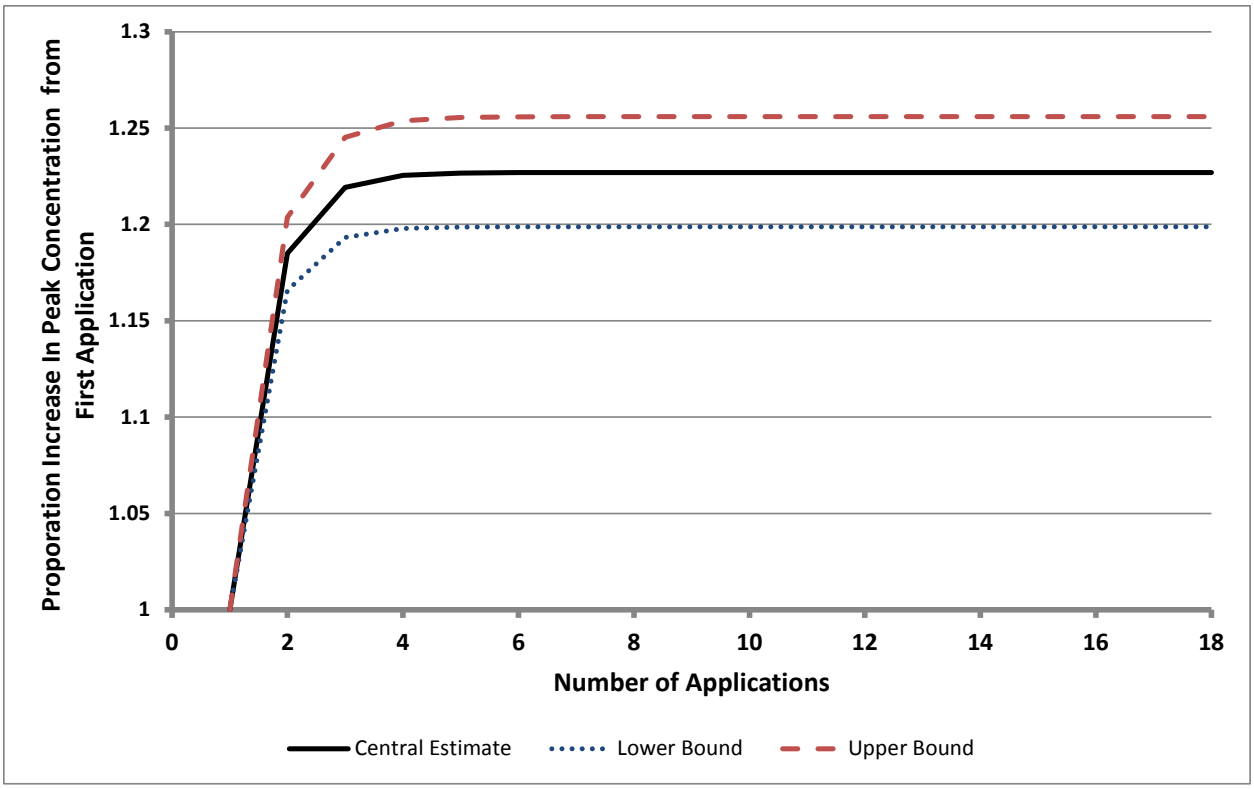


Figure 6: Increase in peak residues on vegetation following multiple applications

Appendix 1: Toxicity to Mammals.

A1 Table 1: Acute Oral and Intraperitoneal LD_{50} Values 168
A1 Table 2: Subchronic and Chronic Toxicity Studies 169
A1 Table 3: Reproductive and Developmental Studies 172
A1 Table 4: Skin Irritation and Sensitization Studies 174
A1 Table 5: Eye Irritation Studies 176
A1 Table 6: Acute and Repeated Dose Dermal Toxicity 177
A1 Table 7: Acute Inhalation Toxicity 179

A1 Table 1: Acute Oral and Intraperitoneal LD_{50} Values

Species	Exposure/ End-Point	Value, Classification/Note	Reference[1]
Clethodim			
Mice, CD-1	RE-45601 (Clethodim Technical), 83.3% a.i.	2,570 mg/kg (M) 2,430 mg/kg (F)	MRID 409745-08 [4, 5]
Rat	RE-51228, 99.9% a.i.	>1,400 mg/kg (F), Core Minimum	MRID 410301-01
Rat	RE-45601, 83.8% a.i.	Could not be determined. Core Supplementary	MRID 410301-01
Rat	RE-47719, 98.6% a.i.	>1,400 mg/kg (F)	MRID 410301-02
Rat	SELECT 2.0 EC, 26.1% a.i.	3,610 mg/kg (M) [≈942 mg a.i./kg] 2,920 mg/kg (F) [≈762 mg a.i./kg]	MRID 409745-06
Rat	RE-45601 (Clethodim Technical), 83.3% a.i.	1,630 mg/kg (M) [≈1358 mg a.i./kg] 1,360 mg/kg (F) [≈1133 mg a.i./kg] **Core Guideline**	MRID 409745-07[2, 4]
Rat	NOS	1133 mg a.s./kg [3]	EFSA 2011
Rats	SX-1688 [technical grade clethodim]	**i.p.** 1040 mg/kg (M) 1200 mg/kg (F)	IPCS 1994
Rabbit	82.5% technical	>2000 mg/kg <4000 mg/kg	IPCS 1994
Clethodim	**imine sulfone**		
Rat	NOS	>1400 mg/kg	EFSA 2011
Clethodim	**5-OH sulfone**		
Rat	NOS	>1400 mg/kg	EFSA 2011
M17R	**Plant Metabolite**		
Rat	NOS	>2000 mg/kg	EFSA 2011

[1] MRID studies from U.S. EPA/OPP/HED 1990 unless otherwise specified
[2] This is the acute toxicity study used in the most recent U.S. EPA/OPP/HED (2014a) risk assessment.
[3] The abbreviation a.s. stands for active substance and is used in some European literature. This term is essentially equivalent to a.i.
[4] Also cited in HSDB 2012.
[5] Cited to Cox & Zoetis, 1986 in IPCS 1994

See Section 3.1.4 for general discussion.
See Section 3.1.14.2 for a discussion of the toxicity of the formulation.

A1 Table 2: Subchronic and Chronic Toxicity Studies

Summaries from U.S. EPA/OPP/HED 1990 unless otherwise specified.

Organism	Exposure	Response	Reference/ Classification
Clethodim			
Dogs, 4/sex/dose	Clethodim TGAI (83.3%). 0, 1, 25, 75 or 125 mg/kg bw/day in gelatin capsules adjusted for changes in bw. **90 days**	In both sexes, increases in absolute and relative liver weights with liver lesions (cytoplasmic vesiculation and vacuolation) at high dose group. In females, increases in mean serum cholesterol and alkaline phosphatase in high dose group. NOAEL: 75 mg/kg bw/day LOEAL: 125 mg/kg bw/day **Working Note: The NOAEL of 75 mg/kg bw/day is used in recent EPA risk assessments (U.S. EPA/OPP/HED 2010a, 2014a) for characterizing risks of occupational exposures with a margin of exposure of 100. This is used in the current FS risk assessment for characterizing risks from worker exposures.**	MRID 410301-06 Core Supplementary
Dogs, beagles, 6 months old at start.	Clethodim TGAI (83.3%). 0, 1, 75 or 300 mg/kg bw/day in gelatin capsules adjusted for changes in bw. **1 year**	NOAEL: 75 mg/kg bw/day LOEAL: 150 mg/kg bw/day based on increases in platelet count, leukocytes, and ALT & ALP activities; decreases in glucose, in RBC, I-IGB, and HCT levels.	MRID 410301-11 Core Supplementary Evaluation from U.S. EPA/OPP/HED 2014a, p. 35
Mice, CD-1, 4 weeks old, 10/sex/dose	Clethodim TGAI (83.3%). 0, 150, 250, 625, 1500, and 4000 ppm in diet. Equivalent doses: 0, 15, 37.5, 93.8, 225.0, 600.0 mg/kg/day based on conversion factor (1 ppm = 0.15 mg/kg/day). **4-weeks**	NOAEL = 600 mg/kg/day (HDT)	MRID 410301-03 Summary from U.S. EPA/OPP/HED 2014a, p. 33-34
Mice	Clethodim TGAI (83.3%). 0, 20, 200, 1000, or 3000 ppm in diet. **18 months** Dose conversion based on 1 ppm = 0.15 mg/kg/day) specified in U.S. EPA/OPP/HED 2014a, p. 35.	No indication of carcinogenicity. NOAEL: 30 mg/kg bw/day LOAEL: 150 mg/kg bw/day based on … *reduced survival; reduced red cell mass; and increased incidences of bile duct hyperplasia, of pigmentation of the liver, and of foci of amphophilic macrophages in the lung.* These details are not provided in U.S. EPA/OPP/ HED (1990). **Working Note: This is the study on which the chronic RfD is based.**	MRID 410301-12 Core Guideline Summary from U.S. EPA/OPP/ HED 2014a, p. 31.

Organism	Exposure	Response	Reference/ Classification
Rats	Clethodim purified (96.2%). 0, 1200 (process neutrals), 6800 (high purity clethodim) ppm 4.9/5.8, 148/175 mg/kg/day (M/F) **5-weeks**	Decreased body weight gains (33.5%-42.4% of controls) with decreases in food consumption and changes in hematology (decreased RBCs). Increased liver weights with hypertrophy. NOAEL: Not established LOAEL: 6800 ppm [148/175 mg/kg/day]	MRID 410301-08 Acceptable nonguideline Mg/kg doses from U.S. EPA/OPP/ HED 2014a, p. 37
Rats	Clethodim (NOS) Dietary concentrations of 0, 5, 200, 1000, 4000, and 8000 ppm. Equivalent doses: 0, 0.256, 12.5, 65.6, 261, 515 mg/kg/day in males and 0, 0.288, 13.9, 70.6, 291, 554 mg/kg/day in females. **5-weeks**	NOAEL = 65.6/ 70.6 mg/kg/day (M/F) LOAEL = 261/291 mg/kg/day (M/F) *based on hematologic effects, increased liver weights with supportive pathology, reduced body weights, and decreased food intake.*	MRID 410301-10 Summary from U.S. EPA/OPP/ HED 2014a, p. 33
Rats	Clethodim TGAI (83.4%). 0, 50, 500, 2500, and 5000 ppm in diet. Equivalent doses: 0, 2.3/2.8, 25/30, 134/159, 279/341 mg/kg/day (M/F) **13-weeks**, with a 6 week recovery period.	NOAEL = 134/159 mg/kg/day (M/F) LOAEL = 279/341 mg/kg/day (M/F) *based on decreased body weights attributable to decreased food consumption, decreased body weight gains, and increased liver weights with a histological correlate of centrilobular hepatic hypertrophy*.	MRID 410301-07 Summary from U.S. EPA/OPP/HED 2014a, p. 34
Rats	Clethodim (NOS), **subacute (NOS)** Dietary concentrations: 0, 500, 1500, or 5000 ppm Equivalent doses: M: 0, 31, 94, and 331 mg/kg/day, F: 0, 38, 115, and 380 mg/kg/day	NOAEL = 94/115 mg/kg/day, M/F LOAEL = 331/380 mg/kg/day, M/F based on decreases in body weight, body weight gain, and food consumption No signs of neurotoxicity.	MRID 487885-03 (full study) MRID 487885-01 (range finding study) Summary from U.S. EPA/OPP/ HED 2014a, p. 37 Acceptable/non-guideline
Rats	Clethodim (NOS), subacute (NOS)	NOAEL: 25 mg/kg bw/day	ESFA 2012

Organism	Exposure	Response	Reference/ Classification
Rats	Clethodim TGAI (83%). 0, 5, 20, 500, 2500 ppm in diet. **2 years**	No indication of carcinogenicity. 2500 ppm: Decreased body weights with decreased food consumption (both sexes) and food conversion efficiency (males only). During first year, increased liver weights with hypertrophy in some rats. Liver weights and histology normal by end of study. NOAEL: 500 ppm (21 mg/kg bw/day) LOAEL: 2500 ppm (113 mg/kg bw/day)	MRID 410301-21 Core Guideline Equivalent doses taken from U.S. EPA/OPP/HED 2014a, p. 35
Clethodim	**Imine Sulfone**	**(RE-47719)**	
Rats	Metabolite (99.3%) at 0, 80.8, 871, 7820 ppm (nominal) in diet. Equivalent doses: 0, 6.7/7.8, 70.9/83.7, 604/723 mg/kg/day (M/F) **5-weeks**	Systemic Toxicity NOAEL = 70.9/83.7 mg/kg/day (M/F) Systemic Toxicity LOAEL = 604/723 mg/kg/day (M/F) *based on increased serum cholesterol and increased liver weights.*	MRID 410301-04 Acceptable non-guideline Summary from U.S. EPA/OPP/HED 2014a, p. 37
Rat	Specified only as a subacute study.	NOAEL: 70.9 mg/kg bw/day	EFSA 2011, p. 29
Clethodim	**5-Hydroxy Sulfone**	**(RE-51228)**	
Rats	Metabolite (94.8%) at 0, 100, 1000, or 8000 ppm (nominal) in diet. **5-weeks**	No compound related effects. NOAEL: 8000 ppm	MRID 410301-05 Core Supplementary
Rats	Specified only as a subacute study.	NOAEL: 5.94 mg/kg bw/day	EFSA 2011, p. 29
M17R	**Plant Metabolite**		
Rat	**28 days**	NOAEL: 400 mg/kg bw/day	EFSA 2011, p. 29

Full DERs for most studies are available in U.S. EPA/OPP/HED 1990.
The subchronic and chronic studies are also summarized in IPCS 1994.

Primary Source: U.S. EPA/OPP/HED 1990 unless otherwise noted.
See Section 3.1.5 for discussion.

A1 Table 3: Reproductive and Developmental Studies

Data from U.S. EPA/OPP/HED 2010a, supplemented with information from U.S. EPA/OPP/HED 1990

Species	Exposure	Response	Reference
Reproduction			
Rat, Full study	Clethodim (83.2%), dietary concentrations of 0, 5, 20, 500, and 2500 ppm. Equivalent doses: Males: 0, 0-1, 1-2, 28-60, 141-295 mg/kg bw/day. Females: 0, 0-1, 1-3, 36-61, 180-282 mg/kg bw/day.	Parental NOAEL: 51 mg/kg bw/day LOAEL: 263 mg/kg bw/day (reduced body weight and food consumption in both sexes of both generations. Working Note: Above dose conversion taken from the full DER. Offspring NOAEL: >263 mg/kg bw/day. LOAEL: Not defined. No adverse effects noted.	MRID 410301-19 (Pilot Study) MRID 410301-20 (Full Study) Full DER in U.S. EPA/OPP/HED 1990 (starting on physical pages 415-436) Also summarized in FAO/IAEA 2013
Rats (NOS)	Clethodim NOS	NOAEL: Parental: 26.7 mg/kg bw/day Offspring: 133.7 mg/kg bw/day	ESFA 2011, p. 29
Rats, Cr1:COBS CD(SD)	Clethodim, dietary concentrations of 0, 5, 20, 500, and 2500 ppm.	NOAEL: Parental: 39 mg/kg bw/day Offspring: 190 mg/kg bw/day	FAO/IAEA 2013 and IPCS 1994
Developmental			
Rat, Full study	Clethodim, gavage doses of 0, 10, 100, 350, or 700 mg/kg bw/day	Maternal NOAEL: 100 mg/kg bw/day LOAEL: 350 mg/kg bw/day (reduced body weight gain as well as salivation). FEL: Mortality in 5 of 25 dams. Salivation, lacrimation, and red nasal discharge. Offspring NOAEL: 100 mg/kg bw/day LOAEL: 350 mg/kg bw/day (reduced body weight and delayed growth [ossification of lower vertebrae] FEL: 700 mg/kg bw/day (rare tail defects)	MRID 410301-14 (Pilot Study) MRID 410301-16 (Full Study) Full DER in U.S. EPA/OPP/HED 1990 (starting on physical page 383) Study also summarized in FAO/IAEA 2013
Rat	Clethodim, NOS	NOAELs Maternal: 83.3 mg/kg bw/day Fetal: 83.3 mg/kg bw/day	ESFA 2011, p. 29

Species	Exposure	Response	Reference
Rabbit, Full study	Clethodim gavage doses of 0, 25, 100, 300 mg/kg bw/day on Days 7 to 19 of gestation.	Maternal NOAEL = 100 mg/kg/day Maternal LOAEL = 300 mg/kg/day *based on clinical signs of toxicity (increased incidence of dried feces), reduced body weight gains, and reduced food consumption.* Developmental NOAEL > 300 mg/kg/day (HDT).	MRID 410301-13 (Pilot Study) MRID 410301-15 (Full Study) Full DER in U.S. EPA/OPP/HED 1990 (starting on physical page 358) Evaluation taken from U.S. EPA/OPP/HED 2014a, p. 34. Study also summarized in FAO/IAEA 2013
Rabbit	Clethodim, NOS	NOAELs Maternal: 20.8 mg/kg bw/day Fetal: 250 mg/kg bw/day	ESFA 2011, p. 29
Clethodim Imine Sulfone			
Rats	Clethodim imine sulfone (98.6%) by gavage doses of 0, 10, 100, 700 mg/kg bw/day	Maternal NOAEL: 10 mg/kg bw/day LOAEL: 100 mg/kg bw/day (reduced body weight gain and food consumption, not statistically significant. FEL: 700 mg/kg bw/day. Significant reductions in food consumption and body weights with salivation. Offspring NOAEL: 100 mg/kg bw/day LOAEL: 700 mg/kg bw/day (reduced body weight and delayed growth [ossification of lower vertebrae].	MRID 410301-17 Core Supplementary Full DER in Full DER in U.S. EPA/OPP/HED 1990, physical page 401. Also cited in ESFA 2011.
Rats	Clethodim imide sulfone (NOS)	NOAELs Maternal: 10 mg/kg bw/day Fetal: 100 mg/kg bw/day	ESFA, 2011, p. 29
Clethodim 5-Hydroxy Sulfone			
Rats, 10/dose.	Clethodim 5-hydroxy sulfone (99.1%) by gavage at doses of 0, 10, 100, 700 mg/kg bw/day.	Maternal NOAEL: 700 mg/kg bw/day LOAEL: Not identified. Offspring NOAEL: 700 mg/kg bw/day LOAEL: Not identified. ESFA (2011) gives a NOAEL of 100 mg/kg bw for the 5-hydroxy sulfone but does not indicate a LOAEL.	MRID 410301-18 Core Supplementary Full DER in Full DER in U.S. EPA/OPP/HED 1990, physical page 371
Rats	Clethodim 5-hydroxy sulfone (NOS)	NOAELs Maternal: 100 mg/kg bw/day Fetal: 100 mg/kg bw/day	ESFA, 2011, p. 29

A1 Table 4: Skin Irritation and Sensitization Studies

Source: U.S. EPA/OPP/HED 1990 unless otherwise specified.
Most studies are also summarized briefly in U.S. EPA/OPP/HED 2010a or 2014a.

Species	Exposure	Response	Reference
Skin Irritation			
Rabbits, male, n=6, New Zealand white, 10-12 weeks old at dosing. Study 1	Clethodim, TGAI, 83.2% a.i. 4 hour exposure period with 14 day observation period.	Slight erythema in 2/6 animals and slight edema in 1/6 animals at 1 hour after dosing. Severe erythema and slight to moderate edema at 72 hours post-dosing in 3/6 animals. By Day 14, slight erythema and edema in 1/6 animals. Category III in U.S. EPA/OPP/HED 2014a, p. 33.	MRID 409745-16 Study 1 Full DER in 1990 compendia, p. 115
Rabbits, male, n=6, New Zealand white, 10-12 weeks old at dosing. Study 2	Clethodim, TGAI, 83.2% a.i. 4 hour exposure period with 14 day observation period.	Slight edema in 1/6 animals at 1 hour after dosing. Slight erythema but no edema in 2/6 animals at 72 hours post-dosing. No effects 14 days after exposure. **Authors state that the more severe results in Study 1 may have been due to incomplete removal of clethodim at 4 hours after dosing. The EPA classification of Category II appears to be based on Study 1.**	MRID 409745-16 Study 2 Full DER in 1990 compendia, p. 115
Skin Sensitization			
Guinea pigs, Hartley, 315-379 g bw, n=15/dose	Clethodim, TGAI, 83.4% a.i. 0.5% and 5% solutions. 22 day induction period with observations at 2 through 72 hours after challenge.	At 5%, erythema in 1/15 animals during induction period. After challenge, no skin responses at 48 or 72 hours. Not a skin sensitizer.	MRID 409745-18 Full DER in EPA 1990 compendia, p. 123 Similar information cited with no details by FAO/IAEA 2013, p. 2 and IPCS 1994, p. 8.

Species	Exposure	Response	Reference
Guinea pigs, albino, Dunkin Hartley, 5-6 weeks old, 360-467 g bw for males and 317-382 g bw for females, n=15/dose	Select 2 EC, 26.4% a.i. Undiluted formulation, 0.3 mL for six hours. Repeated once per week for 3 weeks with change dose (50% or 75%) after an additional 2 weeks.	Results with a 75% challenge concentration were equivocal due to positive reactions (i.e., skin irritation) in control animals. Results with 50% challenge (less irritation) yielded a positive response in 7/20 induced animals but 0/20 control animals. Select 2 EC classified as a potential skin sensitizer in DER. The EPA DER classifies this study as "Acceptable".	Blaszak 1998, MRID 446865-01 EPA/OPP DER dated February 8, 1999 **Working Note: This study is not cited in any of the EPA risk assessments summarized in Table 1.**

Note: EFSA (2011, p. 28) indicates that clethodim is a sensitizer but no details are provided.

A1 Table 5: Eye Irritation Studies

Source: U.S. EPA/OPP/HED 1990 unless otherwise specified.
Studies are also summarized briefly in U.S. EPA/OPP/HED 2010a.

Species	Exposure	Response	Reference
Rabbits, male, n=6, New Zealand white, 11-15 weeks old at dosing.	Clethodim, TGAI, 83.3% a.i. 0.1 mL in conjunctival sac of one eye of each rabbit for 30 seconds. 3/6 washed and 3/6 unwashed	Without wash: moderate to severe redness with slight to severe discharge. With wash: Slight to moderate redness and discharge at 1 hour and slight redness in 2/3 treated eyes at 24 hours. No eye irritation in any animals at 72 hours. No corneal damage at any time in any animal. Category III in U.S. EPA/OPP/HED 2014a, p. 33.	MRID 409745-14 Full DER in EPA 1990 compendia, p. 107. Also summarized in IPCS 1994.

Note: EFSA (2011, p. 28) indicates that clethodim is not an eye irritant but no details are note provided.

A1 Table 6: Acute and Repeated Dose Dermal Toxicity

Source: U.S. EPA/OPP/HED 1990 unless otherwise specified.
Studies are also summarized briefly in U.S. EPA/OPP/HED 2010a unless otherwise specified.

Species	Exposure	Response	Reference
Acute			
Rabbits, New Zealand White, Age 14-17 weeks. 5 animals/sex/dose	Clethodim, TGAI, 83.3% a.i. Doses of 0, 2,500 and 5,000 mg/kg bw. High doses was actually 4,500 to 5,000 mg/kg bw due to rounding errors (NOS). 14 day observation period.	Mortality: Control: 0/6 Low dose: 0/6 High dose: 1M/3, 0F/3 The one male that died exhibited decreased food consumption, decreased activity, diarrhea, and other signs of distress. Skin irritation in the low and high dose groups. LD_{50}: >5,000 mg/kg bw Category IV in U.S. EPA/OPP/HED 2014a, p. 33.	MRID 409745-10 Full DER in EPA 1990 compendia, p. 92 This study is also cited by IPCS 1994, p. 4.
Rat	Clethodim (NOS)	LD_{50} > 4167 mg/kg bw	ESFA 2011
Repeated Dose			
Rats, 6/dose/sex	Clethodim, TGAI, 83.2%. Doses of 0, 10, 100, or 1000 mg/kg bw/day, 6 hours/day for 21 days.	Systemic Effects: No adverse systemic toxicity was found; NOAEL = 1000 mg/kg/day (HDT; limit dose) …*increase in the incidence of anogenital discharge/staining was found in high-dose males and females… Decreases in food efficiency and body weight gain*… noted in both treated and control animals. Effects not judged to be adverse in supplemental DER. Dermal Irritation: Dermal Toxicity LOAEL = 10 mg/kg/day based on skin irritation. Dermal Toxicity NOAEL not established.	Hedhecock 1987, MRID 410301-09 Evaluation taken from supplemental DER and U.S. EPA/OPP/HED 2014a, p. 34. Also summarized in IPCS 1994, p. 3.

Appendix 1: Toxicity to mammals *(continued)*

Species	Exposure	Response	Reference
	Select 2.0 EC, 26.3% a.i. Doses of 0, 10, 50, or 100/200 mg/kg bw/day, 6 hours/day for 21 days. Due to skin irritation, the highest dose was reduced from 200 to 100 mg/kg bw/day after 4 days.	Systemic NOAEL: 2000 mg/kg bw/day Dermal irritation at all doses. Core Supplementary in EPA 1990 and Acceptable/Guideline in EPA 2010a	MRID 410302-01 No DER in EPA 1990. Summary on p. 9. Evaluation taken from U.S. EPA/OPP/HED 2014a, p. 34.
Rat	Clethodim (NOS), 4 week (28 day) exposure.	NOAEL: 83 mg/kg bw/day	ESFA 2011

Note: FAO/IAEA (2013) indicates that clethodim is nontoxic following dermal administration.

A1 Table 7: Acute Inhalation Toxicity

Source: U.S. EPA/OPP/HED 1990 unless otherwise specified.
Studies are also summarized briefly in U.S. EPA/OPP/HED 2010a unless otherwise specified.

Species	Exposure	Response	Reference
Rats, Sprague-Dawley, 96 days old, 5 rats/sex/group.	Clethodim, TGAI, 83.3% a.i., 0 (acetone control) and 3.9 mg a.i./L for 4 hours Observations at 2, 7, and 14 days after exposure.	Salivation in 3/10 animals during and in all animals after exposure. This response not evident in control animals. Trace chronic interstitial pneumonia in 5/5 treated males and 2/5 male controls. No discussion in DER on effects on body weight. LC_{50}: > 3.9 mg/L Category IV in in U.S. EPA/OPP/HED 2014a, p. 33.	MRID 409745-12 Full DER in EPA 1990 compendia, p. 99-102 Also summarized in IPCS 1994, p. 3
Rats, Sprague-Dawley, 55 days old, 5 rats/sex/group.	**Select 2.0 EC**. 1% solution at 5.4 mg/L for 4 hours with 14 day observation period	Salivation in 9/10 animals during and in all animals after exposure. This response not evident in control animals. Decreased body weights in males and females at 7 and 14 days post-exposure.	MRID 409745-13 Full DER in EPA 1990 compendia, p. 103-106 Not cited in EPA 2010a.
Rats	Clethodim (NOS)	LC_{50}: > 3.25 mg a.i./L	ESFA 2011, p. 28

FAO/IAEA (2013) states that clethodim is cited as nontoxic following inhalation administration.

Appendix 2: Toxicity to Birds

A2 Table 1: Acute Oral/Gavage Toxicity to Birds 180
A2 Table 2: Acute Dietary Toxicity to Birds..... 181
A2 Table 3: Reproduction Studies in Birds 182

Unless otherwise indicated, study summaries taken from U.S. EPA/OPP 2007b and supplemented by ECOTOX. The MRID numbers are identified in U.S. EPA/OPP 2007b and the NOEC values are identified in ECOTOX.

A2 Table 1: Acute Oral/Gavage Toxicity to Birds

Species	Exposure	Response	Reference
Bobwhite quail (*Colinus virginianus*), 18-weeks-old, 150-208 g bw.	Clethodim, 81.9 to 82% a.i., 2000 mg/kg bw for 14 days by gavage. 14-day observation period. Doses: 500, 875, 1250, 1650, and 2000 mg/kg bw. Note: ECOTOX indicates capsule dosing. The DER indicates gavage dosing.	LD_{50} >2000 mg/kg bw NOEL = 1250 mg/kg bw (≈ 1025 mg a.i./kg bw correcting for % a.i.) No mortality during study. Toxicity in two highest dose groups: lethargy, wing droop and a ruffled appearance on Day 1. All animals normal by Day 6. Transient loss of body weight with corresponding decrease in food consumption up to Day 3 in all dose groups [EPA assessment].	Hinken and Grimes 1986 MRID 40974525 Summary based on DER. Classification: Core.

A2 Table 2: Acute Dietary Toxicity to Birds

Species	Exposure	Response	Reference
Bobwhite quail (*Colinus virginianus*), 10-days-old	Clethodim, 82% a.i., for 8 days *ad libitum* in the diet Doses in units of mg/kg bw/day are not given in U.S. EPA/OPP 2007b. Based on food consumption from an acute dietary study in quail on aminopyralid (SERA 2007b) – i.e., 30% of body weight per day – the dietary NOAEL corresponds to a dose of ≈1050 mg a.i./kg bw/day.	LC_{50} >4270 ppm NOEL = 4270 ppm (≈1050 mg a.i./kg bw/day)	MRID 40974526
Mallard duck (*Anas platyrhynchos*), 10-days-old	Clethodim, 82% a.i., for 8 days *ad libitum* in the diet. Nominal concentrations of 600, 1290, 2750, and 6000 ppm specified in DER. Measured concentrations given in DER for 6000 ppm nominal group ranged from 3690 to 4480 ppm. Doses in units of mg/kg bw/day are not given in U.S. EPA/OPP 2007b. Based on food consumption from an acute dietary study in mallards on aminopyralid (SERA 2007b) – i.e., 42% of body weight per day – the dietary NOAEL corresponds to a dose of 947.1 mg a.i./kg bw/day.	LC_{50} >3978 ppm NOEL = 2750 ppm (947.1 mg a.i./kg bw/day) DER reports no mortality or signs of toxicity at any concentration. At 6000 ppm, a slight decrease in body weight and food consumption (not otherwise specified in DER). Working Note: The dose is rounded to 950 mg a.i./kg bw in the dose-response assessment.	MRID 40974527 Full DER available as Hinken et al. 1986. DER classifies study as “Core”.

A2 Table 3: Reproduction Studies in Birds

Species	Exposure	Response	Reference
Bobwhite quail (*Colinus virginianus*), 25 weeks old at start of study.	Clethodim, 83.3% a.i., incorporated into food for 22 weeks Concentrations: 0, 100, 250, and 833 ppm based on measured concentrations in chow. Food consumption is not given in DER. Based on food consumption from a quail reproduction study on aminopyralid (SERA 2007b) – i.e., 0.094 of body weight per day – and correcting for the % a.i. The estimated doses are 0, 7.8, 19.6, and 65.2 mg a.i. /kg bw/day.	Reproductive effects: NOEL = 250 ppm (19.6 mg/kg bw/day) LOEL = 833 ppm (65.2 mg/kg bw/day) For 14-day survival, % egg viability, and % egg hatch. Effects on adults: No overt signs of toxicity at any dose. Pathology in birds dying during the study was not related to treatment. Variable food consumption (increases and decreases at different periods and low/mid doses) that were not considered treatment related. No impact on food consumption in high dose group. No effect on body weight gain in adults or offspring. Working Note: The NOAEL dose of 19.6 mg a.i./kg bw is rounded to 20 mg a.i./kg bw in the dose-response assessment. Supplemental Notes on Beavers 1988: DER notes high adult and chick mortality due to incubator failure.	Beavers 1988a, MRID 41030206 Summary based on DER. Classification: Supplemental (U.S. EPA/OPP/EFED 2008a) This study is cited in U.S. EPA/OPP/EFED 1990 as **Invalid** with a handwritten modification to Supplemental. Full DER available as Beavers 1988a.
Mallard duck (*Anas platyrhynchos*)	Clethodim, 83.3% a.i., incorporated into food for 19 weeks Food consumption is not given in U.S. EPA/OPP (2007b) or DER. The doses in mg/kg bw/day are based on food consumption from a mallard reproduction study (0.11 of body weight per day) on aminopyralid (SERA 2007b).	Reproductive effects: NOEL = 833 ppm (≈76.3 mg a.i./kg bw/day) LOEL >833 ppm	Beavers 1988b, MRID 41030205 Classification: Supplemental (U.S. EPA/OPP/EFED 2008a) Full DER available as Beavers 1988b.

Appendix 3: Toxicity to Terrestrial Invertebrates.

A3 Table 1: Toxicity to Bees 183

A3 Table 1: Toxicity to Bees

Species	Exposure	Response	Reference
Honey bee (*Apis mellifera*), workers, 100 bees/dose level.	Clethodim, 87.9% a.i. in contact toxicity assay with an observation period of 48 hours. Doses up to 100 µg/bee. [Dose levels not specified in DER]	Mortality rates not reported in DER. DER states the following: *Due to very low mortality at all levels, no analysis was performed.*	Atkins 1986 MRID 409745-32 Full DER
Honey bee (*Apis mellifera*), workers	Clethodim, 88% a.i. in contact toxicity study for 48 hours.	LD_{50} >100 µg/bee LOEC >100 µg/bee Working Note: This appears to be a summary of Atkins (1986) summarized above.	ECOTOX 2013
Honey bee (*Apis mellifera*), 1- to 4-days-old, 50/test chamber, two replicates/dose with 25 bees/replicate	Select 2.0 EC in 48-hour contact toxicity study. 26% a.i. <u>Treatment levels:</u> Solvent control (acetone), negative control, 13, 22, 36, 60 and 100 µg/bee	LD_{50} >100 µg/bee Working Note: The DER does not give mortality data for each dose. U.S. EPA/OPP/ EFED 2014a notes that no sublethal effects were noted.	Hoxter and Smith 1990 MRID 416851-07 Full DER Also summarized in U.S. EPA/OPP/ EFED 2014a, p. 41

Working Note: An oral toxicity study on honeybees has not been identified and no oral toxicity studies are cited in the U.S. EPA ecological risk assessments on clethodim.

Working Note: The U.S. EPA/OPP/EFED (2008a) cites a honeybee study to MRID 416851-05. Other EPA risk assessments (EPA/OPP/EFED 2007a,b)cite MRID 416851-05 as a plant toxicity study.

Appendix 4: Toxicity to Terrestrial Plants

A4 Table 1: Vegetative Vigor 185
A4 Table 2: Seedling Emergence 186
A4 Table 3: Seed Germination 187
A4 Table 4: Overview of Efficacy Studies 188

Working Note: Tables start on next page.

A4 Table 1: Vegetative Vigor

<table>
<tr><th>Form</th><th>Exposure</th><th>Species</th><th>Response</th><th>Reference [1]</th></tr>
<tr><td>Monocots</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Clethodim, 82.4%., Tier II assay

5 plants/pot, 5 pots/treatment level.

Observation period of 21 days.</td><td>0 (control), 0.0156, 0.0313, 0.0625, 0.125, and 0.25 lb a.i./acre with continuation exposures of 0, 0.002, 0.003, 0.006, 0.013, and 0.025 lb a.i./acre</td><td>See column to the right.</td><td>Plant height
<table>
<tr><th>Species</th><th>EC_{25} (lb a.i./acre)</th><th>NOAEC or EC_{05} (lb a.i./acre)</th></tr>
<tr><td>Onion</td><td>>0.25</td><td>≥0.25</td></tr>
<tr><td>Ryegrass</td><td>0.006</td><td>0.003</td></tr>
<tr><td>Oats</td><td>0.021</td><td>0.013</td></tr>
<tr><td>Corn</td><td>0.010</td><td>0.006</td></tr>
</table>
Dry weight
<table>
<tr><th>Species</th><th>EC_{25} (lb a.i./acre)</th><th>NOAEC or EC_{05} (lb a.i./acre)</th></tr>
<tr><td>Onion</td><td>>0.25</td><td>≥0.25</td></tr>
<tr><td>Ryegrass</td><td>0.003</td><td>0.0023 [1]</td></tr>
<tr><td>Oats</td><td>0.016</td><td>0.013</td></tr>
<tr><td>Corn</td><td>0.010</td><td>0.006</td></tr>
</table>
[1] EC_{05} for most sensitive species/endpoint.

Continuation exposures not used with onion.</td><td>Chetram 1990a

MRID 416851-05

Note: Values taken from EPA 2012 reanalysis in Wendel and Anderson 2012</td></tr>
<tr><td>Dicots</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Clethodim, 82.4%, Tier 1</td><td>0.25 lb a.i./acre with 21 day observation period</td><td>Soybean, Cucumber</td><td>No effects on plant height, dry weight, or visual signs of damage.</td><td>Maggio 1990a

MRID 416851-03</td></tr>
<tr><td></td><td></td><td>Lettuce, Cabbage</td><td>No significant effects on plant height, dry weight, or visual signs of damage. Some cabbage and lettuce plants evidenced an increase (up to 23%) in weight but this effect was not statistically significant.</td><td></td></tr>
<tr><td></td><td></td><td>Carrot</td><td>Visual signs of damage on Days 7 and 14 but not on Day 21.</td><td></td></tr>
<tr><td></td><td></td><td>Tomato</td><td>Significant (-8%) decrease in plant height at Day 21. A decrease of 14% in dry weight relative to controls but this effect was not statistically significant.</td><td></td></tr>
</table>

Note on MRID 416851-03: This study is not discussed in U.S. EPA/OPP /EFED 2007a. U.S. EPA/OPP /EFED 2007b (p. 20) cites study with a NOEC of >0.25 lb a.i./acre but does not discuss the effect on tomato at Day 21.

A4 Table 2: Seedling Emergence

<table>
<tr><th>Form</th><th>Exposure</th><th>Species</th><th>Response</th><th>Reference [1]</th></tr>
<tr><td>Monocots</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Clethodim, 82.4%, Tier II</td><td>10 seeds/pot, 3 pots/ treatment. Observations at 7, 14, and 21 days.

0 (control), 0.016, 0.031, 0.063, 0.125, and 0.25 lb a.i./acre</td><td>See column to the right.</td><td>Plant height
<table>
<tr><th>Species</th><th>EC_{25} (lb a.i./acre)</th><th>NOAEC or EC_{05} (lb a.i./acre)</th></tr>
<tr><td>Onion</td><td>>0.25</td><td>≥0.25</td></tr>
<tr><td>Ryegrass</td><td>0.0561</td><td>0.0313</td></tr>
<tr><td>Oats</td><td>0.0076</td><td>0.0004 [1]</td></tr>
<tr><td>Corn</td><td>0.014</td><td>0.0063</td></tr>
</table>
Dry weight
<table>
<tr><th>Species</th><th>EC_{25} (lb a.i./acre)</th><th>NOAEC or EC_{05} (lb a.i./acre)</th></tr>
<tr><td>Onion</td><td>>0.25</td><td>≥0.25</td></tr>
<tr><td>Ryegrass</td><td>>0.25</td><td>≥0.25</td></tr>
<tr><td>Oats</td><td>0.018</td><td>0.0125</td></tr>
<tr><td>Corn</td><td>0.014</td><td>0.007</td></tr>
</table>
[1]EC_{05} for most sensitive species/endpoint.</td><td>Chetram 1990b.

MRID 416851-04

Note: Values taken from EPA 2012 reanalysis in Wendel and Anderson 2012</td></tr>
<tr><td>Dicots</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Clethodim, 82.4%, Tier I assay</td><td>0.25 lb a.i./acre with 21 day observation period (28 days for carrots).</td><td>Soybean, Lettuce, Carrot, Tomato, Cucumber,</td><td>No effects on emergence, plant height, plant dry weight, or visual signs of toxicity.</td><td>Maggio 1990b

MRID 416851-02

U.S. EPA/OPP /EFED 2014a, p. 41</td></tr>
<tr><td></td><td>10 seeds/pot, 5 pots per group.</td><td>Cabbage</td><td>Significant (p<0.05) reduction (-13%) in seedling emergence.
No effects on plant height, plant dry weight, or visual signs of toxicity.</td><td></td></tr>
</table>

Note on Chetram 1990b Seedling Emergence: U.S. EPA/OPP/EFED (2007a,b) gives the NOAEC for the most sensitive species as 0.004 lb/acre. The U.S. EPA/OPP/EFED (2007b, p. 20) indicates that 0.0063 lb a.i./acre but 0.0063 lb/acre is identified as the NOAEC on p. 49. The DER indicates that 0.0063 lb/acre is an NOEC. The somewhat lower NOEC from U.S. EPA/OPP/EFED (2007b) is used in the current risk assessment. U.S. EPA/OPP/EFED (2014a, p. 41) clarifies the dose of 0.0004 lb a.i./acre as an EC_{05} – i.e., a functional NOEC.

Note on Maggio 1990b: Values from DER are consistent with U.S. EPA/OPP /EFED 2007a, p. 24 and U.S. EPA/OPP /EFED 2007b, p. 49 except that effect on cabbage is not noted.

A4 Table 3: Seed Germination

Form	Exposure	Species	Response	Reference [1]
Monocots				
Clethodim, 82.4%, Tier II assay	Petri plate assay with observations at 7 days.	Oat	Germination NOEC: 0.25 lb a.i./acre Radicle Length NOEC: 0.0063 lb a.i./acre	Chetram 1990b
		Ryegrass	Germination NOEC: 0.0156 lb a.i./acre Radicle Length NOEC: 0.0031 lb a.i./acre	MRID 416851-04
		Corn	Germination NOEC: 0.25 lb a.i./acre. Radicle Length NOEC: 0.0125 lb a.i./acre	NOTE: U.S. EPA/OPP /EFED 2007a,b do not discuss this study.
		Onion	Germination NOEC: 0.25 lb a.i./acre Radicle Length NOEC: 0.25 lb a.i./acre	
Dicots				
Clethodim, 82.4%, Tier I assay	0.25 lb a.i./acre with 7 day observation period. Petri dish assay, 10 seeds/plate, 5 plates per group.	Soybean, Lettuce, Carrot, Tomato, Cucumber, and Cabbage	No effect on any species	Maggio 1990b MRID 416851-02 NOTE: U.S. EPA/OPP /EFED 2007a,b do not discuss this seed germination assay.

A4 Table 4: Overview of Efficacy Studies

Weed Species	Crop	Application Rate (lb a.i. /acre)	Observations [No report of nontarget/crop damage unless otherwise stated.]	Reference
Red Rice *(Oryza sativa)*	Soybean *(Glycine max)*	0.098	Improved control when used after other herbicides	Askew et al. 1998
Bermudagrass (*Cynodon dactylon*)	Sunflowers (*Helianthus annuus*	0.25 to 0.30	About 50 to 90% control (Table 1). Little difference between the application rates.	Bedmar 1992
Bermudagrass (*Cynodon dactylon*)	Sunflowers (*Helianthus annuus*	0.25 to 0.30	No more than 67% control.	Bedmar 1997
Green foxtail and wild oat	*Safflower (Carthamus tinctorius)*	0.0892	Significant increase in crop yield.	Blackshaw et al. 1990
Foxtail Barley (*Hordeum jubatum*)	Spring wheat (*Triticum aestivum*) Flax (*Linum usitatissimum*)	0.04	Effective control.	Blackshaw et al. 1998
Foxtail Barley (*Hordeum jubatum*)	Spring wheat (*Triticum aestivum*) Flax (*Linum usitatissimum*)	0.026	Reduced weed biomass by 63 to 98%. Also assayed in combination with broadleaf herbicides.	Blackshaw et al. 2006
Burmuda grass (*Cynodon dactylon*) and Yellow foxtail	Soybean *(Glycine max)*	0.047	Effective control. Soybean oil not effective as an adjuvant. Also summarizes greenhouse studies.	Bohannan and Jordan 1995.
Mannagrass (*Glyceria declinata*), SouthernWatergrass (*Luziola fluitans*)	Rice (*Oryza sativa*)	0.12 to 0.31	Good control at 0.25 lb a.i./acre. **NB**: Clethodim treatment made prior to planting the crop.	Braverrman 1996
18 grasses	N/A	0.098	Generally good control (67-100%) except for rattail fescue (30%).	Brewster and Spinney 1989
Rhizome Johnsongrass (*Sorghum halepense*)	N/A	0.045	About 40-80% control in replicate experiments with different adjuvants.	Bridges 1989
Tussock sedge (*Carex appressa*)	N/A	0.17 and 0.45	Reduction in cover not significantly different from controls (Table 1)	Campbell et al. 1997

Weed Species	Crop	Application Rate (lb a.i. /acre)	Observations [No report of nontarget/crop damage unless otherwise stated.]	Reference
Barnyard grass (*Echinochloa crus galli*) and bearded spangletop	Rice (*Oryza sativa*)	0.053	Greater than 80-90% control. Visible injury to rice (27%) in one treatment year (Table 1 of paper). **NB:** At least some of the applications appear to have been made concurrently to both the crop and the weed.	Carey et al. 1992
Ryegrass (*Lolium rigidum*) and several volunteer cereals	Lupin (*Lupinus angustifolius*)	0.11	Greater than 98% control.	Chambers et al. 1995
Red Rice *(Oryza sativa* var. *sylvatica)*	Rice (*Oryza sativa*)	0.12 to 0.25	Greater than 95% control. **NB**: Clethodim treatment made prior to planting the crop.	Ferrero 1991
Various annual grasses	Alfalfa	0.07 to 0.25	Effective control with adjuvant (Agri-Dex).	Foy and Wit 1992
Texas Panicum (*Panicum texanum*) Southern Crabgrass (*Digitaria ciliaris*)	Peanut (*Arachis hypogaea*)	0.10 to 0.12	Good control (87-98%) with early postemergence application. Inconsistent control (51% in one year and 95% in another) with late post-emergence application.	Grichar 1991
Burmuda grass (*Cynodon dactylon*)	Peanut (*Arachis hypogaea*)	0.12 and 0.25	Generally moderate to good control (≈70 to 95%) but poor control (43%) in one year at the higher rate (Table 1 of paper).	Grichar 1995
Burmuda grass, coastal (*Cynodon dactylon*)	Peanut (*Arachis hypogaea*)	0.25	Moderate (70% or less) control.	Grichar and Boswell 1989
Itchgrass (*Rottboellia cochinchinensis*)	Soybean (*Glycine max*)	0.06 and 0.13	Good control (82%) at higher application rate.	Griffin 1991
Persian darnel, green foxtail, wild oat, and volunteer cereals	Flax, (*Linum usitatissimum*)	0.017 to 0.05	Good control (≈80 to 100%) at rates of 0.04 lb a.i./acre and higher.	Hunter 1995
Johnsongrass (*Sorghum halepense*)	Soybean (*Glycine max*)	0.06	Good control (81 to 96%) using two applications.	Johnson and Franz 1991
Annual grasses	N/A	0.12	Good control (≈89 to 100%).	Jordan et al. 1993b
Barnyard grass	N/A	0.06 to 0.12	Variable control depending adjuvants. Good control with crop oil concentrates and some commercial adjuvants.	Jordan et al. 1996
Giant foxtail (*Setaria faberi*)	Soybean (*Glycine max*)	0.1	Good control (89-99%) and increased soybean yield.	Krausz et al. 1993

Weed Species	Crop	Application Rate (lb a.i. /acre)	Observations [No report of nontarget/crop damage unless otherwise stated.]	Reference
	Kenaf (dicot)	0.1	Small increase in visual damage but no impact on plant height.	Kurtz and Neil 1992
Several grasses	N/A	0.009 to 0.09	Highly effective 0.09 lb a.i./acre. At lower rates (up to 0.05 lb a.i./acre), poor control of some grasses.	Leys et al. 1988
Johnsongrass (*Sorghum halepense*)	Soybean (*Glycine max*)	0.04 to 0.16	Good (78-98%) control. Minor damage rates (3-7%) to soybean. Not clear that damage is statistically significant.	McKinley et al. 1999
Several grasses	*Aloysia polystachya*	0.21	Control rates of 67-82%	Novo et al. 1998
N.S.	Tall fescue (*Festuca arundinacea*)	0.005 to 0.02	Application rate dependent increase in yield. Similar to sethoxydim.	Reynolds et al. 1994
Johnsongrass (*Sorghum halepense*)	N/A	0.006 to 0.19	80% control at 0.089 lb a.i./acre.	Smeda et al. 1997
Johnsongrass (*Sorghum halepense*)	N/A	0.06	Control rates of 94 to 98%.	Snipes and Allen 1996
Johnsongrass (*Sorghum halepense*) Barnyard grass (*Echinochloa crus galli*)	Soybean (*Glycine max*)	0.093	Good (83-99%) control. See Tables 2 and 3 of paper. Increase in soybean yield.	Vidrine et al. 1995
Bermudagrass (*Cynodon dactylon*)	Peanut (*Arachis hypogaea*)	0.12 and 0.25	Good (90-100%) control at higher application rate. Only 72-76% control at lower rate.	Wilcut 1991

Appendix 5: Toxicity to Fish.

A5 Table 1: Acute Toxicity 191
A5 Table 2: Chronic Toxicity 193

Unless otherwise indicated, study summaries taken from ECOTOX. ECOTOX reports concentrations in units of µg/L (1 µg/L = 0.001 mg/L). Concentrations have been converted to mg/L in this appendix.

A5 Table 1: Acute Toxicity

Species	Exposure	Response	Reference
Freshwater			
Bluegill sunfish (*Lepomis macrochirus*), 0.53 g., 20 (two replicates of 10) per concentration.	Clethodim, 83.8% purity for 96 hours under static conditions. 20°C. Nominal (Measured) Test concentrations: 0, 10 (8.8), 18, 32 (20), 56 and 100 (33) mg a.i./L.	LC_{50} >33 mg a.i./L NOEC = 33 mg a.i./L At 33 mg/L and higher, *yellow oily drops at the bottom of the chambers*. 100 mg/L: Air gulping. **The NOEC of 33 mg/L is used for tolerant species in the current risk assessment.**	ECOTOX 2013 U.S. EPA/OPP 2007a,b, 2014a (p.76) MRID 409745-29 Summary based on DER, Swigert 1986a. Classification: Core
Fathead minnow (*Pimephales promelas*), 0.20 g	Clethodim, 95.4% purity for 96 hours, static renewal.	LC_{50} =110 mg a.i./L NOEC =28 mg a.i./L Sublethal effects at 55 and 115 mg/L a.i. included *…lethargy, surfacing, lying on the bottom, and swollen abdomen*.	ECOTOX 2013 U.S. EPA/ OPP/EFED 2014a MRID 484170-02 Acceptable
Fathead minnow (*Pimephales promelas*), Initial exposure of <24 hour old embryos. 20 embryos/ concentration	Technical grade clethodim, 95.75% Nominal Concentrations: 0, 0 (solvent control), 18, 32, 56, 100, and 180 mg/L 96 hour exposure	LC_{50} =71.91 mg a.i./L	Bidinotto 2003 MRID 481043-03 This is a range-finding study for early life stage study detailed in Table A5-2 below.
Rainbow trout (*Oncorhynchus mykiss*), 0.42 g	Clethodim, 95.4% purity for 96 hours. Static renewal.	LC_{50} >110 mg/L *Sublethal effects observed were lethargy, lying on the bottom, and loss of equilibrium.* This flow-through assay is not cited in U.S. EPA/OPP 2007a,b.	ECOTOX 2013 U.S. EPA/ OPP/EFED 2014a MRID 484170-03 Acceptable

Appendix 6: Toxicity to Aquatic Invertebrates *(continued)*

Species	Exposure	Response	Reference
Rainbow trout (*Oncorhynchus mykiss*), 0.67 g	Clethodim, 83.8% purity for 96 hours under static conditions. Test concentrations: Not reported in ECOTOX.	ECOTOX: LC_{50} =19 mg/L NOEC =18 mg/L Working Note: The relationship of the NOEC to the LC_{50} reported in ECOTOX does not seem credible. The NOEC is not supported by the DER. U.S. EPA/OPP/EFED 2007a,b LC_{50} = 15 mg/L. This is close to the ECOTOX value corrected for compound purity – i.e., 15.9 mg/L. DER: EPA derived LC_{50} of 18 mg/L. U.S. EPA/OPP/EFED 2014a LC_{50} = 24.4 mg a.i./L. NOEC = 7.8 mg a.i./L **The NOEC of 7.8 mg a.i./L is used for sensitive species in the current risk assessment. As specified in the DER, this is based on measured concentrations. This is the most sensitive acute study in fish identified by U.S. EPA/OPP/EFED (2014a, p. 35)**	ECOTOX 2013 U.S. EPA/OPP 2007a,b; 2014a (p. 76). MRID 409745-28 DER available as Swigert 1986b. Acceptable
Zebrafish (*Danio rerio*), 0.271 g	Clethodim (technical grade from Agan), 95.7% purity for 96 hours under flow through conditions.	LC_{50} = 133 mg/L NOEC = 103 mg/L The relationship of the LC_{50} to NOEC seems questionable. The NOEC is not confirmed in U.S. EPA/OPP 2014a which notes that sublethal effects were not reported. Study not used in risk assessment.	ECOTOX 2013 U.S. EPA/OPP 2014a (p. 76). MRID 481043-04. Supplemental
Marine			
Sheepshead minnow (*Cyprinodon variegatus*), 0.16 g	Clethodim, 95.4% purity for 96 hours under static renewal conditions.	LC_{50} >124 mg a.i./L NOEC = 124 mg a.i./L	ECOTOX 2013 U.S. EPA/OPP 2014a (p. 77). MRID 484170-04. Acceptable

A5 Table 2: Chronic Toxicity

<table>
<tr><th>Species</th><th>Exposure</th><th>Response</th><th>Reference</th></tr>
<tr>
<td>Fathead minnow (Pimephales promelas), Initial exposure of <24 hour old embryos. 60 embryos/ concentration as 2 replicates of 30/ replicate</td>
<td>Technical grade clethodim, 95.75%
Nominal Concentrations: 0, 0 (solvent control), 0.01, 0.032, 0.1, 0.32, and 1.0 mg/L
Duration: 32 days.
No measured concentrations.
Solvent: ≤0.125 mL/L
Static renewal.</td>
<td>NOAEC = 0.010 mg a.i./L
LOAEC = 0.031 mg a.i./L, reduced survival.

Complete mortality by Day 32 at all nominal concentrations ≥0.032 mg/L. Other survival rates given below:
<table>
<tr><th>Exposure</th><th>% Mortality</th></tr>
<tr><td>Negative Control</td><td>67</td></tr>
<tr><td>Solvent Control</td><td>65</td></tr>
<tr><td>0.010 mg a.i./L</td><td>75</td></tr>
</table>
At 0.010 mg a.i./L, no effects on growth, length, and dry weights (DER, p. 12).

DER, p. 15: As concentrations of clethodim in the test solutions was not verified, this study is deemed scientifically sound but does not meet guideline requirements and is thus deemed supplemental.

U.S. EPA/OPP/ EFED 2014a, p. 77
Test concentrations were not measured; therefore the results were adjusted for purity of the technical grade material (95.7%). Time to hatch, hatching success, and post-hatch survival were not evaluated; effects on reproduction were not measured in this study.</td>
<td>Bidinotto 2003
MRID 481043-03

Also summarized in U.S. EPA/OPP/ EFED 2014a, p. 77</td>
</tr>
<tr>
<td>Rainbow trout (Oncorhynchus mykiss)</td>
<td>N/A
Estimated NOAEC based on acute-to-chronic ratio.</td>
<td>Estimated NOAEC = 0.002 mg a.i./L

Fathead LC_{50}: 110 mg a.i./L
Trout LC_{50}: 24.4 mg a.i./L.
Fathead NOAEC: 0.010 mg a.i./L

Estimated Trout NOAEC:
0.010 mg a.i./L x (24.4 mg a.i./L ÷ 110 mg a.i./L = 0.002218 mg a.i./L ≈ 0.002 mg a.i./L.

See Section 4.3.3.1.3 for discussion. The current Forest Service risk assessment does not use the approach taken by the EPA.</td>
<td>U.S. EPA/ OPP/EFED 2014a</td>
</tr>
</table>

Appendix 6: Toxicity to Aquatic Invertebrates

A6 Table 1: Acute Toxicity 194
A6 Table 2: Chronic toxicity 196
A6 Table 3: Mesocosm Studies 196

A6 Table 1: Acute Toxicity

Species	Exposure	Response	Reference
Freshwater			
Water flea (*Daphnia magna*), 1st instar (<24-hours old)	Clethodim, technical grade, 83.3%. Nominal concentrations of 6, 12, 25, 50 and 100 mg/L with untreated and acetone control. *…measured concentrations averaged 96 ±8.2% of nominal over the course of the 48-hour study.* EPA Note:"*… it cannot be determined from this study what the actual maximum toxicant exposure concentration was due to test substance insolubility*."	LC_{50}: >100 mg a.i./L NOEC: 50 mg a.i./L `Working Note: This study is not used quantitatively in the current Forest Service risk assessment.`	Forbis 1986, MRID 409745-30 Summary based on full DER. Classification from DER: ***"Invalid"*** *due to the absence of a verifiable LC_{50} value.* Not cited in U.S. EPA/OPP/ EFED 2007a,b, 2014a
Water flea (*Daphnia magna*), 1st instar (<24-hours old), 20 organisms per concentration.	**Clethodim formulation** (specified as Select 2 EC in DER), 25.6% purity, for 48 hours under static conditions. Concentrations: 5.5, 20, 35, 60, and 98 mg formulation/L.	DER and ECOTOX values: EC_{50} = 20.2 mg/L NOEC = 5.5 ppm Above concentrations are in units of formulation. Values corrected for a.i. EC_{50} = ≈5.17 mg a.i./L NOEC = ≈1.41 mg a.i./L NOEC based on mortality: 0/20. U.S. EPA/OPP/EFED (2007a,b) gives the EC_{50} as 5.7 mg a.i./L. U.S. EPA/OPP/EFED (2014a) gives the EC_{50} as 20.2 mg a.i./L, which appears to be incorrect.	Burgess et al., 1990, MRID 416851-01 Acceptable ECOTOX 2013 Cited in U.S. EPA/OPP/ EFED 2007a,b, 2014a

Appendix 6: Toxicity to Aquatic Invertebrates *(continued)*

Species	Exposure	Response	Reference
Marine			
Eastern oyster (*Crassostrea virginica*), 20 organisms per concentration.	Clethodim, 95.4% purity, 96 hours Nominal Test Concentrations: 0, 3.1, 6.3, 13, 25, and 50 mg a.i./L Mean Measured Test Concentrations: 0, 2.6, 5.4, 11, 31, and 56 mg a.i./L.	EC_{50} = 5.3 mg a.i./L based on reduced shell deposition which was seen at all treatment levels. NOAEC: Not determined.	Palmer et al. 2011a, MRID 485630-01 Supplemental Also summarized in U.S. EPA/ OPP/EFED 2014a
Mysid shrimp (*Americamysis bahia*), 5-days-old	Clethodim, 95.4% purity, for 96 hours under static renewal conditions. Nominal Test Concentrations: 0, 7.5, 15, 30, 60, 120 mg a.i./L Mean Measured Test Concentrations: 0, 7.1, 13, 28, 56, 116 mg a.i./L	ECOTOX values: EC_{50} = 33 ppm NOEC = 13 ppm Endpoint: Mortality The EC_{50} corrected for compound purity is 31.3 mg a.i./L. The NOEC corrected for purity is 12.4 mg a.i./L. *Mortality and sublethal effects were observed. sublethal effects included lethargy, surfacing, lying on the bottom of the test and chamber at 28, 56, and 166 mg a.i./L.*	Palmer et al. 2011b, MRID 484170-01 Acceptable Also summarized in ECOTOX 2013 and U.S. EPA/OPP/ EFED 2014a

Note on ECOTOX 2013: The EPA risk assessments give an LC_{50} for *Daphnia* of 5.7 mg a.i./L. This is close to the ECOTOX value correcting for purity – i.e., 20.2 x 0.256 = 5.17 mg a.i./L.

A6 Table 2: Chronic toxicity

Species	Exposure	Response	Reference
Water flea (*Daphnia magna*)	Clethodim (technical grade from Agan), 95.7% purity for 21 days (life-cycle) under static renewal conditions.	Statistically significant effect on growth (general) and reproduction (hatch): ECOTOX and EFED 2014a values: NOAEC =0.94 mg a.i./L LOAEC =3.0 mg a.i./L based on offspring production and body length of offspring. U.S. EPA/OPP/ EFED 2014a, p. 77: *Based on offspring production per female and total length of surviving adults. Survival and treatment-related delay in time to first brood released was observed at the 9.3 mg a.i./L treatment level.*	MRID 481043-05 ECOTOX 2013 U.S. EPA/OPP/ EFED 2014a **Note: U.S. EPA/OPP/ EFED 2007a,b indicated that no chronic studies in *Daphnia* are available. This appears to be an error.**

A6 Table 3: Mesocosm Studies

Species	Exposure	Response	Reference
Mixed plankton	Clethodim (specified only as a Select formulation), 500 liters fiberglass pools. Deposition at rates equivalent to 0.0007, 0.007 and 0.07 kg/ha	Significant (NOS) increase in copepod nauplii at 0.0007 kg/ha rate.	Perschbacher et al. 1997

Appendix 7: Toxicity to Aquatic Plants

A7 Table 1: Algae 197
A7 Table 2: Macrophytes 199

Working Note: ECOTOX toxicity data are reported as test material (not corrected for a.i.). For both the algae and *Lemna* bioassays, the test material specified as Select 2.0 EC in ECOTOX is characterized as 100% a.i. in both EFED risk assessments (U.S. EPA/OPP 2007a,b). Nonetheless, EFED does correct for 25.6% a.i. in the formulation. Thus, the test material appears to be the formulation and not 100% a.i.

Working Note: Have formulation vs a.i. for *Pseudokirchneriella subcapitata* and *Lemna*. For algae, the differences are not remarkable. For *Lemna*, the formulation is less toxic than technical grade clethodim when both values are expressed as a.i.

A7 Table 1: Algae

Species	Exposure	Response	Reference
Blue-green algae *Anabaena flos-aqua*	Clethodim (Select 2.0 EC formulation), 25.6% purity, for 5 days under static conditions.	Endpoint: Population abundance ECOTOX Values: EC_{50} = 65.58 ppm (formulation) NOEC = 22 ppm (formulation) DER and EFED Values* EC_{50} = 16.7 mg a.i./L NOEC = 5.6 mg a.i./L *Corrected for compound purity. The EC_{50} from ECOTOX is 16.79 mg a.i. when corrected for 25.6% a.i. formulation.	Thompson et al. 1991b MRID 420297-05 ECOTOX 2013 U.S. EPA/OPP/ EFED 2007a,b, 2014a Acceptable
Oscillatoria cf. *chalybea*	Clethodim (99% a.i.) at 10-fold concentrations form 0.1 µM (≈0.036 mg/L) to 1000 µM.	A concentration of 1000 µM (≈360 mg/L) is list as causing complete inhibition of growth (Table 2 of paper) and as the lowest concentration tested to cause inhibition of growth (Table 3 of paper). An NOEC of 36 mg/L can be inferred from the experimental design.	Schrader et al. 1998
Freshwater diatom *Navicula pelliculosa*	Clethodim (Select 2.0 EC formulation), 25.6% purity, for 5 days under static conditions.	Endpoint: Population abundance DER and ECOTOX Values: EC_{50} = 42 ppm (formulation) NOEC = 12 ppm (formulation) DER and EFED Values* EC_{50} = 11 mg a.i./L NOEC = 3.1 mg a.i./L *Corrected for compound purity. **Working Note: The NOEC of 3.1 mg a.i./L is used for sensitive species of algae.**	Thompson et al. 1991a MRID 420297-06 ECOTOX 2013 U.S. EPA/OPP/ EFED 2007a,b, 2014a Acceptable

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

Species	Exposure	Response	Reference
Green alga *Pseudokirchneriella subcapitata*, formerly *Selenastrum capricornutum*	Clethodim, 83.3% purity for 5 days under static conditions.	Endpoint: Population abundance DER ECOTOX Values: EC_{50} = >11.4 ppm NOEC = 8 ppm (nominal) EFED Values* EC_{50} = >11.4 mg a.i./L NOEC = >11.4 mg a.i./L (measured) *The EFED assessments correctly use the measured rather than nominal concentrations. The relationship between the nominal (lower) and measured (higher) concentrations is somewhat unusual and is not noted in the DER. This does not impact the current risk assessment because this is not the most sensitive species.	Forbis and Blasberg 1990 MRID 416851-06 Acceptable ECOTOX 2013 U.S. EPA/OPP/ EFED 2007a,b, 2014a
Green alga *Pseudokirchneriella subcapitata*, formerly *Selenastrum capricornutum*	Clethodim (99% a.i.) at 10-fold concentrations form 0.1 µM (≈0.036 mg/L) to 1000 µM.	A concentration of 1000 µM (≈360 mg/L) is list as causing complete inhibition of growth (Table 2 of paper) and as the lowest concentration tested to cause inhibition of growth (Table 3 of paper). An NOEC of 36 mg/L can be inferred from the experimental design.	Schrader et al. 1998
Green alga *Pseudokirchneriella subcapitata*, formerly *Selenastrum capricornutum*	Clethodim (**Select 2.0 EC formulation**), 25.6% purity, for 5 days under static conditions.	Endpoint: Population abundance DER and ECOTOX Values: EC_{50} = 76 ppm (formulation) NOEC = 43.5 ppm (formulation) DER and EFED Values* EC_{50} = 19.5 mg a.i./L NOEC = 11.1 mg a.i./L *Corrected for a.i. in formulation. **Working Note: The NOEC of 11.1 mg a.i./L is used for tolerant species of algae. Higher values are reported in studies from Ma but these do not involve U.S. formulations. See Section 4.3.3.4 for discussion.**	Grimstead et al. 1991 MRID 420297-03 ECOTOX 2013 U.S. EPA/OPP/ EFED 2007a,b, 2014a Acceptable
Green alga *Chlorella pyrenoidosa*	Clethodim (12% EC formulation), 96-hour exposures	EC_{50}: 90.3507 mg a.i./L	Ma and Liang 2001 [1]
Green alga *Chlorella vulgaris*,	Clethodim (12% EC formulation), 96-hour exposures	EC_{50}: 38.7047 mg a.i./L	Ma et al. 2002 [1]
Green alga *Scenedesmus obliqnuus*	Clethodim (12% EC formulation), 96-hour exposures	EC_{50}: 56.8057 mg a.i./L	Ma and Liang 2001 [1]
Green alga *Scenedesmus quadricauda*, (Green alga)	Clethodim (12% EC formulation), 96-hour exposures	EC_{50}: 79.6 mg a.i./L	Ma et al. 2004 [1]
Green alga *Raphidocelis subcapitata*	Clethodim (12% EC formulation), 96-hour exposures	EC_{50}: 22.8676 mg a.i./L	Ma et al. 2006 [1]

Species	Exposure	Response	Reference
Marine diatom *Skeletonema costatum*	Clethodim (Select 2.0 EC formulation), 25.6% purity, for 5 days under static conditions. Concentrations: 11.4, 20.6, 37.4, 60.1, and 105 mg/L.	Endpoint: Population abundance ECOTOX Values: EC_{50} = 33 ppm (formulation) NOEC = 21 ppm (formulation) DER and EFED Values* EC_{50} = 8.6 mg a.i./L NOEC = 5.4 mg a.i./L *Corrected % a.i. in formulation.	Grimes et al. 1991 MRID 420297-04 Acceptable ECOTOX 2013 U.S. EPA/OPP/ EFED 2007a,b, 2014a

[1] The papers by Ma and coworkers do not explicitly state that the results are expressed in units of a.i. The papers, however, report all values in both mg/L and in molar concentrations (which would apply only to clethodim and not the formulation). For example, Ma et al. 2002 report the EC_{50} for clethodim as 38.7047mg/L and 1.08 x 10^{-4} mol/L. Taking the MW for clethodim as 359.91 g/L, the molar concentration corresponds to 38.87 mg/L [1.08 x 10^{-4} mol/L x 359.91 g/L = 0.03887 g/L = 38.87 mg/L]. The U.S. EPA/OPP/EFED (2014a, p. 78) appears to inappropriately correct the EC_{50} reported in Ma et al. 2002 and Ma et al. 2006 for the proportion of a.i. in the formulation (0.12). Continuing with the example from Ma et al. 2002, the U.S. EPA/OPP/EFED (2014a, p. 78) reports the EC50 as 4.6 [38.7047mg/L x 0.12 = 4.6446 mg/L].

A7 Table 2: Macrophytes

Species	Exposure	Response	Reference
Inflated duckweed (*Lemna gibba*)	Clethodim, 82.4% purity, for 14 days under static conditions.	Endpoint: Population abundance DER and ECOTOX Values: EC_{50} = 1.34 ppm (gross a.i.) NOEC = 0.37 ppm (gross a.i.) EFED Values* EC_{50} = 1.1 mg a.i./L NOEC = 0.30 mg a.i./L *EFED values are corrected for compound purity. DER and EXCOTOX value given as TGAI (including impurities).	Rhodes and Hughes 1991 MRID 420297-01 ECOTOX 2013 U.S. EPA/OPP 2007a,b, 2014a Acceptable
Inflated duckweed (*Lemna gibba*)	Clethodim (**Select 2.0 EC formulation**), 25.6% purity, for 14 days under static conditions.	Endpoint: Population abundance ECOTOX Values: EC_{50} = 166 ppm (42.5 mg a.i./L) NOEC = 4.1 ppm (1.05 mg a.i./L). EFED Values* EC_{50} = 42.5 mg a.i./L NOEC = 1.1 mg a.i./L *Corrected for %a.i in formulation.	ECOTOX 2013 U.S. EPA/OPP/ EFED 2007a,b, 2014a MRID 420297-02 Supplemental

Appendix 8: Gleams-Driver Modeling, 1 Application

One Application

Table 1: Effective Offsite Application Rate (lb/acre)

Site	Clay	Loam	Sand
Dry and Warm Location	0.000137 (0 - 0.0036)	0 (0 - 0.00068)	0 (0 - 3.30E-06)
Dry and Temperate Location	0.00033 (0 - 0.0101)	0 (0 - 0.00176)	0 (0 - 1.68E-07)
Dry and Cold Location	0.00195 (0 - 0.011)	0 (0 - 0.00124)	0 (0 - 0)
Average Rainfall and Warm Location	0.008 (0.00076 - 0.036)	0.00129 (2.86E-05 - 0.0141)	1.18E-06 (0 - 0.000171)
Average Rainfall and Temperate Location	0.012 (0.00113 - 0.039)	0.0024 (0.000103 - 0.0157)	4.00E-07 (0 - 0.000163)
Average Rainfall and Cool Location	0.0293 (0.0041 - 0.074)	0.0055 (0.00011 - 0.0207)	2.28E-09 (0 - 0.000097)
Wet and Warm Location	0.0245 (0.00246 - 0.15)	0.0064 (0.000152 - 0.054)	3.70E-06 (2.41E-09 - 0.00181)
Wet and Temperate Location	0.0291 (0.0072 - 0.084)	0.0043 (0.000186 - 0.0182)	4.00E-07 (0 - 0.000213)
Wet and Cool Location	0.026 (0.00299 - 0.072)	0.0047 (2.17E-05 - 0.0247)	7.90E-09 (0 - 0.000137)
		Average of Central Values:	0.00577
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.15
		Summary of Values:	0.0058 (0 - 0.15)

One Application

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.226 (0.219 - 0.239)	0.211 (0.202 - 0.22)	0.209 (0.202 - 0.222)
Dry and Temperate Location	0.269 (0.258 - 0.293)	0.253 (0.243 - 0.267)	0.248 (0.229 - 0.264)
Dry and Cold Location	0.38 (0.37 - 0.39)	0.35 (0.34 - 0.36)	0.35 (0.32 - 0.35)
Average Rainfall and Warm Location	0.218 (0.209 - 0.231)	0.2 (0.192 - 0.21)	0.194 (0.191 - 0.2)
Average Rainfall and Temperate Location	0.253 (0.214 - 0.273)	0.23 (0.195 - 0.252)	0.2 (0.191 - 0.23)
Average Rainfall and Cool Location	0.283 (0.225 - 0.306)	0.259 (0.199 - 0.284)	0.212 (0.192 - 0.262)
Wet and Warm Location	0.208 (0.204 - 0.223)	0.192 (0.189 - 0.202)	0.191 (0.188 - 0.192)
Wet and Temperate Location	0.217 (0.206 - 0.257)	0.193 (0.191 - 0.222)	0.192 (0.191 - 0.195)
Wet and Cool Location	0.227 (0.207 - 0.296)	0.202 (0.191 - 0.253)	0.192 (0.191 - 0.199)
		Average of Central Values:	0.2355
		25th Percentile of Lower Bounds:	0.191
		Maximum Value:	0.39
		Summary of Values:	0.236 (0.191 - 0.39)

One Application

Table 3: Concentration in Top 36 Inches of Soil (ppm)

Site	Clay	Loam	Sand
Dry and Warm Location	0.075 (0.073 - 0.08)	0.07 (0.067 - 0.073)	0.07 (0.067 - 0.074)
Dry and Temperate Location	0.09 (0.086 - 0.098)	0.084 (0.081 - 0.089)	0.083 (0.08 - 0.088)
Dry and Cold Location	0.126 (0.124 - 0.128)	0.116 (0.114 - 0.119)	0.116 (0.114 - 0.118)
Average Rainfall and Warm Location	0.075 (0.072 - 0.079)	0.069 (0.067 - 0.073)	0.068 (0.065 - 0.072)
Average Rainfall and Temperate Location	0.09 (0.085 - 0.094)	0.082 (0.078 - 0.088)	0.081 (0.065 - 0.087)
Average Rainfall and Cool Location	0.1 (0.096 - 0.104)	0.094 (0.09 - 0.098)	0.091 (0.066 - 0.098)
Wet and Warm Location	0.077 (0.069 - 0.081)	0.07 (0.064 - 0.075)	0.064 (0.064 - 0.071)
Wet and Temperate Location	0.094 (0.071 - 0.102)	0.081 (0.064 - 0.092)	0.065 (0.064 - 0.083)
Wet and Cool Location	0.109 (0.077 - 0.116)	0.1 (0.064 - 0.108)	0.065 (0.064 - 0.097)
		Average of Central Values:	0.0854
		25th Percentile of Lower Bounds:	0.065
		Maximum Value:	0.128
		Summary of Values:	0.085 (0.065 - 0.128)

One Application

Table 4: Maximum Penetration into Soil Column (inches)

Site	Clay	Loam	Sand
Dry and Warm Location	18 (12 - 36)	18 (8 - 36)	18 (8 - 36)
Dry and Temperate Location	24 (8 - 36)	18 (8 - 36)	30 (8 - 36)
Dry and Cold Location	24 (18 - 36)	30 (18 - 36)	36 (24 - 36)
Average Rainfall and Warm Location	36 (30 - 36)	36 (30 - 36)	36 (36 - 36)
Average Rainfall and Temperate Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Average Rainfall and Cool Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Warm Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Temperate Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Cool Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
		Average of Central Values:	32
		25th Percentile of Lower Bounds:	18
		Maximum Value:	36
		Summary of Values:	32 (18 - 36)

One Application

Table 5: Stream, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.5	0	0
	(0 - 7)	(0 - 1.68)	(0 - 0.1)
Dry and Temperate	0.8	0	0
Location	(0 - 27.2)	(0 - 6)	(0 - 3.3)
Dry and Cold Location	6.1	0	0.0009
	(0 - 23.4)	(0 - 4.1)	(0 - 12.6)
Average Rainfall and	11.7	3.4	6.7
Warm Location	(1.52 - 42)	(0.23 - 21.3)	(0.23 - 50)
Average Rainfall and	15.5	4	12.7
Temperate Location	(4.8 - 50)	(0.4 - 26.4)	(1 - 110)
Average Rainfall and Cool	29.1	10.4	22.9
Location	(10 - 60)	(2.23 - 46)	(1.71 - 105)
Wet and Warm Location	27.5	13.7	22.6
	(6.9 - 70)	(2.4 - 30.2)	(4.8 - 90)
Wet and Temperate	29.8	14.4	24.8
Location	(13.8 - 58)	(2.66 - 52)	(10.7 - 116)
Wet and Cool Location	30.5	21.6	53
	(11.9 - 58)	(5.4 - 60)	(26.4 - 132)
		Average of Central Values:	13.4
		25th Percentile of Lower Bounds:	0
		Maximum Value:	132
		Summary of Values:	13.4 (0 - 132)

One Application

Table 6: Stream, Annual Average Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.0016 (0 - 0.03)	0 (0 - 0.005)	0 (0 - 0.0011)
Dry and Temperate Location	0.004 (0 - 0.08)	0 (0 - 0.017)	0 (0 - 0.014)
Dry and Cold Location	0.021 (0 - 0.09)	0 (0 - 0.012)	0.000005 (0 - 0.16)
Average Rainfall and Warm Location	0.08 (0.027 - 0.29)	0.03 (0.0017 - 0.6)	0.27 (0.007 - 2.16)
Average Rainfall and Temperate Location	0.13 (0.04 - 1.83)	0.04 (0.006 - 1.79)	0.8 (0.031 - 4.5)
Average Rainfall and Cool Location	0.22 (0.09 - 2.59)	0.1 (0.011 - 3.2)	1.56 (0.09 - 5.9)
Wet and Warm Location	0.6 (0.09 - 3.3)	0.7 (0.06 - 2.95)	2.52 (0.5 - 4.4)
Wet and Temperate Location	1.01 (0.22 - 3.4)	1.84 (0.14 - 4.1)	2.71 (1.47 - 5.7)
Wet and Cool Location	2.53 (0.4 - 5.5)	3.2 (0.7 - 6)	4.7 (3.5 - 6.1)
		Average of Central Values:	0.854
		25th Percentile of Lower Bounds:	0
		Maximum Value:	6.1
		Summary of Values:	0.85 (0 - 6.1)

One Application

Table 7: Pond, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.15	0	0
	(0 - 4)	(0 - 0.8)	(0 - 0.2)
Dry and Temperate	0.4	0	0
Location	(0 - 11)	(0 - 1.95)	(0 - 2.75)
Dry and Cold Location	2.01	0	0.0005
	(0 - 11.6)	(0 - 1.37)	(0 - 14.3)
Average Rainfall and	13	5.5	38
Warm Location	(3.4 - 64)	(0.4 - 70)	(0.8 - 304)
Average Rainfall and	19.1	6	70
Temperate Location	(5.8 - 169)	(1 - 178)	(3.7 - 570)
Average Rainfall and Cool	36	14.7	147
Location	(11.1 - 221)	(2.28 - 320)	(7.9 - 650)
Wet and Warm Location	43	42	159
	(8.9 - 246)	(4.5 - 214)	(32 - 500)
Wet and Temperate	46	62	83
Location	(17.5 - 114)	(6.2 - 217)	(44 - 440)
Wet and Cool Location	106	121	160
	(19.5 - 223)	(35 - 238)	(87 - 268)
		Average of Central Values:	43.5
		25th Percentile of Lower Bounds:	0
		Maximum Value:	650
		Summary of Values:	43.5 (0 - 650)

One Application

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.05	0	0
	(0 - 1.68)	(0 - 0.4)	(0 - 0.14)
Dry and Temperate	0.14	0	0
Location	(0 - 5.8)	(0 - 1)	(0 - 1.71)
Dry and Cold Location	0.9	0	0.0002
	(0 - 4.9)	(0 - 0.6)	(0 - 5.8)
Average Rainfall and	7.3	2.75	18.1
Warm Location	(2.02 - 34)	(0.19 - 50)	(0.4 - 173)
Average Rainfall and	11.6	3.5	50
Temperate Location	(3.6 - 87)	(0.5 - 132)	(1.5 - 410)
Average Rainfall and Cool	20.9	7.9	71
Location	(7.2 - 135)	(1.23 - 177)	(2.44 - 420)
Wet and Warm Location	18.8	21.1	74
	(4.2 - 117)	(1.8 - 123)	(17.4 - 204)
Wet and Temperate	22	33	45
Location	(7.7 - 66)	(2.96 - 90)	(25.7 - 180)
Wet and Cool Location	37	50	87
	(5.1 - 118)	(8.2 - 144)	(31 - 149)
		Average of Central Values:	21.6
		25th Percentile of Lower Bounds:	0
		Maximum Value:	420
		Summary of Values:	21.6 (0 - 420)

Appendix 9: Gleams-Driver Modeling, 2 Applications

Two Applications

Table 1: Effective Offsite Application Rate (lb/acre)

Site	Clay	Loam	Sand
Dry and Warm Location	0.00031	0	0
	(0 - 0.0082)	(0 - 0.00124)	(0 - 0.000004)
Dry and Temperate	0.00077	0	0
Location	(0 - 0.015)	(0 - 0.00221)	(0 - 6.00E-07)
Dry and Cold Location	0.0036	0	0
	(0 - 0.0223)	(0 - 0.00258)	(0 - 0)
Average Rainfall and	0.0162	0.00293	3.06E-06
Warm Location	(0.00137 - 0.097)	(0.000063 - 0.036)	(0 - 0.00033)
Average Rainfall and	0.0271	0.0049	0.000001
Temperate Location	(0.0069 - 0.079)	(0.000146 - 0.037)	(0 - 0.00048)
Average Rainfall and Cool	0.067	0.0139	8.40E-10
Location	(0.0167 - 0.137)	(0.00057 - 0.041)	(0 - 0.000093)
Wet and Warm Location	0.06	0.0153	1.58E-05
	(0.0062 - 0.195)	(0.000146 - 0.105)	(8.30E-10 - 0.00184)
Wet and Temperate	0.052	0.012	1.05E-06
Location	(0.0128 - 0.126)	(0.0014 - 0.057)	(0 - 0.000195)
Wet and Cool Location	0.058	0.0096	2.72E-08
	(0.0124 - 0.153)	(0.00039 - 0.053)	(0 - 0.00035)
		Average of Central Values:	0.01273
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.195
		Summary of Values:	0.0127 (0 - 0.195)

Two Applications

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.44 (0.43 - 0.48)	0.41 (0.39 - 0.45)	0.41 (0.39 - 0.45)
Dry and Temperate Location	0.54 (0.51 - 0.61)	0.5 (0.47 - 0.57)	0.49 (0.46 - 0.55)
Dry and Cold Location	0.75 (0.74 - 0.77)	0.7 (0.69 - 0.71)	0.69 (0.67 - 0.71)
Average Rainfall and Warm Location	0.42 (0.41 - 0.48)	0.39 (0.37 - 0.46)	0.37 (0.37 - 0.45)
Average Rainfall and Temperate Location	0.5 (0.43 - 0.55)	0.45 (0.38 - 0.49)	0.39 (0.37 - 0.45)
Average Rainfall and Cool Location	0.56 (0.44 - 0.61)	0.5 (0.39 - 0.57)	0.42 (0.38 - 0.53)
Wet and Warm Location	0.4 (0.38 - 0.43)	0.37 (0.35 - 0.38)	0.36 (0.314 - 0.37)
Wet and Temperate Location	0.42 (0.39 - 0.5)	0.39 (0.35 - 0.45)	0.37 (0.249 - 0.38)
Wet and Cool Location	0.49 (0.41 - 0.61)	0.4 (0.38 - 0.54)	0.38 (0.38 - 0.41)
		Average of Central Values:	0.463
		25th Percentile of Lower Bounds:	0.375
		Maximum Value:	0.77
		Summary of Values:	0.46 (0.375 - 0.77)

Two Applications

Table 3: Concentration in Top 12 Inches of Soil (ppm)

Site	Clay	Loam	Sand
Dry and Warm Location	0.148 (0.143 - 0.16)	0.136 (0.131 - 0.15)	0.136 (0.131 - 0.15)
Dry and Temperate Location	0.179 (0.171 - 0.204)	0.167 (0.158 - 0.189)	0.166 (0.156 - 0.187)
Dry and Cold Location	0.251 (0.248 - 0.256)	0.232 (0.229 - 0.237)	0.232 (0.228 - 0.237)
Average Rainfall and Warm Location	0.144 (0.139 - 0.165)	0.133 (0.128 - 0.153)	0.132 (0.125 - 0.153)
Average Rainfall and Temperate Location	0.177 (0.167 - 0.188)	0.163 (0.151 - 0.174)	0.158 (0.129 - 0.175)
Average Rainfall and Cool Location	0.2 (0.192 - 0.221)	0.185 (0.176 - 0.201)	0.184 (0.141 - 0.202)
Wet and Warm Location	0.147 (0.132 - 0.157)	0.133 (0.121 - 0.143)	0.123 (0.12 - 0.134)
Wet and Temperate Location	0.182 (0.138 - 0.196)	0.168 (0.127 - 0.184)	0.127 (0.12 - 0.165)
Wet and Cool Location	0.221 (0.172 - 0.235)	0.197 (0.131 - 0.217)	0.136 (0.127 - 0.196)
		Average of Central Values:	0.1688
		25th Percentile of Lower Bounds:	0.1285
		Maximum Value:	0.256
		Summary of Values:	0.169 (0.1285 - 0.256)

Two Applications

Table 4: Maximum Penetration into Soil Column (inches)

Site	Clay	Loam	Sand
Dry and Warm Location	18 (12 - 36)	18 (8 - 36)	18 (8 - 36)
Dry and Temperate Location	24 (8 - 36)	18 (8 - 36)	30 (8 - 36)
Dry and Cold Location	30 (18 - 36)	30 (18 - 36)	36 (24 - 36)
Average Rainfall and Warm Location	36 (30 - 36)	36 (36 - 36)	36 (36 - 36)
Average Rainfall and Temperate Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Average Rainfall and Cool Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Warm Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Temperate Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Cool Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
		Average of Central Values:	32.2
		25th Percentile of Lower Bounds:	18
		Maximum Value:	36
		Summary of Values:	32.2 (18 - 36)

Two Applications

Table 5: Stream, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	1	0	0
	(0 - 22.3)	(0 - 2.55)	(0 - 0.7)
Dry and Temperate	2.05	0	0
Location	(0 - 32)	(0 - 4.4)	(0 - 6.1)
Dry and Cold Location	12.6	0	0.0024
	(0 - 52)	(0 - 8.4)	(0 - 4.9)
Average Rainfall and	22.4	6.7	10.1
Warm Location	(4.4 - 66)	(0.6 - 35)	(0.6 - 106)
Average Rainfall and	28.8	10.4	25
Temperate Location	(11 - 71)	(1.3 - 60)	(1.5 - 168)
Average Rainfall and Cool	69	25.2	57
Location	(20.4 - 144)	(4.5 - 68)	(3.9 - 211)
Wet and Warm Location	45	23.4	47
	(21.9 - 94)	(9.4 - 96)	(9.4 - 149)
Wet and Temperate	42	21.6	56
Location	(25.8 - 66)	(5.6 - 52)	(21.8 - 218)
Wet and Cool Location	59	43	92
	(22.8 - 118)	(13.3 - 98)	(49 - 270)
		Average of Central Values:	25.9
		25th Percentile of Lower Bounds:	0
		Maximum Value:	270
		Summary of Values:	25.9 (0 - 270)

Two Applications

Table 6: Stream, Annual Average Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.004	0	0
	(0 - 0.1)	(0 - 0.007)	(0 - 0.0023)
Dry and Temperate	0.008	0	0
Location	(0 - 0.11)	(0 - 0.013)	(0 - 0.05)
Dry and Cold Location	0.04	0	0.000008
	(0 - 0.18)	(0 - 0.024)	(0 - 0.06)
Average Rainfall and	0.17	0.06	0.4
Warm Location	(0.05 - 0.9)	(0.01 - 1.01)	(0.012 - 4.2)
Average Rainfall and	0.27	0.09	1.93
Temperate Location	(0.1 - 1.42)	(0.012 - 4.2)	(0.05 - 8.4)
Average Rainfall and Cool	0.5	0.17	3.7
Location	(0.2 - 4.3)	(0.04 - 5.8)	(0.17 - 13)
Wet and Warm Location	1.27	1.63	4.6
	(0.29 - 7.1)	(0.15 - 8.1)	(1.27 - 10.4)
Wet and Temperate	1.78	2.36	5.6
Location	(0.31 - 7.1)	(0.22 - 7)	(3.2 - 12)
Wet and Cool Location	3.8	6.4	9.3
	(0.8 - 10.2)	(0.9 - 11.5)	(7.3 - 11.5)
		Average of Central Values:	1.63
		25th Percentile of Lower Bounds:	0
		Maximum Value:	13
		Summary of Values:	1.63 (0 - 13)

Two Applications

Table 7: Pond, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.3 (0 - 11.5)	0 (0 - 1.46)	0 (0 - 0.6)
Dry and Temperate Location	0.8 (0 - 16.2)	0 (0 - 2.43)	0 (0 - 6.7)
Dry and Cold Location	3.9 (0 - 24.4)	0 (0 - 2.86)	0.001 (0 - 5)
Average Rainfall and Warm Location	27.3 (6.7 - 119)	10.9 (1.5 - 165)	50 (1.95 - 600)
Average Rainfall and Temperate Location	37 (14.3 - 153)	15.4 (2.18 - 420)	161 (6.2 - 1050)
Average Rainfall and Cool Location	79 (24.8 - 410)	38 (6.3 - 590)	320 (18.6 - 1160)
Wet and Warm Location	79 (20.6 - 490)	88 (13.1 - 730)	340 (71 - 910)
Wet and Temperate Location	87 (30.5 - 234)	91 (10.9 - 258)	183 (86 - 900)
Wet and Cool Location	154 (33 - 380)	259 (49 - 480)	320 (166 - 540)
		Average of Central Values:	86.8
		25th Percentile of Lower Bounds:	0
		Maximum Value:	1160
		Summary of Values:	86.8 (0 - 1160)

Two Applications

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.11	0	0
	(0 - 4.9)	(0 - 0.4)	(0 - 0.3)
Dry and Temperate	0.4	0	0
Location	(0 - 8.3)	(0 - 1.21)	(0 - 1.43)
Dry and Cold Location	1.59	0	0.0004
	(0 - 10.1)	(0 - 1.18)	(0 - 1.49)
Average Rainfall and	14.7	5.4	29
Warm Location	(4 - 57)	(1 - 81)	(1 - 360)
Average Rainfall and	23.1	9.7	103
Temperate Location	(9.3 - 83)	(1.34 - 330)	(2.87 - 590)
Average Rainfall and Cool	49	20.9	171
Location	(15.8 - 192)	(3.9 - 291)	(7.1 - 790)
Wet and Warm Location	34	45	131
	(10.1 - 154)	(5.6 - 257)	(34 - 380)
Wet and Temperate	42	49	95
Location	(13 - 119)	(5.7 - 140)	(49 - 370)
Wet and Cool Location	51	92	163
	(9 - 202)	(12 - 259)	(57 - 304)
		Average of Central Values:	41.8
		25th Percentile of Lower Bounds:	0
		Maximum Value:	790
		Summary of Values:	41.8 (0 - 790)

Appendix 10: Gleams-Driver Modeling, 4 Applications

Four Applications

Table 1: Effective Offsite Application Rate (lb/acre)

Site	Clay	Loam	Sand
Dry and Warm Location	0.00106	0	0
	(0 - 0.0256)	(0 - 0.0047)	(0 - 2.11E-05)
Dry and Temperate	0.00148	0	0
Location	(0 - 0.0285)	(0 - 0.0053)	(0 - 3.90E-06)
Dry and Cold Location	0.0071	0	0
	(0 - 0.044)	(0 - 0.00259)	(0 - 0)
Average Rainfall and	0.033	0.0071	4.50E-06
Warm Location	(0.0034 - 0.16)	(0.000171 - 0.059)	(0 - 0.00095)
Average Rainfall and	0.053	0.0105	0.000001
Temperate Location	(0.0145 - 0.159)	(0.00053 - 0.05)	(0 - 0.00102)
Average Rainfall and Cool	0.087	0.014	1.76E-08
Location	(0.0178 - 0.201)	(0.00092 - 0.06)	(0 - 0.00059)
Wet and Warm Location	0.11	0.0286	0.000046
	(0.0164 - 0.296)	(0.00169 - 0.113)	(3.20E-09 - 0.00208)
Wet and Temperate	0.084	0.0208	3.50E-06
Location	(0.0277 - 0.18)	(0.00192 - 0.07)	(0 - 0.00111)
Wet and Cool Location	0.147	0.028	1.51E-07
	(0.0187 - 0.287)	(0.00066 - 0.081)	(0 - 0.00233)
		Average of Central Values:	0.02343
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.296
		Summary of Values:	0.0234 (0 - 0.296)

Four Applications

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.84	0.76	0.77
	(0.78 - 0.98)	(0.72 - 0.91)	(0.71 - 0.93)
Dry and Temperate	1.06	0.96	0.95
Location	(0.99 - 1.16)	(0.91 - 1.08)	(0.85 - 1.1)
Dry and Cold Location	1.5	1.39	1.38
	(1.47 - 1.53)	(1.36 - 1.42)	(1.33 - 1.41)
Average Rainfall and	0.77	0.71	0.69
Warm Location	(0.73 - 0.88)	(0.67 - 0.83)	(0.66 - 0.81)
Average Rainfall and	0.95	0.86	0.73
Temperate Location	(0.78 - 1.04)	(0.71 - 0.96)	(0.62 - 0.86)
Average Rainfall and Cool	1.03	0.9	0.7
Location	(0.73 - 1.18)	(0.62 - 1.09)	(0.51 - 0.95)
Wet and Warm Location	0.7	0.64	0.55
	(0.57 - 0.77)	(0.5 - 0.69)	(0.33 - 0.66)
Wet and Temperate	0.8	0.73	0.69
Location	(0.68 - 0.95)	(0.64 - 0.86)	(0.41 - 0.73)
Wet and Cool Location	0.96	0.79	0.76
	(0.82 - 1.21)	(0.75 - 1.07)	(0.74 - 0.89)
		Average of Central Values:	0.873
		25th Percentile of Lower Bounds:	0.63
		Maximum Value:	1.53
		Summary of Values:	0.87 (0.63 - 1.53)

Four Applications

Table 3: Concentration in Top 36 Inches of Soil (ppm)

Site	Clay	Loam	Sand
Dry and Warm Location	0.278 (0.261 - 0.33)	0.254 (0.24 - 0.305)	0.256 (0.238 - 0.31)
Dry and Temperate Location	0.35 (0.33 - 0.39)	0.32 (0.303 - 0.36)	0.32 (0.301 - 0.37)
Dry and Cold Location	0.5 (0.49 - 0.51)	0.46 (0.46 - 0.47)	0.46 (0.45 - 0.47)
Average Rainfall and Warm Location	0.267 (0.252 - 0.299)	0.246 (0.23 - 0.278)	0.244 (0.222 - 0.285)
Average Rainfall and Temperate Location	0.34 (0.32 - 0.36)	0.313 (0.295 - 0.33)	0.301 (0.244 - 0.33)
Average Rainfall and Cool Location	0.39 (0.36 - 0.41)	0.36 (0.307 - 0.38)	0.34 (0.25 - 0.38)
Wet and Warm Location	0.26 (0.243 - 0.285)	0.242 (0.223 - 0.262)	0.225 (0.181 - 0.248)
Wet and Temperate Location	0.35 (0.264 - 0.39)	0.32 (0.245 - 0.35)	0.248 (0.233 - 0.301)
Wet and Cool Location	0.43 (0.305 - 0.47)	0.39 (0.254 - 0.45)	0.269 (0.252 - 0.4)
		Average of Central Values:	0.323
		25th Percentile of Lower Bounds:	0.2415
		Maximum Value:	0.51
		Summary of Values:	0.32 (0.2415 - 0.51)

Four Applications

Table 4: Maximum Penetration into Soil Column (inches)

Site	Clay	Loam	Sand
Dry and Warm Location	18 (12 - 36)	18 (8 - 36)	18 (8 - 36)
Dry and Temperate Location	24 (8 - 36)	24 (8 - 36)	30 (8 - 36)
Dry and Cold Location	30 (18 - 36)	30 (18 - 36)	36 (30 - 36)
Average Rainfall and Warm Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Average Rainfall and Temperate Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Average Rainfall and Cool Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Warm Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Temperate Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Cool Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
		Average of Central Values:	32.4
		25th Percentile of Lower Bounds:	18
		Maximum Value:	36
		Summary of Values:	32.4 (18 - 36)

Four Applications

Table 5: Stream, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	4	0	0
	(0 - 40)	(0 - 9.8)	(0 - 0.4)
Dry and Temperate	3.6	0	0
Location	(0 - 48)	(0 - 11.4)	(0 - 12.2)
Dry and Cold Location	20.1	0	0.005
	(0 - 99)	(0 - 16.1)	(0 - 24.8)
Average Rainfall and	43	15.7	28.2
Warm Location	(9.4 - 126)	(1.18 - 60)	(1.26 - 222)
Average Rainfall and	44	16.5	69
Temperate Location	(13.9 - 106)	(2.79 - 103)	(4.5 - 380)
Average Rainfall and Cool	70	30.8	105
Location	(30.6 - 130)	(8.4 - 178)	(7.3 - 298)
Wet and Warm Location	59	32	86
	(27.9 - 104)	(12.5 - 105)	(18 - 304)
Wet and Temperate	61	41	105
Location	(28.6 - 97)	(11.5 - 129)	(46 - 288)
Wet and Cool Location	122	99	202
	(46 - 264)	(25.6 - 223)	(104 - 440)
		Average of Central Values:	46.6
		25th Percentile of Lower Bounds:	0
		Maximum Value:	440
		Summary of Values:	46.6 (0 - 440)

Four Applications

Table 6: Stream, Annual Average Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.012 (0 - 0.2)	0 (0 - 0.04)	0 (0 - 0.0016)
Dry and Temperate Location	0.018 (0 - 0.2)	0 (0 - 0.04)	0 (0 - 0.12)
Dry and Cold Location	0.08 (0 - 0.3)	0 (0 - 0.05)	0.00002 (0 - 0.3)
Average Rainfall and Warm Location	0.4 (0.12 - 1.68)	0.13 (0.011 - 2.14)	1.06 (0.04 - 9.7)
Average Rainfall and Temperate Location	0.5 (0.15 - 4.4)	0.16 (0.04 - 8.5)	4.2 (0.19 - 16.5)
Average Rainfall and Cool Location	0.7 (0.4 - 8.6)	0.7 (0.08 - 12)	7 (0.26 - 22.1)
Wet and Warm Location	2.3 (0.5 - 12.3)	3.12 (0.32 - 12.6)	8.7 (2.63 - 21.1)
Wet and Temperate Location	4.3 (0.6 - 13.6)	5.1 (0.6 - 15)	11.2 (6.1 - 19.5)
Wet and Cool Location	7.4 (1.44 - 21)	14.9 (2.18 - 24)	19.3 (14.4 - 24.4)
		Average of Central Values:	3.38
		25th Percentile of Lower Bounds:	0
		Maximum Value:	24.4
		Summary of Values:	3.38 (0 - 24.4)

Four Applications

Table 7: Pond, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	1.18	0	0
	(0 - 29)	(0 - 5.4)	(0 - 0.3)
Dry and Temperate	1.62	0	0
Location	(0 - 30.9)	(0 - 5.7)	(0 - 15.2)
Dry and Cold Location	7.4	0	0.0016
	(0 - 46)	(0 - 5.5)	(0 - 24.2)
Average Rainfall and	58	24.7	144
Warm Location	(15.1 - 241)	(1.93 - 299)	(4.8 - 1480)
Average Rainfall and	72	32	390
Temperate Location	(20 - 380)	(5.6 - 840)	(16.5 - 2160)
Average Rainfall and Cool	109	76	640
Location	(62 - 740)	(13.5 - 1130)	(25.9 - 2210)
Wet and Warm Location	148	160	550
	(62 - 670)	(36 - 810)	(110 - 1880)
Wet and Temperate	177	207	360
Location	(38 - 470)	(34 - 450)	(196 - 1230)
Wet and Cool Location	297	550	650
	(67 - 820)	(122 - 960)	(350 - 1130)
		Average of Central Values:	172
		25th Percentile of Lower Bounds:	0
		Maximum Value:	2210
		Summary of Values:	172 (0 - 2210)

Four Applications

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.31	0	0
	(0 - 10.4)	(0 - 2.36)	(0 - 0.14)
Dry and Temperate	0.7	0	0
Location	(0 - 9.5)	(0 - 2.95)	(0 - 9)
Dry and Cold Location	3.3	0	0.0006
	(0 - 19.5)	(0 - 2.27)	(0 - 8.3)
Average Rainfall and	32	12.4	74
Warm Location	(8.6 - 119)	(1.27 - 174)	(2.13 - 760)
Average Rainfall and	46	17.3	247
Temperate Location	(13.7 - 270)	(3.05 - 440)	(7.2 - 1300)
Average Rainfall and Cool	65	34	320
Location	(36 - 440)	(8.5 - 660)	(8.7 - 1440)
Wet and Warm Location	63	82	254
	(21 - 340)	(13 - 370)	(59 - 860)
Wet and Temperate	90	108	189
Location	(19.2 - 249)	(14.6 - 265)	(100 - 550)
Wet and Cool Location	95	231	370
	(18.1 - 440)	(29.8 - 530)	(69 - 630)
		Average of Central Values:	86.4
		25th Percentile of Lower Bounds:	0
		Maximum Value:	1440
		Summary of Values:	86.4 (0 - 1440)

Appendix 11: Gleams-Driver Modeling, 18 Applications

18 Applications

Table 1: Effective Offsite Application Rate (lb/acre)

Site	Clay	Loam	Sand
Dry and Warm Location	0.0102	0	0
	(0 - 0.191)	(0 - 0.056)	(0 - 0.000106)
Dry and Temperate	0.0155	0	0
Location	(0 - 0.119)	(0 - 0.033)	(0 - 8.40E-06)
Dry and Cold Location	0.0277	0	0
	(0 - 0.125)	(0 - 0.0186)	(0 - 0)
Average Rainfall and	0.18	0.047	0.000107
Warm Location	(0.038 - 0.42)	(0.0036 - 0.125)	(2.67E-08 - 0.0034)
Average Rainfall and	0.21	0.054	2.93E-05
Temperate Location	(0.052 - 0.39)	(0.00233 - 0.135)	(0 - 0.00206)
Average Rainfall and Cool	0.195	0.036	9.10E-08
Location	(0.0272 - 0.37)	(0.00245 - 0.117)	(0 - 0.00109)
Wet and Warm Location	0.28	0.093	0.000116
	(0.037 - 0.54)	(0.00312 - 0.222)	(1.60E-07 - 0.0041)
Wet and Temperate	0.33	0.06	0.000045
Location	(0.028 - 0.53)	(0.0062 - 0.16)	(3.50E-09 - 0.0026)
Wet and Cool Location	0.67	0.144	0.000304
	(0.054 - 0.99)	(0.0063 - 0.283)	(4.50E-07 - 0.0045)
		Average of Central Values:	0.0871
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.99
		Summary of Values:	0.087 (0 - 0.99)

18 Applications

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

Site	Clay	Loam	Sand
Dry and Warm Location	1.89 (1.64 - 2.34)	1.69 (1.47 - 2.12)	1.71 (1.48 - 2.07)
Dry and Temperate Location	3.24 (2.84 - 3.69)	3.04 (2.62 - 3.39)	2.9 (2.47 - 3.4)
Dry and Cold Location	6.21 (5.91 - 6.79)	5.71 (5.46 - 6.43)	5.65 (4.98 - 6.29)
Average Rainfall and Warm Location	1.62 (1.33 - 1.93)	1.43 (1.19 - 1.76)	1.25 (0.92 - 1.56)
Average Rainfall and Temperate Location	2.65 (2.02 - 3.18)	2.37 (1.73 - 2.86)	1.87 (1.38 - 2.56)
Average Rainfall and Cool Location	3.32 (2.06 - 4.07)	2.76 (1.9 - 3.65)	2.04 (1.27 - 2.98)
Wet and Warm Location	1.58 (1.09 - 1.98)	1.45 (0.88 - 1.73)	1.04 (0.71 - 1.39)
Wet and Temperate Location	2.48 (1.84 - 3.22)	2.15 (1.71 - 2.76)	1.86 (1.2 - 2.24)
Wet and Cool Location	2.66 (1.61 - 3.6)	2.29 (1.33 - 2.95)	1.75 (0.97 - 2.41)
		Average of Central Values:	2.54
		25th Percentile of Lower Bounds:	1.23
		Maximum Value:	6.79
		Summary of Values:	2.54 (1.23 - 6.79)

18 Applications

Table 3: Concentration in Top 36 Inches of Soil (ppm)

Site	Clay	Loam	Sand
Dry and Warm Location	0.63 (0.55 - 0.78)	0.57 (0.49 - 0.71)	0.57 (0.5 - 0.69)
Dry and Temperate Location	1.08 (0.95 - 1.23)	1.02 (0.87 - 1.13)	0.98 (0.84 - 1.15)
Dry and Cold Location	2.08 (1.98 - 2.26)	1.91 (1.82 - 2.14)	1.92 (1.83 - 2.12)
Average Rainfall and Warm Location	0.59 (0.5 - 0.72)	0.54 (0.45 - 0.64)	0.52 (0.43 - 0.64)
Average Rainfall and Temperate Location	1 (0.88 - 1.18)	0.91 (0.81 - 1.07)	0.88 (0.69 - 1.04)
Average Rainfall and Cool Location	1.31 (1.17 - 1.47)	1.22 (1.08 - 1.36)	1.13 (0.75 - 1.31)
Wet and Warm Location	0.68 (0.6 - 0.83)	0.62 (0.52 - 0.75)	0.55 (0.41 - 0.65)
Wet and Temperate Location	1.2 (0.85 - 1.38)	0.98 (0.77 - 1.28)	0.81 (0.62 - 1.02)
Wet and Cool Location	1.48 (0.84 - 1.77)	1.15 (0.73 - 1.57)	0.9 (0.49 - 1.16)
		Average of Central Values:	1.01
		25th Percentile of Lower Bounds:	0.51
		Maximum Value:	2.26
		Summary of Values:	1.01 (0.51 - 2.26)

18 Applications

Table 4: Maximum Penetration into Soil Column (inches)

Site	Clay	Loam	Sand
Dry and Warm Location	24 (12 - 36)	18 (8 - 36)	18 (8 - 36)
Dry and Temperate Location	24 (8 - 36)	24 (8 - 36)	30 (8 - 36)
Dry and Cold Location	30 (24 - 36)	30 (18 - 36)	36 (30 - 36)
Average Rainfall and Warm Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Average Rainfall and Temperate Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Average Rainfall and Cool Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Warm Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Temperate Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Cool Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
		Average of Central Values:	32.7
		25th Percentile of Lower Bounds:	21
		Maximum Value:	36
		Summary of Values:	32.7 (21 - 36)

18 Applications

Table 5: Stream, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	33 (0 - 243)	0 (0 - 107)	0 (0 - 60)
Dry and Temperate Location	33 (0 - 248)	0 (0 - 77)	0 (0 - 123)
Dry and Cold Location	74 (0 - 390)	3.1E-06 (0 - 62)	0.008 (0 - 20.5)
Average Rainfall and Warm Location	90 (46 - 189)	40 (18.7 - 142)	84 (3.7 - 920)
Average Rainfall and Temperate Location	99 (60 - 271)	45 (18.8 - 303)	268 (11.2 - 1050)
Average Rainfall and Cool Location	107 (53 - 510)	55 (17.8 - 490)	330 (22.3 - 1230)
Wet and Warm Location	110 (67 - 287)	68 (29.2 - 390)	310 (79 - 720)
Wet and Temperate Location	158 (78 - 590)	215 (46 - 580)	540 (214 - 1500)
Wet and Cool Location	223 (84 - 490)	283 (71 - 680)	560 (350 - 990)
		Average of Central Values:	138
		25th Percentile of Lower Bounds:	0
		Maximum Value:	1500
		Summary of Values:	138 (0 - 1500)

18 Applications

Table 6: Stream, Annual Average Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.11	0	0
	(0 - 1)	(0 - 0.5)	(0 - 0.17)
Dry and Temperate	0.17	0	0
Location	(0 - 0.8)	(0 - 0.23)	(0 - 0.6)
Dry and Cold Location	0.29	9.0E-09	0.00006
	(0 - 1.12)	(0 - 0.18)	(0 - 0.23)
Average Rainfall and	1.53	0.5	2.99
Warm Location	(1 - 5.3)	(0.21 - 4.7)	(0.13 - 38)
Average Rainfall and	1.66	0.5	13.6
Temperate Location	(1 - 23.1)	(0.18 - 21.7)	(0.4 - 68)
Average Rainfall and Cool	1.68	1.6	19.2
Location	(0.8 - 43)	(0.19 - 35)	(0.7 - 83)
Wet and Warm Location	10	8.6	38
	(2.27 - 51)	(1.02 - 54)	(11.2 - 71)
Wet and Temperate	16.3	35	60
Location	(2.42 - 73)	(2.66 - 72)	(30.6 - 97)
Wet and Cool Location	22.3	40	67
	(3.8 - 72)	(4.6 - 78)	(46 - 88)
		Average of Central Values:	12.6
		25th Percentile of Lower Bounds:	0
		Maximum Value:	97
		Summary of Values:	12.6 (0 - 97)

18 Applications

Table 7: Pond, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	11.1 (0 - 206)	0 (0 - 67)	0 (0 - 24.8)
Dry and Temperate Location	16.9 (0 - 125)	0 (0 - 35)	0 (0 - 108)
Dry and Cold Location	29.6 (0 - 134)	0.000001 (0 - 20.7)	0.005 (0 - 18.4)
Average Rainfall and Warm Location	275 (156 - 770)	103 (39 - 720)	440 (17.6 - 5580)
Average Rainfall and Temperate Location	278 (158 - 2580)	108 (29.4 - 2330)	1250 (39 - 6690)
Average Rainfall and Cool Location	250 (114 - 3590)	189 (24.9 - 3170)	1900 (80 - 8270)
Wet and Warm Location	600 (218 - 2550)	480 (88 - 3130)	2070 (750 - 4580)
Wet and Temperate Location	720 (140 - 2920)	1450 (86 - 3440)	1790 (1010 - 3350)
Wet and Cool Location	1100 (235 - 2800)	1640 (360 - 2920)	2000 (1340 - 3630)
		Average of Central Values:	619
		25th Percentile of Lower Bounds:	0
		Maximum Value:	8270
		Summary of Values:	619 (0 - 8270)

18 Applications

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

Site	Clay	Loam	Sand
Dry and Warm Location	3.3	0	0
	(0 - 68)	(0 - 30.2)	(0 - 6)
Dry and Temperate	7.9	0	0
Location	(0 - 57)	(0 - 15.4)	(0 - 49)
Dry and Cold Location	12.7	4.0E-07	0.0018
	(0 - 57)	(0 - 8.5)	(0 - 7.7)
Average Rainfall and	174	59	173
Warm Location	(97 - 360)	(19.6 - 380)	(5.8 - 4310)
Average Rainfall and	171	60	700
Temperate Location	(89 - 1340)	(18.1 - 1240)	(13.3 - 4230)
Average Rainfall and Cool	154	77	840
Location	(80 - 1870)	(14.6 - 1520)	(14.9 - 5370)
Wet and Warm Location	237	198	1040
	(94 - 1350)	(41 - 1600)	(360 - 2520)
Wet and Temperate	340	760	960
Location	(60 - 1530)	(40 - 1820)	(560 - 1750)
Wet and Cool Location	340	570	1010
	(96 - 1050)	(101 - 1300)	(620 - 1770)
		Average of Central Values:	292
		25th Percentile of Lower Bounds:	0
		Maximum Value:	5370
		Summary of Values:	292 (0 - 5370)