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Imazapyr

Human Health and Ecological Risk Assessment

FINAL REPORT

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
AEL	adverse-effect level
a.e.	acid equivalent
a.i.	active ingredient
ALS	acetolactate synthase
APHIS	Animal and Plant Health Inspection Service
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
calc	calculated value
CBI	confidential business information
ChE	cholinesterase
CI	confidence interval
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
DER	data evaluation record
d.f.	degrees of freedom
EC_x	concentration causing X% inhibition of a process
EC_{25}	concentration causing 25% inhibition of a process
EC_{50}	concentration causing 50% inhibition of a process
EHE	2-ethylhexyl ester
EFED	Environmental Fate and Effects Division (U.S. EPA/OPP)
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
g	gram
GLP	Good Laboratory Practices
ha	hectare
HED	Health Effects Division (U.S. EPA/OPP)
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IPA	Isopropylamine
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
MSMA	monosodium methanearsonate
MW	molecular weight
NAWQA	USGS National Water Quality Assessment
NCI	National Cancer Institute
NCOD	National Drinking Water Contaminant Occurrence Database
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOS	not otherwise specified
NRC	National Research Council
NTP	National Toxicology Program
OM	organic matter
OPP	Office of Pesticide Programs
OPPTS	Office of Pesticide Planning and Toxic Substances
OSHA	Occupational Safety and Health Administration
Pa	Pascal
PBPK	physiologically-based kinetic
ppm	parts per million
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
TEP	typical end-use product
T.G.I.A.	Technical grade active ingredient
TIPA	Triisopropanolamine
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

COMMON UNIT CONVERSIONS AND ABBREVIATIONS

To convert ...	Into ...	Multiply by ...
acres	hectares (ha)	0.4047
acres	square meters (m^2)	4,047
atmospheres	millimeters of mercury	760
centigrade	Fahrenheit	1.8 C+32
centimeters	inches	0.3937
cubic meters (m^3)	liters (L)	1,000
Fahrenheit	centigrade	0.556 F-17.8
feet per second (ft/sec)	miles/hour (mi/hr)	0.6818
gallons (gal)	liters (L)	3.785
gallons per acre (gal/acre)	liters per hectare (L/ha)	9.34
grams (g)	ounces, (oz)	0.03527
grams (g)	pounds, (oz)	0.002205
hectares (ha)	acres	2.471
inches (in)	centimeters (cm)	2.540
kilograms (kg)	ounces, (oz)	35.274
kilograms (kg)	pounds, (lb)	2.2046
kilograms per hectare (hg/ha)	pounds per acre (lb/acre)	0.892
kilometers (km)	miles (mi)	0.6214
liters (L)	cubic centimeters (cm^3)	1,000
liters (L)	gallons (gal)	0.2642
liters (L)	ounces, fluid (oz)	33.814
miles (mi)	kilometers (km)	1.609
miles per hour (mi/hr)	cm/sec	44.70
milligrams (mg)	ounces (oz)	0.000035
meters (m)	feet	3.281
ounces (oz)	grams (g)	28.3495
ounces per acre (oz/acre)	grams per hectare (g/ha)	70.1
ounces per acre (oz/acre)	kilograms per hectare (kg/ha)	0.0701
ounces fluid	cubic centimeters (cm^3)	29.5735
pounds (lb)	grams (g)	453.6
pounds (lb)	kilograms (kg)	0.4536
pounds per acre (lb/acre)	kilograms per hectare (kg/ha)	1.121
pounds per acre (lb/acre)	mg/square meter (mg/m^2)	112.1
pounds per acre (lb/acre)	µg/square centimeter ($\mu g/cm^2$)	11.21
pounds per gallon (lb/gal)	grams per liter (g/L)	119.8
square centimeters (cm^2)	square inches (in^2)	0.155
square centimeters (cm^2)	square meters (m^2)	0.0001
square meters (m^2)	square centimeters (cm^2)	10,000
yards	meters	0.9144

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

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

Imazapyr is a herbicide used in Forest Service vegetation management programs, primarily in the Southern United States, to control a variety of grasses, broadleaf weeds, vines, and brush species. Imazapyr may also be used to control aquatic macrophytes. The present document provides risk assessments for human health and ecological effects to support an assessment of the human health and environmental consequences of using this herbicide. There are numerous formulations of imazapyr. Toxicity data, however, are available only on Arsenal, a formulation supplied by BASF, because toxicity data are available on this formulation. Nonetheless, these human health and ecological risk assessments encompass all formulations of the isopropylamine salt of imazapyr registered for forestry or other related applications, including applications for the control of emergent aquatic vegetation.

The quantitative risk characterization in both the human health and in the ecological risk assessments is based on the hazard quotient (HQ), which is defined as the anticipated exposure divided by the toxicity value. Although the current risk assessments are based on the unit application rate of 1 lb a.e./acre, other applications are considered in the risk characterization up to the maximum labeled rate of 1.5 lbs a.e./acre.

Imazapyr is an effective herbicide for the control of both terrestrial and aquatic vegetation. Under some conditions, terrestrial applications of imazapyr could damage nontarget terrestrial vegetation. Effective aquatic applications of imazapyr will most certainly damage aquatic macrophytes and may damage some species of algae. While imazapyr is an effective terrestrial herbicide, the exposure scenarios developed for terrestrial and aquatic plants in the current risk assessments lead to a wide range of HQs, some of which are far below the level of concern and others which exceed the level of concern substantially. This apparent ambiguity relates to the attempt made in the exposure assessments to encompass a wide range of potential exposures associated with different weather patterns and other site-specific variables. Thus, for applications of imazapyr in areas where potential effects on nontarget plants are a substantial concern, refinements to the exposure scenarios for nontarget plants would be appropriate.

While adverse effects on plants may be anticipated, there is no basis for asserting that applications of imazapyr will pose any substantial risk to humans or other species of animals. The U.S. EPA/OPP classifies imazapyr as *practically non-toxic* to mammals, birds, honeybees, fish, and aquatic invertebrates. This classification is clearly justified. None of the expected (non-accidental) exposures to these groups of animals raise substantial concern; indeed, most accidental exposures raise only minimal concern. The major uncertainties regarding potential toxic effects in animals are associated with the lack of toxicity data on reptiles and amphibians.

Terrestrial or aquatic applications of any effective herbicide are likely to alter vegetation within the treatment area, which may lead to secondary effects on terrestrial or aquatic animals as well as nontarget plants. While these concerns are acknowledged, they are common to any effective method for vegetation management, including mechanical methods that do not involve herbicide use.

1. INTRODUCTION

1.1. Chemical Specific Information

This document provides risk assessments for human health effects and ecological effects to support an assessment of the environmental consequences of using imazapyr in Forest Service vegetation management programs. This risk assessment is an update to previous USDA Forest Service risk assessments of imazapyr (SERA 1999, 2004a).

The previous risk assessments cover only terrestrial applications of imazapyr. Imazapyr is now registered by the U.S. EPA for the control of emergent aquatic weeds. This new use is covered in the updated risk assessment along with the uses of imazapyr in terrestrial applications. Moreover, the number of formulations considered in this updated risk assessment is greater because imazapyr is now off-patent. Accordingly, in addition to the formulations considered in the previously conducted risk assessments (i.e., Arsenal, Arsenal AC, Chopper, and Stalker), this update considers a number of new formulations, as discussed further in Section 2.2.

In the preparation of this risk assessment, an updated literature search of imazapyr was conducted using TOXLINE. The open literature on imazapyr is sparse. There are published reviews and commentaries regarding the human health or ecological effects of imazapyr (Cox 1996; Entrix 2003; Gagne et al. 1991; Peoples 1984; Pless 2005; Tu et al. 2001, 2003). Generally, these reviews are used only to identify published studies to ensure adequate coverage of the literature. Similarly, the recent risk assessment on imazapyr conducted by AMEC Geomatrix (2009) for the Washington State Department of Agriculture was reviewed as a source of information.

Almost all of the relevant mammalian toxicology studies and most of the ecotoxicology studies are unpublished reports submitted to the U.S. EPA as part of the registration process for imazapyr. The most recent Forest Service risk assessment on imazapyr (SERA 2004a), identifies numerous registrant submissions on imazapyr and imazapyr formulations. Of these, 127 submissions (i.e., full copies of the studies submitted to the U.S. EPA) were kindly provided by the U.S. EPA Office of Pesticide Programs. The U.S. EPA/OPP no longer provides full copies of registrant studies for risk assessments conducted in support of activities outside of U.S. EPA/OPP. Consequently, summaries of the studies contained in SERA (2004a) are included in this updated risk assessment on imazapyr. The registrant-submitted studies are cited using standard author/year designations and are identified in Section 5 (References) as MRID04. Information on other registrant-submitted studies is taken from various U.S. EPA/OPP risk assessments and designated in the body of the current Forest Service risk assessment only by MRID number with a reference to the U.S. EPA risk assessment from which the information is taken.

Since the preparation of the SERA (2004a) risk assessment on imazapyr, the U.S. EPA completed the Reregistration Eligibility Decision (RED) document for imazapyr (U.S. EPA/OPP 2006a) as well as an ecological risk assessment for the California Red Legged Frog (U.S. EPA/OPP 2007a). Both of these documents as well as risk assessments by the U.S. EPA/OPP Health Effects Division (U.S. EPA/OPP 2005a) and the U.S. EPA/OPP Environmental Fate and Effects Division (U.S. EPA/OPP 2005a) are key sources of information in the current Forest

Service risk assessment on imazapyr. Additional sources of information include files from the U.S. EPA/OPP E-Docket that are associated with the 2006 RED (U.S. EPA/OPP 2005c-m). As a final point, a recent U.S. EPA/OPP ecological risk assessment for the aquatic application of imazapyr (U.S. EPA/OPP 2010d) was consulted.

The U.S. EPA/OPP is in the process of reviewing the registration of many pesticides (http://www.epa.gov/oppsrrd1/registration_review). The review of imazapyr, however, is not scheduled to begin until 2014 (U.S. EPA/OPP 2010a, p. 19). Thus, while the registration review may have an impact on the next Forest Service risk assessment on imazapyr, the EPA review process has no impact on the current Forest Service risk assessment.

As noted above, many registrant-submitted studies are reviewed in the SERA (2004a) risk assessment. In the meantime, several new studies were submitted to the EPA. Although the EPA no longer releases full studies, cleared reviews of some of the new studies are available and were obtained from the EPA web site (http://www.epa.gov/pesticides/foia/reviews.htm). All studies for which cleared reviews are available are cited in the current risk assessment using standard author/year designations and are identified in Section 5 (References) as ClrRev. The cleared reviews most often take the form of Data Evaluation Records (DERs), which are discussed further below.

In any risk assessment based largely on registrant-submitted studies, as is the case with imazapyr, 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/opptsfrs/home/guidelin.htm. All studies 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. In addition, each DER undergoes internal review (and sometimes several layers of review).

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 imazapyr is discussed throughout the document.

This risk assessment is accompanied by two EXCEL workbooks. One workbook covers all terrestrial broadcast applications of imazapyr including directed foliar, ground broadcast, and aerial applications (Attachment 1). The second workbook covers aquatic applications of imazapyr (Attachment 2). The relationship of these workbooks to the risk assessment is discussed further in the following section.

1.2. General Information

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 2007a). 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 current Forest Service risk assessment is an update to previous risk assessments on imazapyr (SERA 1999, 2004a). At some point in the future, the Forest Service will update this risk assessment again 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. They are included in the body of the document.

Some of the calculations, however, are cumbersome. For those calculations, EXCEL workbooks (sets of EXCEL worksheets) are included as attachments to this risk assessment. The worksheets

provide the detail for the estimates cited in the body of the document. Documentation for the use of these workbooks is presented in SERA (2010a, 2011a).

The EXCEL workbooks are an integral part 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

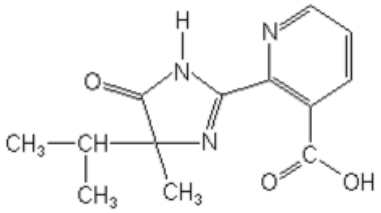
Imazapyr is a nonselective herbicide used to control a variety of grasses, broadleaf weeds, vines, and brush species. In Forest Service programs, imazapyr is used primarily in the Southern United States for noxious weed control, conifer release, and site preparation. Previous Forest Service risk assessments on imazapyr consider only four BASF formulations: Arsenal, Arsenal AC (applicators concentrate), Chopper, and Stalker, all of which contain imazapyr as the isopropylamine salt. Imazapyr is now off patent, and numerous formulations are available both from BASF and other companies. The current risk assessment explicitly considers 16 formulations of imazapyr but is intended to encompass all formulations of the isopropylamine salt of imazapyr registered for forestry or other related applications including applications for the control of emergent aquatic vegetation.

While imazapyr formulations can be used in pre-emergence applications, the most common and effective applications are post-emergent when the vegetation to be controlled is growing vigorously. The most common methods of ground application involve backpack (selective foliar) and boom spray (broadcast foliar) operations. Cut surface treatment methods may also be used in Forest Service programs involving imazapyr. Boom spray applications are used primarily in rights-of-way management. Several formulations are registered for aerial applications; however, in Forest Service programs, aerial applications are restricted to helicopter only.

Imazapyr is not used extensively in agriculture, except for applications to corn in the central United States. At least in the southeastern United States, forestry applications of imazapyr may be greater than agricultural applications. This also appears to be the case in California, although these forestry uses in California are not directly associated with Forest Service programs. Current information on the use of imazapyr in forestry applications in other regions of the United States is sparse.

2.2. Chemical Description and Commercial Formulations

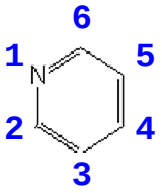
Imazapyr is the common name for 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5oxo-1*H*-imidazol-2-yl]-3-pyridinecarboxylic acid:



Selected chemical and physical properties of imazapyr are summarized in Table 1.

Imazapyr is a member of the imidazolinone class of herbicides which also includes imazapic, imazamox, imazethapyr, imazamethabenz, and imazaquin. Forest Service risk assessments have been prepared on imazamox (SERA 2010c) and imazapic (SERA 2004b). As illustrated in

Figure 1, imazapyr is structurally similar to imazapic, imazamox, and imazethapyr, except that 5-carbon on the pyridine ring,



is unsubstituted in imazapyr; whereas, the 5-carbon of the pyridine rings contains a methyl group in imazapic, dimethyl ether moiety in imazamox, and an ethyl group in imazethapyr. All of the imidazolinone herbicides share a common mechanism of herbicidal action which involves the inhibition of acetolactate synthase (ALS). ALS is an enzyme found in plants and required for the synthesis of essential branched chain amino acids (i.e., valine, leucine, and isoleucine), all of which are important for plant growth (Tan et al. 2005). Imazapyr is classified as a broad range (i.e., nonselective) herbicide with registered uses for the pre- and post-emergent control of many terrestrial weeds as well as emergent aquatic weeds. Agricultural uses of imazapyr are limited to corn and grass (U.S. EPA/OPP 2006a).

Imazapyr was introduced as a herbicide by American Cyanamid in 1985 (Tomlin 1985). In 2000, American Cyanamid was acquired by BASF (http://www2.basf.us/corporate/news2000/newsamericancyanamid.html). Imazapyr, however, is now off-patent and several new imazapyr formulations have become available.

The representative formulations of imazapyr are summarized in Table 2. All of these formulations contain the isopropylamine salt of imazapyr. These formulations include the four formulations covered in previous Forest Service risk assessments on imazapyr (SERA 1999, 2004a) —i.e., Arsenal, Arsenal AC, Chopper, and Stalker—all of which are manufactured by BASF. Table 2 is divided into upper and lower sections. The upper section is based on information from the product labels, while the lower section is based on information from the material safety data sheets (MSDS) for the formulations. As indicated in Table 2, many formulations of imazapyr are labeled specifically for forestry applications. In addition, several formulations are labeled for aquatic applications. Two formulations, Arsenal Railroad and Polaris RR, are not specifically labeled for either forestry or aquatic applications. As discussed below, these formulations are included as examples of imazapyr formulations known to contain surfactants. It is not clear, however, that these formulations will be used in Forest Service programs.

The third column in the upper section of Table 2 specifies the U.S. EPA registration number for each 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 Arsenal, a BASF formulation, is 241-346, with 241 the company code for BASF and 346 the product code for Arsenal. 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. For example, the U.S. registration number for Polaris, a Nufarm formulation, is 241-346-228. The first two elements are identical to the registration number for Arsenal and the third element is the company code for Nufarm.

This code indicates that the Polaris formulation is identical to Arsenal and that the formulation is manufactured by BASF for Nufarm and that Nufarm markets and sells the Polaris formulation.

The last column in the upper section of Table 2 indicates information on surfactants in the formulations. As discussed further in Section 3.1.14, pesticide formulations contain other ingredients, formerly referred to as *inerts*, and the identity of the other ingredients is typically classified as proprietary or Confidential Business Information (CBI). U.S. EPA/OPPTS (2003, p. 5-2) encouraged but did not require expanded inert statements on product labels which specifically identify the inert ingredients in the product, and this recommendation appears to be reflected in some product labels. Specifically, the product labels for Arsenal AC and Polaris AC specifically state that the formulations do not contain a surfactant, and the product labels for Arsenal Railroad and Polaris RR state that the formulations do contain a surfactant. Other formulations do not specifically note whether or not the formulations contain surfactants. As also indicated in the last column of Table 2 and discussed further in Section 2.4.1, most formulations of imazapyr recommend the use of nonionic surfactants prior to application.

Information in the bottom section of Table 2 is included in an attempt to differentiate characteristics among formulations. As noted above, this information is taken from the material safety datasheets (MSDS) for the formulations. MSDS, however, vary according to the level of detail; moreover, many cited values (e.g., pH and formulation density) are given as ranges. The ranges are understandable and probably reflect normal batch-to-batch variation in formulations. Several formulations indicate the presence of an organic solvent but only indirectly. Most of the designations in Table 2 indicating that a specific formulation may contain an organic solvent are based on statements in the corresponding MSDS that vapor pressure or other similar characteristics apply to a solvent and not the active ingredient.

The list of formulations in Table 2 is not intended to be exclusive. Other formulations of imazapyr are available commercially, and new formulations of imazapyr are being developed (e.g., Radian and Mishael 2008). The Forest Service may elect to use any formulation of imazapyr registered for forestry applications. As discussed further in Section 3.1.14 and detailed in Appendix 1 (Table A1-1), some information is available on the acute toxicity of various formulations. If other formulations are used in Forest Service programs, attempts should be made to identify similar information on mammalian toxicity to ensure that the formulation under consideration is comparable in toxicity to that of the formulations explicitly designated in Table 2.

2.3. Application Methods

2.3.1. Terrestrial Applications

As summarized in Table 3, various methods may be used to apply imazapyr formulations, including ground or aerial broadcast, directed foliar (including spot treatments), and various cut surface treatments. In Forest Service programs, the most common methods of ground application for formulations such as Arsenal and Chopper involve backpack (selective foliar) and boom spray (broadcast foliar) operations. In selective foliar applications, the herbicide sprayer or container is carried by backpack, and the herbicide is applied to selected target vegetation. Application crews may treat up to shoulder high brush, which means that chemical contact with the arms, hands, or face is a credible risk. To reduce the likelihood of significant exposure,

application crews are directed not to walk through treated vegetation and not to spray above shoulder height. Usually, a worker treats approximately 0.5 acre/hour with a plausible range of 0.25-1.0 acre/hour.

Formulations such as Stalker, Arsenal AC, and several other imazapyr formulations involve cut surface treatment methods. These methods involve creating a cut surface on the tree by either cutting the tree down [cut stump treatment] or piercing the bark of a standing tree with a hatchet [hack and squirt] or an injector [injection]. The herbicide is then applied using a backpack sprayer [cut stump], squirt bottle [hack and squirt], or the injector itself [injection]. These treatments are used to eliminate large trees during site preparation, pre-commercial thinning, and release operations.

Ground broadcast (boom spray) application is used primarily in rights-of-way management. Spray equipment mounted on tractors or trucks is used to apply the herbicide on either side of the roadway. Usually, about 8 acres are treated in a 45-minute period (approximately 11 acres/hour). Some special truck mounted spray systems may be used to treat up to 12 acres in a 35-minute period with approximately 300 gallons of herbicide mixture (approximately 21 acres/hour and 510 gallons/hour) (USDA 1989b, p 2-9 to 2-10).

Several formulations of imazapyr are registered for aerial applications. Some formulations such as Arsenal are registered for fixed-wing or helicopter applications; whereas, other formulations such as Arsenal AC are labeled for aerial applications by helicopter only. In Forest Service programs, aerial applications for imazapyr are restricted to helicopter only. The imazapyr formulation is applied under pressure through specially designed spray nozzles and booms. The nozzles are designed to minimize turbulence and maintain a large droplet size, both of which contribute to a reduction in spray drift. In aerial applications, approximately 40-100 acres may be treated per hour.

2.3.2. Aquatic Applications

As indicated in Table 3, several imazapyr formulations, including, Arsenal, Habitat, and the Ecomazapyr 2 SL formulations from both Alligare and Vegetation Management, are labeled for the control of emergent aquatic weeds. Application methods for the control of emergent weeds are essentially identical to broadcast ground applications. Aerial applications to emergent vegetation are allowed, but only using helicopters. Applications may be made to a variety of aquatic sites. The description of the different types of aquatic sites is similar on all labels for aquatic formulations. The following list is taken from the product label for Arsenal:

> *lakes, rivers, streams, ponds, seeps, drainage ditches, canals, reservoirs, swamps, bogs, marshes, estuaries, bays, brackish water, transitional areas between terrestrial and aquatic sites, riparian sites, and seasonal wet areas.*
>
> Arsenal 2011 Product Label, NVA 2010-04-104-0192

All product labels stress that the imazapyr formulations are not effective for the control of submergent aquatic vegetation; accordingly, no imazapyr formulations are labeled for submergent applications.

2.4. Mixing and Application Rates

2.4.1. Terrestrial Broadcast Applications

As summarized in Table 3, the labeled broadcast application rates for imazapyr formulations range from 0.125 to 1.5 lb a.e./acre, depending on the target vegetation and the purpose of the application. As also summarized in the Table 3, the range of recommended application rates differs among formulations. For example, Arsenal AC, Polaris AC, and Chopper may be applied at application rates of up to 1.25 lb a.e/acre; whereas, Arsenal, Polaris, and Stalker have maximum labeled application rates of 1.5 lb a.e./acre. The rationale for the different maximum application rates of the various imazapyr formulations is not discussed in the available literature; presumably, the different application rates reflect differences in the target vegetation and/or intended uses of the various formulations.

As summarized in Table 4 and discussed further in Section 2.5, the Forest Service reported forest-level uses of pesticides up to 2004. Based on the available Forest Service use statistics for 2004, the average application rate used in Forest Service programs is about 0.3 lb a.e./acre, which falls in the lower range of the labeled application rates. For the current risk assessment, a unit application rate of 1 lb a.e./acre is used. The use of this unit application rate is a standard approach used in most Forest Service risk assessments. The consequences of using lower or higher application rates are discussed in the risk characterization for both human health effects (Section 3.4) and ecological effects (Section 4.4).

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 imazapyr is diluted prior to application primarily influences dermal and direct spray scenarios, both of which depend on 'field dilution' (i.e., the concentration of imazapyr in the applied spray). In all cases, the higher the concentration of imazapyr (i.e., equivalent to the lower dilution of imazapyr), the greater is the risk. As summarized in Table 3, the recommended application volumes for imazapyr formulations range from 5 to 100 gallon/s acre. This range of application volumes is used in the EXCEL workbook for terrestrial applications that accompanies the current risk assessment (Attachment 1). The central estimate of the application volume is taken as 20 gallons/acre, the geometric mean of the lower and upper bounds rounded to one significant place [$(5 \times 100)^{0.5} \approx 22.36$]. As detailed in Worksheet A01 of Attachment 1, these dilution volumes result in field solutions that contain concentrations of imazapyr of 6 (1.2 to 24) mg a.e./mL at an application rate of 1 lb a.e./acre.

As indicated in Table 2, most product labels for imazapyr recommend the use of nonionic surfactants for broadcast foliar applications at a concentration of at least 0.25% v/v and up to 1.0% v/v. Those formulations that do not specifically recommend the use of a nonionic surfactant over a specified range of concentrations – i.e., Chopper, Polaris SP, and Stalker – do, nonetheless, suggest that the use of a surfactant or penetrating agent could improve efficacy. The impact of the use of surfactants 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.

2.4.2. Spot (Foliar) Treatments

Spot applications are examples of non-contiguous applications in which the pesticide is applied to small areas within a field or other defined area. Spot applications are encompassed by the current risk assessment; however, a separate workbook for this treatment method is not included with the current risk assessment. As discussed in the documentation for the worksheets that accompany this risk assessment (SERA 2010a, 2011, Section 2.4.1), spot foliar applications are handled as a special case of broadcast foliar applications in which the functional application rate is calculated based on the total amount of pesticide applied to a field divided by the total area of the field. In all other respects, spot applications are assessed in the same manner as broadcast applications.

2.4.3. Cut Surface and Basal Bark Treatments

The term *cut surface treatment* is used in this risk assessment (and in many of the product labels for imazapyr) to include treatments such as the direct application of herbicide to cut stumps or cut stems or the injection of a chemical into stems. In basal bark applications, the herbicide is sprayed on to the bark of the lower 12-18 inches of trees or bushes to control undesirable hardwoods.

These treatments are similar to spot applications in that they involve treatments of noncontiguous areas (i.e., specific trees) within a field or other defined area. Unlike spot foliar treatments, however, the nature of the applications are fundamentally different from broadcast applications in that they are focused on a specific tree and often involve the use of different equipment from that which is used for broadcast applications. In addition, the herbicide concentrations used in cut surface applications are typical of the upper bound concentrations used in foliar applications.

For example, the product label for Stalker specifies that from 8 to 12 fluid oz (0.0625 to 0.09375 gallon) of Stalker should be mixed with one gallon of a penetrating oil. Stalker contains 2 lbs a.e./gallon. Thus, the applied solution contains about 0.125 to 0.1885 lbs a.e. per gallon [(2 lbs a.e./gallon x 0.0625 to 0.9375 gallon) ÷ 1 gallon oil], which is equivalent to about 15 to 22.6 mg/L—i.e., 1 lb/gallon = 119.8 mg/mL. The upper bound concentration of 22.6 mg/L for basal bark applications is comparable to the upper bound of 24 mg a.e./L for foliar broadcast applications (Section 2.4.1). Other formulations, however, such as Arsenal Applicators Concentrate, specify that the formulation may be applied undiluted in some cut surface treatments, such as hack and squirt. In this case, the concentration of the handled formulation would be or 4 lbs a.e./gallon or about 479.2 mg/mL. This concentration is a factor of about 20 times greater than the upper bound concentration that is likely to be used in foliar broadcast applications [479.2 mg/mL ÷ 24 mg a.e./L ≈ 19.9666]. The use of such highly concentrated solutions of imazapyr is discussed further in Section 3.4.2.

2.4.4. Aquatic Applications

As summarized in Table 3, the recommended application rates for imazapyr formulations labeled for the control of emergent weeds are given on the product labels as 2 to 6 pints/acre. Since all of the aquatic formulations of imazapyr contain 2 lbs a.e./gallon, these rates are equivalent to the application rates recommended for terrestrial applications (i.e., 0.5 to 1.5 lb a.e./acre)—i.e., 1 gallon = 8 pints, 2 lbs a.e./gallon = 0.25 lb a.e./pint.

As with terrestrial broadcast applications, a unit application rate of 1 lb a.e./acre is used in the EXCEL workbook for aquatic applications (Attachment 2), and the consequences of using lower or higher application rates are discussed in the risk characterization for both human health effects (Section 3.4) and ecological effects (Section 4.4).

Recommended spray volumes for aquatic applications are not clearly proscribed on the product labels; generally, however, spray volumes recommended for aquatic applications appear to be somewhat lower than those for terrestrial applications with a minimum recommended spray volume of at least 2 gallons/acre. The product labels also note that additional adjuvants, as specified in Table 3, are required for application volumes greater than 30 gallons/acre. In the EXCEL workbook that accompanies this risk assessment, the application volumes are taken as 2 to 30 gallons/acre with a central estimate of 10 gallons/acre.

The adjuvants recommended on the product labels for aquatic applications include nonionic surfactants, methylated seed oils or vegetable oil concentrates, silicon based surfactants, antifoaming agents, spray indicators (i.e., dyes), and drift reduction agents. It is beyond the scope of the current risk assessments to discuss all of the potential adjuvants in detail. The available information specific to imazapyr in the current risk assessment is discussed further in Section 3.1.14.2 with respect to the human health risk assessment and in 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). Information on agricultural use is compiled by the U.S. Geological Survey (http://water.usgs.gov/nawqa/pnsp/usage/maps/). In addition, detailed pesticide use statistics are compiled by the state of California (http://www.calepa.ca.gov/).

The USDA Forest Service tracks and reports pesticide use by geographical areas referred to as "*Regions*". The Forest Service classification divides the United States into nine regions designated from Region 1 (Northern) to Region 10 (Alaska). [Note: There is no *Region 7* in the Forest Service system.] The use of imazapyr in Forest Service regions for the year 2004 (the most recent year for which statistics are available) is illustrated in Figure 2 and detailed further in Table 4.

For 2004, the Forest Service reports a total used of about 1500 pounds, concentrated primarily in Region 8 (Southern Region) which accounted for nearly 90% of imazapyr use. Region 8 is designated as the primary area of imazapyr use in the previous Forest Service risk assessment on imazapyr (SERA 2004). The remainder of imazapyr use is accounted for by Region 1 (Northern Region with 7.7% of total use) and Region 2 (Rocky Mountain Region with 1.8% of total use). The use of imazapyr in other Forest Service regions during 2004 was negligible.

The use of imazapyr in agriculture is limited. The USGS (2003a) provides national agricultural use statistics for 2002 and reports a total agricultural use of about 4350 lbs. As illustrated in Figure 3, imazapyr is applied only to corn, primarily in Iowa, Indiana, and the western section of

Kentucky. With the exception of western Kentucky (which is in Forest Service Region 8), the states associated with the greatest agricultural uses of imazapyr do not parallel the geographical distribution of use by the Forest Service. Consequently, in most areas of Forest Service Region 8, the Forest Service use of imazapyr would appear to be more substantial than the use of imazapyr in agriculture.

Based on Forest Service use statistics for 2004, the use of imazapyr by the Forest Service in other regions, relative to agricultural use, appears to be negligible. The basis for detailed comparisons, however, is limited because more recent use statistics are not available from the Forest Service. California provides more recent and very detailed annual use reports for pesticides (http://www.cdpr.ca.gov/docs/pur/). The use statistics from California for 2009, the most recent year for which statistics are available, indicate that a total of about 19,108 pounds of the isopropylamine salt of imazapyr were used (CDPR 2010, p. 360). The major uses appear to be related to forestry: forest timberland (≈50%) and rights-of-way management (≈35%). The agricultural uses of imazapyr in California are very minor. Thus, the use of imazapyr in forestry appears to be substantial relative to agricultural uses. The use of imazapyr in California, however, is associated with private industry (for plantation release) and not with Forest Service programs (Bakke 2011).

3. HUMAN HEALTH

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

The toxicity of imazapyr is relatively well-characterized in experimental studies conducted on mammals. Most of the available information on the toxicity of imazapyr to mammals comes from standard studies submitted to the U.S. EPA/OPP in support of the registration of imazapyr. As discussed in Section 1, full copies of these studies, which are considered proprietary, were not available for the preparation of the current Forest Service risk assessment; however, these studies were available during the preparation of the previous Forest Service risk assessment (SERA SERA 2004a). Furthermore, most of the important mammalian studies associated with potential risks to humans have been reviewed and are summarized in the risk assessment prepared by the Health Effects Division of the U.S. EPA/OPP (2005a). Some clinical case reports of intentional (attempted suicide) or accidental ingestion of large amounts of Arsenal are reported in the open literature. The reported signs and symptoms of imazapyr poisoning include vomiting, impaired consciousness, and respiratory distress requiring intubation. There are no reports of human fatality due to imazapyr ingestion.

Although the mode of action regarding the toxicity of imazapyr to humans or other mammals is unclear, this lack of understanding is at least partially a reflection of the apparently low and essentially undetectable acute and chronic systemic toxicity of imazapyr. The acute oral LD_{50} of unformulated imazapyr is greater than 5000 mg/kg, and the chronic dietary NOAEL for imazapyr is 10,000 ppm in dogs, rats, and mice. In the dog, this dietary concentration is equivalent to a daily dose of 250 mg/kg/day. In the other species, the equivalent daily doses are greater than 250 mg/kg/day. An adequate number of multi-generation reproductive and developmental studies were conducted with imazapyr, none of which indicates adverse effects on reproductive capacity or normal development. Also, the results of assays for carcinogenicity and mutagenicity are consistently negative. Accordingly, U.S. EPA categorizes the carcinogenic potential of imazapyr as *Class E: evidence of non-carcinogenicity*.

Increased food consumption is reported in chronic toxicity studies in which imazapyr was added to the diets of male and female mice as well as female rats. It is unclear whether this effect is attributed to toxicity or to an increase in the palatability of the chow. The weight of evidence suggests that imazapyr is not directly neurotoxic. Moreover, the available data do not suggest that systemic toxic effects are plausible after dermal or inhalation exposures to imazapyr. Finally, while the available data are limited, there is no basis for asserting that either the metabolites of imazapyr or the impurities or adjuvants in the formulated products are likely to have an impact on the risk assessment.

Imazapyr and imazapyr formulations can be mildly irritating to the eyes and skin. From a practical perspective, irritation to the eyes or skin would most likely to be associated with the application of this compound only if proper personal protection practices are not followed.

3.1.2. Mechanism of Action

As noted in Section 2.2 and discussed further in Section 4.1.2.5, the mechanism for the phytotoxicity of imazapyr and other imidazolinone herbicides, namely, the inhibition of

acetolactate synthase (ALS), is well understood. Since the ALS enzyme is found only in plants and microorganisms (e.g., Bernasconi et al. 1995), its inhibition is not relevant to potential adverse effects in humans and other mammals. As summarized in Appendix 1 and discussed further in the following subsections, imazapyr does not appear to cause any specific signs of toxicity in mammals. In the few acute toxicity studies that report treatment-related responses, the observed effects may be attributable to the physical response associated with gross over-exposures or irritant effects. In other words, imazapyr does not appear to have a specific mechanism of action associated with toxicity in mammals. This determination is reflected in the EPA human health risk assessment imazapyr in which no data gaps or endpoints of concern associated with systemic toxic effects are identified for acute or chronic exposures (U.S. EPA/OPP 2005a, Section 4.5, p. 28 ff).

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 imazapyr 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 imazapyr behaves in the body, another consideration is the behavior of imazapyr in the environment and the extent to which the metabolism of imazapyr 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

The metabolism and kinetics of imazapyr has been studied in rats (Mallipudi et al. 1983b; Mallipudi and Wu 1994) and lactating goats (Zdybak 1992). The available data in these species suggest that orally administered imazapyr is well absorbed and that the majority of the administered dose is rapidly excreted, unchanged, in urine and feces.

In the earlier study in rats by Mallipudi et al. (1983b), ^{14}C-imazapyr labeled on the carboxyl group, dissolved in ethanol/water, was administered to 15 male Sprague Dawley rats (225 g) by gavage at a dose of 4.4 mg/kg. Imazapyr was excreted in the urine and feces, and 87.2% and 93.3% of the administered dose was recovered from urine and feces on days 1 and 2 (respectively) after dosing. Approximately 98% of the administered dose was recovered in the urine and feces after 8 days as parent compound with no residues in liver, kidneys, muscle, or blood. No metabolites were identified (Mallipudi et al. 1983b).

The later study in rats by Mallipudi and Wu (1994) involved both intravenous and oral dosing with ^{14}C-imazapyr labeled on the 6-carbon of the pyridine ring. In the intravenous phase of the study, imazapyr was injected into male and female rats at a dose of 9.94 mg/kg bw. Imazapyr was rapidly excreted, primarily in the urine (87-95%) and to a lesser extent in the feces (≈6%). In the oral phase of the study, male and female rats were administered single gavage doses of

imazapyr at 9.5 and 924 mg/kg bw as well as 14-day daily doses of unlabeled imazapyr at 9.26 mg/kg bw/day followed by a single oral dose of labeled imazapyr at 9.26 mg/kg bw. Excretion was rapid with 68-81% of the dose recovered in the urine within 4 hours of treatment. Virtually the entire administered dose (i.e., ≥99.5%) was excreted as unchanged imazapyr. Only two very minor metabolites were detected in the urine and feces, CL60,032 (2-carbomoyo-nicotinic acid) and CL252,974. The structure of these and other metabolites of imazapyr (discussed further in Section 3.1.15) is given in Figure 4.

Zdybak (1992) administered ^{14}C-imazapyr acid (labeled on the 6-carbon of the pyridine ring) in gelatin capsules to lactating goats at doses equivalent to dietary exposures of 0, 17.7, or 42.5 ppm for 7 days (Zdybak 1992). As in the metabolism studies in rats, most of the radioactivity, 60–65% of the administered dose, was excreted in the urine as parent compound; a smaller portion, 16–19% of the administered dose, was recovered from feces. Only very small amounts were recovered from milk, blood, kidneys, liver, muscle, and fat.

The only other metabolism study on imazapyr was conducted on white leghorn chickens (Tsalta 1995). As with the mammalian studies, the only significant component excreted was the parent compound (i.e., imazapyr).

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. Thus, it is necessary to assess the consequences of dermal exposure relative to oral exposure and the extent to which imazapyr is likely to be absorbed from the surface of the skin.

Two types of dermal exposure scenarios are considered: immersion and accidental spills. As detailed in SERA (2007a), the calculation of absorbed dose for dermal exposure scenarios involving immersion or prolonged contact with chemical solutions uses Fick's first law and requires an estimate of the permeability coefficient, K_p, expressed in cm/hour. For exposure scenarios like direct sprays or accidental spills, which involve deposition of the compound on the surface of the skin, dermal absorption rates (proportion of the deposited dose that is absorbed per unit time) rather than dermal permeability rates are used in the exposure assessment.

Studies regarding the dermal absorption kinetics of imazapyr were not identified in the available literature. In the absence of experimental data, quantitative structure activity relationships, detailed in SERA (2007a), are used to estimate dermal absorption rates. For estimating the dermal permeability coefficient, U.S. EPA/ORD (1992, 2007) developed an algorithm based on the K_{ow} and molecular weight. Taking the approach used by U.S. EPA/OPP (2005a) in the human health risk assessment conducted in the support of the Reregistration Eligibility Decision for imazapyr (U.S. EPA/OPP 2006a), the molecular weight of imazapyr acid is taken as 261.3 g/mole and the K_{ow} is taken as 1.3 (Table 2). As detailed in Worksheet B03a of Attachment 1, the estimated dermal permeability coefficient for imazapyr is about 0.000056 cm/hour with a 95% confidence interval of 0.000028-0.00011 cm/hour. These estimates are used in all exposure assessments based on the assumption of zero-order dermal absorption kinetics. Note that the

values for K_p given in Worksheet B03a are not rounded. The values for K_p used in all exposure assessments (i.e., those entered in worksheet B01) are rounded to two significant places.

As discussed in SERA (2007a, Section 3.1.3.2, Eq. 3-3), a similar algorithm, also based on molecular weight and K_{ow}, has been developed for estimating first-order dermal absorption rates. Applying the above values for the molecular weight and K_{ow} of imazapyr, the estimated first-order dermal absorption rate coefficient for imazapyr is estimated at 0.0011 $hour^{-1}$ with a 95% confidence interval of 0.00044-0.0029 $hour^{-1}$. The calculations for these estimates are detailed in Worksheet B03b in the EXCEL workbooks that accompany this risk assessment. As with the estimates of the K_p, the values given in Worksheet B03b are not rounded; however, the values given in Worksheet B01 and used in all exposure assessments involving first-order dermal absorption are rounded to two significant figures.

The use of quantitative structure activity relationships, unsupported by experimental data, to estimate the dermal absorption of imazapyr adds substantial uncertainty to the scenarios associated with dermal exposures. This type of uncertainty is common to any risk assessment for which studies on dermal absorption kinetics are unavailable. For imazapyr, however, an additional uncertainty involves the estimate of the K_{ow}. As summarized in Table 1, most standard reference sources give a K_{ow} of about 1.3 for imazapyr (USDA/ARS 1995; Tomlin 2004). This value is apparently taken from the registrant-submitted study by Reichert and Stanley-Millner (1983). Two published studies (Chambarlain et al. 1995; Gennari et al. 1998), both of which involved experimental determinations of the K_{ow} of imazapyr give different values. Gennari et al. (1998) reports a K_{ow} of <0.01 for imazapyr at neutral pH and Chambarlain et al. (1995) reports a K_{ow} of 1.66 at neutral pH. The reason for the discrepancies between these two studies is not apparent. From a practical perspective, the differences in the values reported in these two published studies do not have a substantial impact on the risk assessment. As discussed further in Section 3.4 (risk characterization), all of the hazard quotients for imazapyr associated with dermal exposure scenarios are far below the level of concern (HQ=1). The very low value reported by Gennari et al. (1998) would lead to lower estimates of dermal exposures (i.e., the HQs would decrease). The K_{ow} of 1.6 reported by Chambarlain et al. (1995) is only modestly higher than the K_{ow} of 1.3 used in the current risk assessment and the use of the K_{ow} reported by Chambarlain et al. (1995) would not have any impact on the risk characterization.

For some compounds, acute dermal and oral LD_{50} values can be used to assess the plausibility of the estimated dermal absorption rates relative to oral absorption rates. This approach is not possible for imazapyr due to its low toxicity which resulted in a lack of definitive LD_{50} values in the acute oral toxicity studies (Section 3.1.4) and acute dermal toxicity studies (Section 3.1.12).

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 coefficient 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:

$$\frac{X_{N\,Dose}}{X_{1Dose}} = \frac{(1-\left(e^{-kt*}\right)^{N})}{1-e^{-kt*}} \qquad \text{(Eq. 1)}$$

As the number of doses (***N***) increases, the numerator in Equation 2 approaches a value of 1. Over an infinite period of time, the plateau or steady-state body burden (***X_Inf***) can be calculated as:

$$\frac{X_{Inf}}{X_1} = \frac{1}{1-e^{-kt*}} \qquad \text{(Eq. 2)}$$

As discussed in Section 3.1.3.1, imazapyr is eliminated rapidly from the body (i.e., 68-81% of the dose was recovered in the urine within 4 hours after a single gavage dose). For estimating body burden using the plateau principle, whole body excretion rates are generally preferable to urinary excretion rates. Nonetheless, the use of urinary excretion rates is acceptable because imazapyr is eliminated almost exclusively in the urine. Based on first-order elimination kinetics, the proportion (*P*) eliminated by a given time (*t*) is:

$$P = e^{-kt} \qquad \text{(Eq. 3)}$$

Rearranging to solve for k, the first-order excretion rate coefficient,

$$k = -\ln(P) \div t \qquad \text{(Eq. 4)}$$

Taking *P* as 0.75 (i.e., the average of the range of 0.68 to 0.81) and *t* as 4 hours, the first-order elimination rate (*k*) is about 0.072 $hour^{-1}$. An excretion rate of 0.072 $hour^{-1}$ corresponds to a rate of about 1.7 day^{-1}. Substituting this value into the above equation for the plateau principle, the estimated plateau in the body burden after daily doses over a prolonged period of time would be about 1.2 [$1 \div (1 - e^{-1.7}) \approx 1.22352$]. In other words, daily doses of imazapyr should not lead to any substantial accumulation in humans over prolonged periods of exposure. As discussed further in Section 3.1.5, this assessment is consistent with the lack of toxic effects observed in longer-term toxicity studies in mammals.

3.1.4. Acute Oral Toxicity

3.1.4.1. Experimental Mammals

Basic acute toxicity values include time-specific LD_{50} or LC_{50} values (i.e., doses or concentrations of a toxicant that result in or are estimated to result in 50% mortality of the test species during a specified exposure or observation period). These values can be viewed as an index of acute lethal potency. LD_{50} studies involve different levels of oral exposure which result in mortality rates that bracket 50% of the treated animals. These data are then used to estimate an oral LD_{50}. In the registration process, however, the U.S. EPA will accept *limit tests* in which the compound is tested at only a single high dose, typically 2000 mg/kg bw or 5000 mg/kg bw. If the compound does not cause mortality rates of 50% or more, the requirement for a full study to determine the LD_{50} value may be waived. In these instances, LD_{50} values are expressed as greater than the limit dose—e.g., >2000 mg/kg bw or >5000 mg/kg bw. Consistent with the terminology used in U.S. EPA/OPP risk assessments, LD_{50} values expressed as greater than a particular value are referred to as *non-definitive* LD_{50} values, and LD_{50} values expressed as a specific value (with or without confidence intervals) are referred to as *definitive* LD_{50} values.

The LD_{50} values reported on the Material Safety Data Sheets (MSDS) for various imazapyr formulations are summarized in Appendix 1, Table 1; the registrant-submitted studies on imazapyr and imazapyr formulations are summarized in Appendix 1, Table 2. Ideally, it would be beneficial to be able to identify and link LD_{50} values from MSDS with specific registrant-submitted studies, which is not possible for most pesticides, including imazapyr. For imazapyr, however, the issue is of no consequence to the risk assessment since all of LD_{50} values are non-definitive—i.e., the LD_{50} values are reported as >5000 mg/kg bw for all registrant-submitted studies (Appendix 1, Table 2) and most formulations (Appendix 1, Table 1). For two formulations, Imazapyr 4 SL from Alligare and Rotary 2 SL, the LD_{50} values reported on the MSDS are >2000 mg/kg. These LD_{50} values are presumably from one or more registrant-submitted studies which have not been identified. No oral LD_{50} values of >2000 mg/kg bw are cited in U.S. EPA/OPP risk assessments (U.S. EPA/OPP 2005a, 2006a, 2007a). It is possible that the LD_{50} values given as >2000 mg/kg bw are from studies in which 5000 mg/kg bw was the limit dose, and the MSDS reports the value as >2000 mg/kg bw to meet the U.S. EPA/OPP criteria for classifying compounds as *practically non-toxic*.

It is worth noting that the number of registrant-submitted studies is substantially less than the number of LD_{50} values reported on different MSDS. This difference may reflect *data bridging*. While the U.S. EPA/OPP generally requires at least acute toxicity data on pesticide formulations, it will sometimes allow toxicity studies on one formulation to support the registration of another formulation. This general approach is sometimes referred to as *bridging*. If the two formulations are identical (i.e., the same formulation is marketed under different names) data bridging makes sense. If the two formulations are substantially different, however, bridging is not permitted and formulation-specific data are required. The imazapyr literature does not specifically address the issue of data bridging.

The signs of toxicity in rats exposed to oral doses of 5000 mg/kg bw are not remarkable, and neither are the differences among the formulations that were tested (Appendix 1, Table 2). In the gavage toxicity study on technical grade imazapyr (Lowe 1999) and the gavage study on a 2 lbs a.e./gallon formulation (Fischer 1983), one of five male rats died, but no signs of toxicity were

observed in female rats. Given the small numbers of rats tested in these studies, five males and five females, the difference in the responses between the sexes is not statistically significant according to the Fisher Exact Test (i.e., a *p*-value of 0.5 for responses of 0/5 versus 1/5); moreover, incidental mortality following gavage dosing is not uncommon.

3.1.4.2. Case Reports (Human Poisoning)

As summarized in Table 5, information on the toxicity of imazapyr in humans is available from reports of six cases of acute poisoning in Taiwan (Lee et al. 1999). Five of the cases were adults (four men, one woman) who attempted suicide by ingesting concentrated (undiluted) Arsenal herbicide formulation (23.1% w/w imazapyr as the isopropylamine salt). The sixth case was a 4-year-old boy who was forced to swallow approximately 2 mL of Arsenal. Lee et al. (1999) provide estimates of the volume of Arsenal consumed based on patient history (e.g., number of mouthfuls ingested) and/or physical evidence such as the size of the bottle and remaining contents. As 23.1% Arsenal formulation does not precisely correspond to any of the formulations considered in the current risk assessment (Table 2) but is close to the 27.6% formulations that contain 2 lbs a.e./gallon or about 239,653 mg a.e./L, the estimated amount of imazapyr consumed, as given in Table 5, is based on the estimated volume of Arsenal consumed multiplied by the concentration of 239,653 mg a.e./L. For comparison to the available animal studies, the doses must be expressed in units of mg/kg bw.

Lee et al. (1999) do not provide information on the body weights of the individuals. Based on the most recent EPA recommendation, typical body weights for 50-year-old males and females are about 90 kg and 77.5 kg, respectively; a typical body weight for a 3- to 6-year-old child is about 18 kg (U.S. EPA/NCEA 2011a, pp. 8-13 to 8-15). While these body weights are reasonable for individuals in the United States, they are probably high for individuals in Taiwan. Definitive statistics on body weights for individuals in Taiwan were not located in the available literature. Somewhat lower body weights of 70 kg (adult male), 60 kg (adult female), and 14 kg (young child) are used in Table 5 to render a crude approximation of the ingested doses.

Based on the above assumptions, the doses to the adults in the case reports from Lee et al. (1999) are estimated to range from about 260 to 1200 mg a.e./kg bw. The dose to the child is estimated at 34 mg a.e./kg bw. The case reports from Lee et al. (1999) are consistent with the acute toxicity data in rats (Section 3.1.4.1) in that none of the individuals died. Doses of about 340 to 1700 mg a.e./kg bw were, however, associated with relatively severe signs of toxicity. This is not consistent with the acute studies in rats involving the 2 lbs a.e./gallon formulation of imazapyr (i.e., except for the one rat that died, none of the other rats showed signs of toxicity following a single gavage dose of 5000 mg a.e./kg bw). As discussed in Section 3.1.4.1, the death in the one male rat from the study by Fischer (1983) may have been incidental to gavage administration.

The most reasonable explanation for the apparent differences between rats and humans may involve vomiting. As summarized in Table 5, vomiting was noted in all six individuals cited in the case reports. As discussed by Lee et al. (1999), many of the other signs of toxicity noted in the six individuals may have been associated with pulmonary aspiration secondary to vomiting. Rats, on the other hand, do not vomit, and, therefore, would not display respiratory effects associated with aspiration.

One other unusual effect noted in the case reports by Lee et al. (1999) involves eye irritation. As summarized in Table 5, this effect was seen only in the 52-year-old male who consumed the greatest amount of the Arsenal formulation (i.e., about 500 mL equivalent, to a dose of about 1700 mg a.e./L). As discussed further in Section 3.1.11, imazapyr and some imazapyr formulations may cause eye irritation following ocular exposures. Eye irritation following oral exposure is unusual. Nonetheless, the brief note of this effect in the Lee et al. (1999) publication does not demonstrate that the eye irritation was actually caused by the ingestion of Arsenal.

3.1.5. Subchronic or Chronic Systemic Toxic Effects

As discussed in SERA (2007a, Section 3.1.5), *subchronic* and c*hronic* are somewhat general terms which refer to studies involving repeated dosing. Some studies are designed to detect 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-adverse-effect levels (NOAELs) for the identified endpoints as well as levels associated with adverse effects—i.e., lowest-observed-adverse-effect-levels (LOAELs).

An overview of the subchronic and chronic toxicity studies in mammals is given in Table 6; additional details on these studies are given in Appendix 1 (Table 10 for subchronic studies and Table 11 for chronic studies). Table 6 also includes other repeated dose studies including gavage developmental studies and a multigeneration reproduction dietary study in rats. Details of these studies are provided in Appendix 1 (Table 8 for developmental studies and Table 9 for the reproduction study). The developmental and reproduction studies are discussed in Section 3.1.9, while signs of frank toxicity in the developmental studies are discussed below in the current section.

Chronic dietary toxicity studies on imazapyr have been conducted in three species: dogs (Shellenberger 1987), mice (Auletta 1988; Hess 1992), and rats (Daly 1988; Hess 1992). The study by Khunachak (1999) in cows is a residue study included in Table 6 simply because no adverse effects were noted. The most remarkable aspect of all of the subchronic and chronic studies is the failure to note any adverse effects at doses of up to about 2000 mg/kg bw/day in rats and mice and about 250 mg/kg bw/day in dogs.

All of the subchronic and chronic studies involve dietary exposures. As discussed further in Sections 3.1.6 and 3.1.9, two standard developmental (i.e., teratology) studies in Charles River rats involving gavage administration report dose-related increases in salivation among females at doses ranging from 250 to 2000 mg/kg bw (Salamon et al. 1983c,d). Salivation can be considered a sign of neurotoxicity. On the other hand, salivation, was not observed in a dietary reproduction study involving Sprague-Dawley rats (Robinson 1987) or in any of the acute toxicity studies summarized in Section 3.1.4 or in the chronic toxicity studies summarized in Table 6.

As indicated in Appendix 1, somewhat unusual effects on food consumption are reported in some studies. In chronic dietary studies conducted with rats (Daly 1988) and mice (Auletta 1988), there was a slight, and in some cases statistically significant, increase in food consumption with no corresponding increase in body weight. Three classes of mechanisms

could produce this effect: a biochemical basis, such as uncoupling of oxidative phosphorylation; an endocrine basis (e.g. changes in thyroid hormone secretion, or increased corticosteroid levels) or a neurological basis involving hyperactivity. Imazapyr has been implicated in the development of thyroid tumors (Section 3.1.10). While a detailed review of the carcinogenicity studies does not support the assertion that imazapyr is carcinogenic, changes in appetite could be associated with thyroid effects. Without additional mechanistic studies, however, the basis for the observed effects on food consumption remains speculative.

The subchronic (13-week) study (Hess 1992) was conducted in rats exposed to imazapyr at dietary concentrations higher than the maximum tested in the chronic studies summarized above. Exposure to levels of 15,000 or 20,000 ppm caused no toxicity in either sex, as evaluated by a comprehensive range of endpoints. The 13-week study establishes a subchronic dietary NOAEL at the highest dose tested 20,000 ppm in rats, which corresponds to daily doses of about 1700 mg/kg/day according to Hess (1992). This NOAEL in rats is several-fold higher than the NOAEL in dogs established by Shellenberger (1987). Nonetheless, as with all of the subchronic and chronic studies, the NOAEL in dogs is free-standing (i.e., no adverse effect level was identified in dogs). Thus, the lower NOAEL in dogs is an artifact of the study design and does not indicate that dogs are more sensitive than other mammalian species. Even so, as discussed further in Section 3.3 (Dose-Response Assessment), the current RfD for imazapyr is based on the study in dogs.

3.1.6. Effects on Nervous System

In support of the Reregistration Eligibility Decision for imazapyr (U.S. EPA/OPP 2006a), the Health Effects Division of the U.S. EPA/OPP reviewed the available toxicity studies on imazapyr and concluded that there is no concern for neurotoxicity:

> *The HIARC* [Hazard Identification Assessment Review Committee] *concluded that there is not a concern for neurotoxicity resulting from exposure to imazapyr. The transient salivation seen in the developmental toxicity study was not considered to be evidence of neurotoxicity, since transient salivation is a common finding in oral rat studies, it occurred at the limit dose, and there is no evidence of neurotoxicity in any other studies.*
>
> U.S. EPA/OPP (2005a, p. 18).

As discussed below, the current risk assessment concurs with the EPA's position, although issues associated with the EPA rationale require clarification.

The neurotoxicity study being referenced by U.S. EPA/OPP (2005a) in the above quotation is the study by Salamon et al. (1983c ,MRID 131611). Various sections of the EPA discussion (U.S. EPA/OPP 2005a, pages 5 and 14) indicate that the salivation was seen only at the mid-dose group—i.e., 300 mg/kg bw/day and not the high dose group:

> *…however maternal toxicity, based on salivation, was observed in rats at the mid-dose of 300 mg/kg/day. This was not considered to be evidence of neurotoxicity, since it occurred at the limit dose and there is no evidence of neurotoxicity in any other studies.*
>
> U.S. EPA/OPP (2005a, p. 14).

The above statement is incorrect in that the salivation was observed only in the 1000 mg/kg bw/day dose group, as summarized in Appendix 1 (Table 8) of the current risk assessment as well as in other sections of the discussion in U.S. EPA/OPP (2005a, pages 16, p. 19 (Section 4.2.3.1) and p. 21).

The above statement by the EPA is also incorrect in that salivation in rats was also noted in the study by Salamon et al. (1983d, MRID No. 00131612], which was a pilot study for Salamon et al. (1983c). As summarized in Appendix 1 (Table 8) of the current risk assessment, the developmental study in rats by Salamon et al. (1983d) involved groups of five pregnant Charles River rats given gavage doses of 0, 250, 500, 1000, and 2000 mg/kg bw day. Salivation was noted in this study at response rates of salivation: 1/5 (250 mg/kg); 2/5 (500 mg/kg); 3/5 (1000 mg/kg); and 5/5 (2000 mg/kg). While U.S. EPA/OPP (2005a) cites the study by Salamon et al. (1983d), the results from this study are not discussed.

Using the Cochran-Armitage tests from U.S. EPA's Benchmark Dose Software (U.S. EPA/NCEA 2011b), the dose-response relationship in the study by Salamon et al. (1983c) is statistically significant at $p<0.0001$, and the dose-response relationship in the study by Salamon et al. (1983d) is statistically significant at $p=0.0003$. The EPA's misstatement that the salivation in the study by Salamon et al. (1983c) was noted only in the 300 mg/kg bw/day dose group is important in that, if this were correct, the dose-response relationship would not be statistically significant ($p=0.6136$).

The toxicity studies briefly summarized by Cyanamid (Japan) (1997) also suggestive possible neurological effects. In these studies, male mice or male rabbits were orally administered imazapyr isopropylamine at levels of 1000, 3000, or l0,000 mg/kg to define the effect on gross behavior, central nervous system, and digestive system. In addition, male rabbits or male rats were administered intravenously imazapyr isopropylamine at 100, 300, 1000, and 3000 mg/kg to define the effect on skeletal muscle and respiratory and circulatory systems. Administration of imazapyr isopropylamine produced … *a stimulant effect on gross behavior and increased the sleeping time induced by hexobarbital at high doses in mice, slightly increased muscle contractility in rats, depressed gross behavior at high doses in rabbits, slightly changed respiratory rate, blood pressure, and heart rate in rabbits, and increased the volume of urine at high doses in both mice and rabbits*. These studies are attributed to Medical Scientific Research Laboratory (1992) without additional details.

While somewhat speculative and perhaps tenuous, the statistically significant dose-response relationships noted in the studies by Salamon et al. (1983c,d) could suggest a possible neurological effect. Schwarcz et al. (1983) noted that quinolinic acid, a photolytic (though not metabolic) breakdown product of imazapyr, causes neurotoxic effects at very low doses when injected directly into the brains of rats (i.e., intracerebral injection). Nonetheless, as noted in Section 3.1.15.1, quinolinic acid levels in the brain are regulated by an active transport system, and it does not seem likely that sufficient quinolinic acid would be present in imazapyr to cause frank signs of toxicity. This supposition is supported by the fact that signs of neurotoxicity have not been noted in other studies on reproductive or developmental effects, and neurotoxicity has not been noted in standard acute and chronic toxicity studies. In addition, none of the studies in

the imazapyr database reported histopathological changes in nervous tissue. Thus, the weight of evidence, consistent with the position taken in U.S. EPA/OPP (2005a), does not support the assertion that imazapyr is likely to be a neurotoxin.

3.1.7. Effects on Immune System

There are various methods for assessing the effects of chemical exposure on immune responses, including assays of antibody-antigen reactions, changes in the activity of specific types of lymphoid cells, and assessments of changes in the susceptibility of exposed animals to resist infection from pathogens or proliferation of tumor cells.

With the exception of skin sensitization studies (Section 3.1.11.2), specific studies regarding the effects of pesticides on immune function are not required for pesticide registration. Nonetheless, typical subchronic or chronic animal bioassays conduct morphological assessments of the major lymphoid tissues, including bone marrow, major lymph nodes, spleen and thymus (organ weights are sometimes measured as well), and blood leukocyte counts. These assessments can detect signs of inflammation or injury indicative of a direct toxic effect of the chemical on the lymphoid tissue. Changes in morphology/cellularity of lymphoid tissue and blood, indicative of a possible immune system stimulation or suppression, can also be detected. As discussed in Section 3.1.5, however, the subchronic and chronic toxicity studies on imazapyr failed to note any adverse effects in blood or other tissue. Although these studies did not focus on the immune system, changes in the immune system (which could be manifested as increased susceptibility to infection compared to controls) were not observed in any of the available long-term animal studies (Appendix 1). Thus, there is no basis for suggesting that imazapyr has an adverse effect on immune function.

3.1.8. Effects on Endocrine System

The direct effects of pesticides on endocrine function are most often assessed in mechanistic studies of estrogen, androgen, corticosteroid, or thyroid hormone systems (i.e., assessments on hormone synthesis, hormone receptor binding, or post-receptor processing). U.S. EPA/OPP (2011b) developed a battery of screening assays for endocrine disruption. Imazapyr was not selected as one of the pesticides for which the screening assays are required (U.S. EPA/OPP 2009).

In terms of functional effects that have important public health implications, effects on endocrine function could be expressed as diminished or abnormal reproductive performance. This issue is addressed specifically in the following section (Section 3.1.9).

The available toxicity studies do not report histopathological changes in endocrine tissues that were examined as part of the standard battery of tests. As discussed in Section 3.1.5, the increased food consumption without a corresponding change in body weight noted in some chronic feeding studies in rodents (Auletta 1988; Daly 1988) could be associated with endocrine function (i.e., a change in thyroid status). Even so, none of the animal studies reports abnormal thyroid histology or hormone levels in the standard clinical chemistry results attributed to imazapyr exposure. The study by Auletta (1988) also notes an increase in the incidence of elevated seminal vesicle weight. While Auletta (1988) suggests that this condition is among *"common findings in old mice,"* the response appears to be dose-related, and the development of the seminal vesicles is stimulated by androgenic hormones. In the absence of a consistent pattern

of effects on seminal vesicle weight in other studies, however, the weight of evidence suggests that the observations by Auletta (1988) are incidental.

In the review of the mammalian toxicity data on imazapyr, U.S. EPA/OPP (2005a, p. 29) concludes that *…there was no evidence of estrogen, androgen and/or thyroid agonistic or antagonistic activity shown*. This conclusion is reasonable, based on the review of the available information conducted as part of the current risk assessment.

3.1.9. Reproductive and Developmental Effects

3.1.9.1. Developmental Studies

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

As summarized in Table 6 and detailed further in Appendix 1 (A1 Table 8), standard developmental toxicity studies were conducted with rabbits (Salamon et al. 1993a,b) and rats (Salamon et al. 1993c,d). The available developmental studies are preliminary pilot studies (Salamon et al. 1993a,d) and full studies (Salamon et al. 1993b,c). Unlike all of the other repeated dosing studies in mammals, the developmental toxicity studies were conducted using gavage administration. Gavage administration involves the use of a specialized device (an intubation syringe) to insert the test compound directly into the stomach of the test organisms. Generally, gavage dosing leads to signs of toxicity at lower doses than observed in dietary exposures, and this pattern is evident with imazapyr.

While the studies in rats and rabbits yielded no signs of frank malformations, these gavage developmental studies are the only repeated dose studies that yield any signs of toxicity. In rats, the signs of toxicity are relatively mild, consisting only of increased salivation, as discussed in Section 3.1.6. In rabbits, however, the signs of toxicity are much more severe, consisting of mortality in both adult female rabbits and rabbit fetuses at a dose 1000 mg/kg bw/day in the pilot study (Salamon et al. 1993b). In the full study with rabbits (Salamon et al. 1993b), however, no signs of toxicity were evident at gavage doses of 400 mg/kg bw/day. By comparison, the comparable studies in rats noted no mortality in adult or fetal rats at doses of up to 2000 mg/kg bw/day. This is the only example of an apparent species difference in the sensitivity of imazapyr to mammals. Given the route of exposure (i.e., gavage rather than dietary) as well as the very high doses of imazapyr that were administered, this observation has little practical impact on the current risk assessment, as discussed further in the risk characterization for humans (Section 3.4) and mammalian wildlife (Section 4.4.2.1).

3.1.9.2. Reproduction Studies

Reproduction studies involve exposing one or more generations of the test animal to a chemical compound. Generally, the experimental method involves dosing the parental (P or F_0) generation (i.e., the male and female animals used at the start of the study) to the test substance prior to mating, during mating, after mating, and through weaning of the offspring (F_1). In a 2-generation reproduction study, this procedure is repeated with male and female offspring from the F_1 generation to produce another set of offspring (F_2). During these types of studies, standard observations for gross signs of toxicity are made. Additional observations often include the length of the estrous cycle, assays on sperm and other reproductive tissue, and number, viability, and growth of offspring. The EPA requires only one acceptable multi-generation reproduction study.

As summarized in Appendix 1 (A1 Table 8), a single 2-generation reproduction study in rats (Robinson 1987) was submitted to and accepted by the EPA (U.S. EPA/OPP 2005a, p. 20). This study involved dietary exposures of rats to imazapyr at concentrations of 0, 1000, 5000, or 10,000 ppm (mg a.e/kg diet). No dose-related signs of toxicity were observed in either adults or offspring. Based on measured food consumption, the 10,000 dietary exposure groups corresponded to doses of 483.4 to1471.8 mg a.e./kg bw/day in males and 761.3 to 1537.1 mg a.e./kg/day in females. As detailed in Appendix 1 (A1 Table 9), the U.S. EPA/OPP (2005a) gives estimated doses of 738 mg/kg bw/day for males and 933.3 mg/kg bw/day for females. These dose estimates are somewhat lower than the mean of the ranges, which is not unusual in that the distribution of doses was probably log-normally distributed.

3.1.10. Carcinogenicity and Mutagenicity

3.1.11.1. Mutagenicity

As reviewed in U.S. EPA/OPP (2005a, pp. 13-14), imazapyr was tested in several standard assays for mutagenicity, including reverse mutation assays in *Salmonella*, *in vitro* assays for mutagenic activity in mammalian cell cultures, *in vitro* chromosomal aberrations in Chinese hamster ovary cells, assays for unscheduled DNA synthesis, and an *in vivo* assay for dominant lethal mutations in mice. None of these assays is positive for mutagenic activity. The two gene mutation studies (*Salmonella typhimurium/Escherichia coli* and Chinese hamster ovary cell gene mutation) and one chromosomal aberration study (Chinese hamster ovary cells) are classified as acceptable and negative for potential mutagenic activity. An additional chromosomal aberration study (dominant lethal assay) was also negative but was classified as inadequate because the complete spermatogenic cycle was not evaluated. In a re-review of this study, however, U.S. EPA (1997) recommends that the study be upgraded to acceptable. Further support for lack of genotoxic activity comes from other mutagenicity studies conducted and submitted to U.S. EPA in support of the registration of imazapyr (Allen et al. 1983; Cortina 1984; Enloe et al. 1985; Johnson and Allen 1984; Sernau 1984). All of these studies demonstrate a negative response. More recently, both technical grade imazapyr and a Brazilian Arsenal formulation were negative in a mouse micronucleus assay, a common screening test for mutagenic activity (Grisolia 2002, 2004). While it is impossible, by definition, to prove the negative, the available data appear to be of sufficient quality and detail on which to base the assertion that imazapyr does not appear to be genotoxic or mutagenic.

3.1.11.2. Carcinogenicity

In terms of a quantitative significance to the human health risk assessment, carcinogenicity is an issue only if the data are adequate to support the derivation of a cancer potency factor. A cancer potency factor is typically derived based on a dose-related increase in malignant tumors from a chronic toxicity study in mammals which encompasses a significant portion of the test animals' lifespan.

As summarized in Appendix 1 (A1 Table 11), chronic dietary exposures were conducted over a substantial portion of the lifespan of mice (Auletta 1988) and rats (Daly 1988). The study in mice by Auletta (1988) was unequivocal with no indication of carcinogenic activity. In the study in rats by Daly (1988), however, the combined incidence of benign and malignant brain astrocytomas was increased. As detailed Appendix 1 (A1 Table 11), analyses of the tumor conducted as part of the current risk assessment indicated a significant dose-response relationship based on the Cochran-Armitage trend test (p=0.0175) but no significant differences between the control response and any treated dose group (a minimum p-value of 0.2265). This analysis is consistent with the EPA analyses provided in U.S. EPA/OPP (2005a, p. 25). As detailed further in U.S. EPA/OPP (2005a, pp. 26-27), the study in rats by Daly (1988) was reviewed in detail by U.S. EPA/OPP's Cancer Assessment Review Committee. The evaluation by the Cancer Assessment Review Committee included a review of the brain slides. The EPA concluded that the responses in rats offered … *equivocal evidence for carcinogenicity*… but: *When other data are considered, the overall weight of the evidence indicates no concern for human carcinogenicity*. The EPA discussion also notes that one individual on the Cancer Assessment Review Committee did not concur with this decision.

Forest Service risk assessments defer to EPA evaluations of carcinogenicity, unless there is a compelling reason to do otherwise (i.e., new information that the EPA has not considered). In the case of the Daly (1988) study on imazapyr, it is clear that the EPA carefully considered all available information. Consequently, the current risk assessment defers to the judgment made in U.S. EPA/OPP (2005a), and carcinogenicity is not identified as an endpoint of concern in the quantitative assessment of risk.

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 2011a). For all three endpoints, the U.S. EPA/OPP uses a ranking system for response ranging from Category I (most severe response) to Category IV (least severe response). These studies on these endpoints are summarized in Appendix 1: A1 Table 4 for skin irritation, A1 Table 5 for skin sensitization, and A1 Table 6 for eye irritation. Summaries of the results of formulation-specific studies, taken from formulation MSDS, are given in Appendix 1, A1 Table 1.

3.1.11.1. Skin Irritation

Appendix 1 (A1 Table 4) summarizes four registrant-submitted studies on skin irritation. Two of these studies appear to be directly relevant to the current risk assessments, including Fischer (1983) conducted with a 2 lbs a.e./gallon formulation and Fisher (1986a) conducted with Chopper. As indicated in Table 2 in the main body of this risk assessment, Chopper is one of the herbicides used in Forest Service programs; moreover, many of the other imazapyr formulations used in Forest Service programs contain imazapyr at a concentration of 2 lbs a.e./gallon. The

specific 2 lbs a.e./gallon formulation tested by Fischer (1983) is not clear. It is also not clear whether there are substantial differences among 2 lbs a.e./gallon formulations of imazapyr. As noted in Section 3.1.4.1, the U.S. EPA/OPP will often allow data bridging among formulations; however no discussions of data bridging were identified in the literature on imazapyr. Nonetheless, both the skin irritation study on Chopper (Fisher 1986a) and the 2 lbs a.e./gallon formulation (Fischer 1983) note mild skin irritation. As summarized in Appendix 1 (A1 Table 1), these results are consistent with the MSDS for Chopper as well as several other 2 lbs a.e./gallon formulations. The other two studies summarized in Appendix 1 (A1 Table 4) also note mild skin irritation.

The MSDS for three of the formulations listed in Appendix 1 (A1Table 1) indicate that they are non-irritating to the skin—i.e., Ecomazapyr 2SL (Alligare), Imazapyr 4 SL (Alligare), and Rotary 2 SL. While there is no reason to doubt the information on the MSDS, studies which correspond to non-irritating effects on the skin have not been identified in the available literature. It should be noted that the study on Chopper (Fisher 1986a) is consistent with mild irritation; yet, the MSDS for Chopper indicates only that Chopper may cause skin irritation. This is not a contradiction. MSDS terminology is variable and sometimes imprecise. The indication on the MSDS that Chopper may cause skin irritation is consistent with the finding by Fisher (1986a) that the irritation may be mild.

None of the available information on imazapyr formulations suggests the likelihood of severe skin irritation, which is consistent with the EPA classification of imazapyr as a Category IV skin irritant (U.S. EPA/OPP 2005a, p. 15)—i.e., non-irritating to slight erythema and edema. As noted at the start of Section 3.1.11, this classification is the least severe of the categories for skin irritation used by U.S. EPA/OPP.

3.1.11.2. Skin Sensitization

Appendix 1 (A1 Table 4) summarizes three registrant-submitted studies on skin sensitization in guinea pigs, including an assay on technical grade imazapyr (Ledoux 1983), an assay on Chopper RTU (American Cyanamid Co. 1988a), and an assay on a granular Arsenal formulation (Costello 1986). No signs of skin sensitization were observed in any of the assays, which is consistent with the EPA classification of imazapyr as *negative* for skin sensitization (U.S. EPA/OPP 2005a).

Notwithstanding the above classification, the MSDS for three formulations of imazapyr explicitly considered in this risk assessment indicate slight or mild skin sensitization (i.e., Chopper, Polaris SP, and Stalker). All of these formulations contain imazapyr at 22.6% (w/w) a.e and a concentration of 2 lbs a.e./gallon. While studies supporting this classification were not identified in the literature, there is no reason to question the information on the MSDS. Accordingly, slight to mild skin sensitization cannot be ruled out for at least some of the imazapyr formulations.

3.1.11.3. Ocular Effects

Appendix 1 (A1 Table 7) summarizes four registrant-submitted studies on eye irritation in rabbits, including assays on a 2 lbs a.e./gallon formulation (Fischer (1983), a 5% granular Arsenal formulation (Fischer 1986a), Chopper (Fischer 1986b), and a 6% RTU formulation (Fischer 1989b). The first three formulations yielded evidence of eye irritation, and the 6% RTU

formulation indicated minimal eye irritation. The MSDS for several formulations in Appendix 1 (A1 Table 1) indicate that some formulations, including Arsenal, Arsenal AC, and Ecomazapyr 2 SL (Alligare), are non-irritating; yet, studies to support this classification were not identified in the literature on imazapyr.

Neither the studies summarized in Appendix 1 (A1 Table 7) nor the data on the MSDS for the formulations specified in Appendix 1 (A1 Table 1) indicate that imazapyr or imazapyr formulations are severe eye irritants. Nonetheless, U.S. EPA/OPP (2005a, p. 15) identifies two studies on 99.3% imazapyr powder [MRID 41551001 and 93048019] indicating that this material is severely irritating to the eyes and causes irreversible eye damage (Category I). This finding is not remarkable. Instilling the powder of a weak acid directly into the eye is likely to cause severe damage to the eyes. This finding is not directly relevant to the current risk assessment because individuals involved in applications relevant to Forest Service programs or projects will not use concentrated imazapyr powder.

3.1.12. Systemic Toxic Effects from Dermal Exposure

As summarized in Appendix 1 (A1 Table 3), several acute dermal toxicity studies were conducted on imazapyr formulations, and one subchronic toxicity study was conducted on technical grade imazapyr (Larson and Kelly 1983).

As with the acute oral toxicity data in rats (Section 3.1.4.1), all of the acute dermal toxicity LD_{50} values are non-definitive—i.e., >2000 mg/kg bw for rabbits (Fischer 1983; Fischer 1986b; Fischer 1989a) and >5000 mg/kg bw for rats (Lowe and Bradley 1996). All of the acute dermal toxicity studies involved only single limit doses. Thus, the difference in the reported non-definitive LD_{50} values simply reflects differences in the doses used in the rat and rabbit studies, rather than species sensitivity differences. Based on these studies, imazapyr is classified by the U.S. EPA/OPP (2005a, p. 15) as Category III (the second to the least toxic category). Notably, this classification reflects the doses used in the toxicity studies rather than the inherent dermal toxicity of imazapyr. In order to be classified as Category IV, a compound must be tested at doses >20,000 mg/kg bw (SERA 2007a, Table 3-2). Since the acute oral LD_{50} values for imazapyr are >5000 mg/kg (Section 3.1.4.1), the lack of apparent toxicity at dermal doses of up to 5000 mg/kg/day is to be expected; accordingly, these studies add little to the assessment of acute dermal toxicity.

In the subchronic study (Larson and Kelly 1983), groups of 20 rabbits (10 per sex) were dosed with technical grade imazapyr at 0, 100, 200, or 400 mg a.e./kg bw/day, 5 days/week, for 3 weeks. While two animals died during the study, the deaths were due to pneumonia and not related to treatment (U.S. EPA/OPP 2005a, p. 55). Thus, in the absence of any signs of toxicity, the U.S. EPA/OPP (2005a) classifies the subchronic dermal dose of 400 mg a.e./kg bw/day as a NOAEL.

3.1.13. Inhalation Exposure

As summarized in Appendix 1 (A1 Table 6), three inhalation toxicity studies are available on imazapyr, including one on technical grade imazapyr (Voss et al. 1983) and two on imazapyr formulations, Arsenal 4-AS (Hershman and Moore 1986) and a Chopper RTU (Werley 1987). All of these rat studies involved whole body exposures to concentrations in excess of 1 mg/L (1000 mg/m^3).

In the study by Voss et al. (1983) conducted with technical grade imazapyr, no mortality or signs of toxicity attributable to treatment were noted over the 14-day post-exposure observation period following a 4-hour exposure at a measured concentration of 1.3 mg a.e./L. During and immediately after exposure, animals evidenced signs of nasal irritation, which is not unusual in acute inhalation studies. All animals were normal by Day 2 of the study. Based on this study, the U.S. EPA/OPP (2005a, p. 15) classifies imazapyr as Category 3—i.e., the second to the least toxic classification.

The U.S. EPA/OPP (2005a) does not cite or discuss the formulation studies; moreover, these studies are not discussed in the Reregistration Eligibility Decision on imazapyr (U.S. EPA/OPP 2006a). The study by Hershman and Moore (1986) suggests a greater inhalation toxicity for a formulation designated as *Arsenal 4AS*. In this assay, lung pathology was noted. While this assay did not involve a control group (which is a common practice in limit assays), it appears that the lung pathology could be related to treatment. The practical significance of this observation to the current risk assessment is not completely clear, since the assay involved an exposure to a very high concentration (4.62 mg/L or 4620 mg/m^3) and there is no information in the literature about Arsenal 4As to suggest that it is currently in use. In addition, the Forest Service has not designated Arsenal 4AS as one of the formulations likely to be used in Forest Service programs (Table 2).

3.1.14. Adjuvants and Other Ingredients

3.1.14.1. 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.

Information provided by the U.S. EPA/OPP on all of the inerts used in imazapyr formulations was reviewed in the previous Forest Service risk assessment (SERA 2004a). Specific notes are included in Appendix 1 concerning those toxicity studies in which information on inerts is specified. This information, however, is considered proprietary under FIFRA. Other than to state that no apparently hazardous materials have been identified, this information cannot be disclosed in detail.

All of the technical formulations of imazapyr covered in this risk assessment involve the isopropylamine or isopropanolamine salts of imazapyr. Little toxicity data are available for these compounds. Isopropanolamine is classified in U.S. EPA (2007b) as a List 3 inert. These are compounds that the U.S. EPA cannot classify as hazardous or non-hazardous based on the available information. Isopropyl alcohol, isopropylamine, and numerous other derivatives of isopropanol are used as food additives and classified as GRAS (generally recognized as safe) compounds (Clydesdale 1997). Isopropyl alcohol is classified as a List 4B inert, and

isopropanolamine as well as a number of related compounds are classified by U.S. EPA as List 3 inerts (U.S. EPA/OPP 2007).

The Northwest Coalition for Alternatives to Pesticides (NCAP) obtained information on the identity of the inerts in Arsenal AC from U.S. EPA, under the Freedom of Information Act. This listing is no longer posted on the NCAP web site; however, the information was reviewed in the SERA (2004a) risk assessment. The only inert other than water listed at NCAP site was glacial acetic acid (CAS No. 64-19-7). Dilute acetic acid is an approved food additive and is also classified as a GRAS compound (Clydesdale 1997). Acetic acid is a major component of vinegar and is a List 4B inert (U.S. EPA/OPP 2003).

3.1.14.2. Adjuvants

As summarized in Table 2, adjuvants including nonionic surfactants, methylated seed oils, or vegetable oil concentrates are recommended in both terrestrial and aquatic applications of imazapyr. Most product labels recommend the use of a nonionic surfactant at a concentration of at least 0.25% v/v and some formulations recommend concentrations of up to 1% v/v. For some herbicides such as glyphosate, studies are available suggesting that at least some nonionic surfactants may be much toxic than the herbicide itself to both humans as well as nontarget species (e.g., SERA 2011b). Although the use of adjuvants may enhance the efficacy of imazapyr, there is no information regarding the impact of adjuvants in combination with imazapyr or imazapyr formulations on humans or other mammals.

Methylated seed oils and vegetable oil concentrates are somewhat vague terms, but there is no basis for asserting that these adjuvants are likely to enhance the toxicity of imazapyr 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 imazapyr 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 imazamox to aquatic species (Section 4.1.3.5).

3.1.15. Impurities and Metabolites

3.1.15.1. Metabolites

The *in vivo* mammalian metabolism of imazapyr is considered in Section 3.1.3; this section of the risk assessment concerns the metabolism of imazapyr in the environment. The environmental metabolism of a pesticide may need to be considered quantitatively if the metabolites are more toxic and/or more persistent than the parent compound.

The chemical structures of imazapyr and its known metabolites are illustrated in Figure 4. The nomenclature of many of the metabolites of imazapyr is complex. Following the approach taken by U.S. EPA/OPP (2005a), alphanumeric codes are used in Figure 4 to designate the metabolites of imazapyr with more complex chemical names. For example, the methyl ester of imazapyr is formed in grass and water and the chemical name for the ester is 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-methyl ester nicotinic acid. For simplicity and as illustrated in Figure 4, this compound is referenced as CL 240 000.

Information on the metabolites of imazapyr comes primarily from registrant-submitted studies, which are discussed in detail in U.S. EPA/OPP (2005a). Very little information is available on the toxicity of most metabolites of imazapyr. One exception is nicotinic acid, also known as niacin or Vitamin B3. As noted in U.S. EPA/OPP (2005a), high doses of nicotinic acid may be toxic, although nicotinic acid is an essential nutrient with a recommended daily allowance of 20 mg/kg bw/day. In the absence of information suggesting that any of the metabolites of imazapyr are substantially more toxic than imazapyr itself, the U.S. EPA/OPP (2005a, Section 3.4.1) designates imazapyr as the only agent of concern for all routes of exposure.

3.1.15.2. Impurities

There is no information in the published literature concerning the manufacturing impurities in imazapyr. Nonetheless, virtually no chemical synthesis yields a totally pure product. Technical grade imazapyr, as with other technical grade products, contains some impurities. These impurities, which were disclosed to U.S. EPA, were reviewed as part of the previous Forest Service risk assessment (SERA 2004a) on imazapyr. Because specific information concerning impurities may provide insight into the manufacturing process used to synthesize imazapyr, such information is considered proprietary, is protected under FIFRA (Section 10), and is not discussed in this or the SERA 2004 risk assessment.

To some extent, concern for impurities in technical grade imazapyr is reduced by the fact that the existing toxicity studies on imazapyr were conducted with the technical grade product or formulated products. Thus, if toxic impurities are present in the technical grade product, the toxic potential of the impurities is likely to be encompassed by the available toxicity studies on the technical grade product.

3.1.16. Toxicological Interactions

No information is available on the interactions of imazapyr with other compounds. As discussed above, there is remarkably little information suggesting that imazapyr will have substantial toxicological effects on mammals. Consequently, there is no basis for inferring toxicological interactions of imazapyr with other agents. Nonetheless, imazapyr is a weak acid. In terms of mechanism of action, it is likely that imazapyr would influence and be influenced by other weak acids excreted by the kidney. These influences, however, would be significant only at relatively high doses that saturate the active transport processes involved in excretion by the kidney (e.g., Schnermann and Sayegh 1998).

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 terrestrial applications and Attachment 2 for aquatic applications. 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 (2010a, 2011). All exposure assessments for both terrestrial and aquatic applications are based on the unit application rate of 1.0 lb a.e./acre.

For terrestrial applications, worker exposures are modeled for backpack spray, broadcast ground spray, and aerial spray. In non-accidental scenarios involving the normal application of imazapyr, central estimates of exposure for workers are approximately 0.013 mg/kg/day for backpack applications, 0.02 mg/kg/day for ground broadcast applications, and 0.015 mg/kg bw/day for aerial spray. Upper ranges of exposures are approximately 0.08 mg/kg/day for backpack and aerial applications and 0.15 mg/kg/day for ground broadcast applications. Aquatic applications of imazapyr are associated with doses of 0.009 (0.004 to 0.02) mg/kg bw/day. All of the accidental exposure scenarios for workers involve dermal exposures. The accidental exposure scenarios lead to dose estimates which are less than those associated with the general exposure levels estimated for workers. This point reflects the limited exposure periods (i.e., 1 minute and 1 hour) used for the accidental exposure scenarios. For terrestrial applications, the upper bound estimate of the absorbed dose is about 0.03 mg/kg bw, if contaminated gloves are worn for 1 hour. If contaminated gloves were worn for an 8-hour workday, the absorbed dose would be about 0.24 mg/kg bw, which is higher than any of the dose estimates for general (non-accidental) exposure scenarios.

For the general public (Worksheet E03), acute non-accidental exposure levels associated with terrestrial applications range from very low (e.g., $\approx 9 \times 10^{-6}$ mg/kg/day) to 1.35 mg/kg bw at the unit application rate of 1.0 lb a.e./acre. The upper bound of exposure of 1.35 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. Of the accidental exposure scenarios, the greatest exposure levels are associated with the consumption of contaminated water by a small child, for which the upper bound dose is about 2 mg/kg bw/day. For aquatic applications, the consumption of contaminated terrestrial vegetation is not a relevant route of exposure. The highest non-accidental exposure scenario for aquatic applications is associated with the consumption of contaminated water for which the upper bound of the estimated dose is about 0.04 mg/kg bw/day.

The chronic or longer-term exposure levels are much lower than the estimates of corresponding acute exposures. For terrestrial applications, the highest longer-term exposure levels are associated with the consumption of contaminated vegetation, and the upper bound for this scenario is about 0.6 mg/kg/day, which is followed by the scenario for the longer-term consumption of contaminated fruit with an upper bound of 0.09 mg/kg/day. The lowest longer-term exposure levels are associated with the consumption of contaminated fish. For aquatic

applications, the highest longer-term exposure level is about 0.01 mg/kg bw/day, the upper bound of the estimated dose associated with the consumption of contaminated water.

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 unit application rate of 1.0 lb a.e./acre for both terrestrial applications (Attachment 1) and aquatic applications (Attachment 2). For most exposure scenarios, exposure and consequent risk will scale linearly with the application rate. The consequences of using lower or higher application rates are considered in the risk characterization (Section 3.4).

3.2.2.1. General Exposures

3.2.2.1.1. Terrestrial Applications

As described in SERA (2007a), 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, default exposure rates are estimated for three different types of applications: directed foliar (backpack), boom spray (hydraulic ground spray), and aerial. These exposure rates, taken from Table 3-3 in SERA (2007a), are summarized in Table 7 of the current Forest Service risk assessment. The ranges of estimated occupational exposure rates vary substantially among individuals and groups, (i.e., by a factor of 50 for backpack applicators and a factor of 100 for mechanical ground and aerial applications).

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 7. These values are based on treatment rates used in several Forest Service Environmental Impact Statements (USDA/Forest Service 1989a,b,c).

Attachment 1, the EXCEL workbook for terrestrial applications, is modified to include three worksheets for general exposures, including backpack applications (Worksheet C01a), ground broadcast applications (Worksheet C01b), and aerial applications (Worksheet C01c). As noted in Section 2.3.1, other application methods may be used for imazapyr, including foliar spot, hack and squirt, cut stump, and basal bark applications. Standard exposure rates for these application methods have not been developed for Forest Service risk assessments. In addition, the U.S. EPA has not developed worker exposure assessments for these application methods for the Reregistration Eligibility Decision on imazapyr, U.S. EPA/OPP (2005j). The most prudent approach to evaluating Forest Service programs that use these application methods is to calculate the amount of imazapyr that a worker would apply in a single day and use the exposure rates for backpack applications given in Table 4.

For some pesticides, either the product label or standard Forest Service practice will require the use of personal protective equipment (PPE). When handling concentrated formulations, the

product labels for most formulations require the use of chemically resistant gloves. Otherwise, no special PPE is required. This level of PPE is typical in many pesticide applications, including those in the worker exposure studies that are the basis for the worker exposure rates provided in Table 7. Consequently, the worksheets for worker exposures (i.e., C01 series) use a clothing protection factor of 0 (i.e., no protection). As documented in Section 3.4.2 (Risk Characterization for Workers), all of the HQs for general worker exposure are substantially below the level of concern, and the lack of a requirement for extraordinary PPE does not have an impact the risk characterization for workers.

Typical occupational exposures involve multiple routes of exposure, including oral, dermal, and inhalation. The exposure rates used in the current Forest Service risk assessment are all based on estimates of absorbed doses during field applications. Thus, the general exposure assessments for workers encompass all routes of exposure.

3.2.2.1.2. Aquatic Applications

The literature on imazapyr does not include data regarding absorbed doses in workers involved in aquatic applications. This situation is similar to that encountered in Forest Service risk assessments on fluridone (SERA 2008a), rotenone (SERA 2008b), and imazamox (SERA 2010c). In these risk assessments, a study on worker exposure rates associated with aquatic applications of 2,4-D (Nigg and Stamper 1983) is used as a surrogate study for worker exposure. The study involved the application of a liquid formulation of 2,4-D by airboat handguns to control water hyacinths. The absorbed doses of 2,4-D were assayed in four workers as total urinary elimination over a 24-hour period. The estimated occupational exposure rates for the workers applying 2,4-D were 0.0009 (0.0004-0.002) mg/kg body weight per lb handled.

As noted in the Forest Service risk assessment on endothall (SERA 2010d), much lower worker exposure rates are used—i.e., 0.000039 (0.000033 to 0.000054) mg/kg bw per lb handled. As detailed in the endothall risk assessment, these lower worker exposure rates are based on an occupational exposure rate developed by the EPA which considers the severe dermal irritant effects of endothall (U.S. EPA/OPP 2005n). As noted in Section 3.1.11.1, however, imazapyr causes only slight skin irritation. Consequently, the higher worker exposure rates of 0.0009 (0.0004-0.002) mg/kg body weight per lb handled are used to estimate exposure levels for workers involved in aquatic applications of imazapyr.

As shown in Worksheet A01 of Attachment 2 (EXCEL workbook for aquatic applications of imazapyr), the amount handled is calculated as the product of the application rate and number of acres of water to be treated. The number of acres to be treated is likely to vary substantially among sites and programs. For the current risk assessment, the use of 10 acres is based on the U.S. EPA occupational risk assessment for aquatic applications of imazapyr from boats (U.S. EPA/OPP 2005j, p. 14). As discussed further in Section 3.4.2 (risk characterization for workers), the HQs for workers involved in aquatic applications of imazapyr are far below the level of concern, and reasonable variations in the acres of water surface to be treated are not likely to have an impact on the risk characterization for workers.

Some imazapyr formulations (e.g., Habitat) are labeled for aquatic applications by helicopter. For such applications, the exposure assessment given in Attachment 1 for aerial applications could be used with any necessary site specific modifications.

3.2.2.2. Accidental Exposures

The skin surface and eyes of workers are most likely to be affected by accidental spills or splashes of pesticide solutions. Quantitative exposure scenarios for eye exposures are not developed in this or other Forest Service risk assessments. As discussed in Section 3.1.11.3 (Ocular Effects), some formulations of imazapyr may cause eye irritation. Quantitative exposure and dose-response assessments for eye irritation are not developed. The potential for eye irritation is 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 imazapyr are characterized either by immersion of the hands in a field solution for 1 hour or wearing pesticide contaminated gloves for 1 hour. The assumption that the hands or any other part of a worker's body will be immersed in a chemical solution for a prolonged period of time may seem unreasonable; however, it is 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 imazapyr are provided in Section 3.1.3.2.

The amount of the pesticide absorbed per unit time depends directly on the concentration of the chemical in solution. For terrestrial applications, the current risk assessment uses an application volume of 20 gallons/acre with a range of 5 to100 gallons per acre, which encompasses the potential range of applications to be used in ground, aerial, and aquatic applications (Section 2.4.1). At a unit application rate of 1 lb a.e./acre, the estimated concentrations in a field solution are 6 mg/mL with a range of 1.2 to 24 mg/mL (Worksheet A01 in Attachments 1 and 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, and the duration of exposure. As with the zero-order dermal absorption rate, the first-order absorption rate (k_a) is derived in Section 3.1.3.2.

Numerous exposure scenarios could be developed for direct contact or accidental spills by varying the amount or concentration of the chemical on, or in contact with, the skin surface, the surface area of the affected skin, and the duration of exposure. As discussed further in the risk characterization (Section 3.4.2), however, the accidental scenarios lead to exposure levels far below the level of concern. What is more, reasonable variations in these exposure scenarios would not affect the assessment of potential risks to workers.

3.2.3. General Public

3.2.3.1. General Considerations

3.2.3.1.1. Likelihood and Magnitude of Exposure

Members of the general public could be exposed to imazapyr in Forest Service applications involving the treatment of recreational areas, including campgrounds, picnic areas, and trails. Because of the conservative exposure assumptions used in the current risk assessment, neither the probability of exposure nor the number of individuals who might be exposed has a substantial impact on the risk characterization presented in Section 3.4. As noted in Section 1 (Introduction) and detailed in SERA (2007a, 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 M*aximum Exposed Individual*. As this name implies, exposure assessments that use the MEI approach attempt to characterize the extreme but still plausible upper limit on exposure. This common approach to exposure assessment is used by U. S. EPA, other government agencies, and the International Commission on Radiological Protection (e.g., ATSDR 2002; ICRP 2005; Payne-Sturges et al. 2004). In the current risk assessment, all upper bounds on exposure are 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.

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 imazapyr 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–D11).

As summarized in Worksheet E03, the kinds of exposure scenarios developed for the general public include acute accidental, acute non-accidental, and longer-term or chronic exposures. The accidental exposure scenarios assume that an individual is exposed to the compound of concern either during or shortly after its application. The nature of the accidental exposures is intentionally extreme. Non-accidental exposures involve dermal contact with contaminated vegetation as well as the consumption of contaminated fruit, vegetation, water, 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 in the routine uses of imazapyr at a unit application rate of 1 lb a.e./acre for both terrestrial and aquatic applications. 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 on the risk characterization is discussed in Section 3.4.

For terrestrial foliar applications (Attachment 1), a standard set of exposure assessments used in all Forest Service risk assessments for broadcast applications are considered. The exposure assessments for aquatic applications include all of the exposure assessments for terrestrial applications, except for the exposure assessments involving direct spray (Section 3.2.3.2), dermal contact with contaminated vegetation (Section 3.2.3.3), and the consumption of contaminated vegetation (Section 3.2.3.6).

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 and more credible. 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 detailed in Section 3.1.9.1, the only adverse effects associated with exposure to imazapyr, albeit at very high doses, are those noted in developmental toxicity studies. 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 worksheets (SERA 2010a, 2011).

3.2.3.3. Dermal Contact with Contaminated Vegetation

In this exposure scenario, it is assumed that the herbicide is sprayed at a given application rate 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 imazapyr. 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 imazapyr. 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 the previous section.

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 imazapyr 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 consumption. 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 imazapyr 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 imazapyr in a small pond ranges from about 0.09 to about 18 mg/L, with a central estimate of about 2.3 mg/L (Attachment 1, Worksheet B04b).

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

Estimates of imazapyr concentrations in ponds and streams due to drift are developed only for terrestrial applications (Attachment 1). The exposure scenarios involving drift are less severe but more plausible than the accidental spill scenario described above. U.S. EPA typically uses a 2-meter-deep pond to develop exposure assessments (SERA 2007b). If such a pond is directly sprayed with imazapyr at the unit application rate of 1 lb a.e./acre, the peak concentration in the pond would be about 0.122 mg/L (Worksheet B04c). This concentration is a factor of about 150 below the upper bound of the peak concentration of 18 mg/L after the accidental spill (Section 3.2.3.4.1, Worksheets D05) [18 mg/L ÷ 0.122 mg/L ≈ 147.54]. Worksheet D10a also models concentrations at distances of from 25 to 900 feet down wind based on standard values adapted from AgDrift for the different terrestrial broadcast application methods considered in this risk assessment (SERA 2011). Based on these estimates, imazapyr concentrations in a small pond contaminated by drift from an application made 25 feet upwind would range from about 0.0009 (backpack application) to 0.025 mg/L (aerial application).

Similar calculations can be made for scenarios involving a stream contaminated either by direct spray or drift (Worksheet 10d). 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 0.09 mg/L. For an application made 25 feet upwind of the stream, the estimated concentrations of imazapyr in stream water range from about 0.0008 (backpack application) to 0.02 mg/L (aerial application).

3.2.3.4.3. GLEAMS Modeling

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

Gleams-Driver offers the option of conducting exposure assessments using site-specific weather files from Cligen, a climate generator program developed and maintained by the USDA Agricultural Research Service (http://horizon.nserl.purdue.edu/Cligen). Gleams-Driver was used in the current risk assessment to model imazapyr concentrations in a small stream and a small pond.

As summarized in Table 8, nine locations are used in the Gleams-Driver modeling. As discussed in SERA (2007b), these locations are standard sites use 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). The characteristics of the fields and waterbodies used in the simulations are summarized in Table 9. 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.e./acre, and each of the simulations was followed for a period of about 1½ years post application.

Table 10 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 U.S. EPA/OPP in PRZM/EXAMS modeling of imazapyr done for the risk assessment for the California Red Legged Frog (U.S. EPA/OPP 2007a, Appendix D, Table D.1.4, p. 6). 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 EPA by registrants as well as standard values for GLEAMS modeling recommended by Knisel and Davis (2000). The notes to Table 10 indicate the specific sources of the chemical properties used in the GLEAMS modeling effort.

Five of the chemical input parameters used in Gleams-Driver modeling are based on distributions rather than single values – i.e., half-lives for residues in water, soil, and vegetation as well as soil K_{oc} and sediment K_d. The use of distributions differs from the approach used in the EPA modeling, which used single values for each input parameter (U.S. EPA/OPP 2007a).

For soil half-life, the U.S. EPA/OPP (2007a) assumes that imazapyr is stable in soil in terms of aerobic soil metabolism – i.e., the compound does not degrade. The documentation for this estimate is referenced to MRID 131619 (U.S. EPA/OPP 2007a, Appendix D, Table D.1.4, p. 6). A full reference for this MRID is not given in U.S. EPA/OPP (2007a). This MRID is cited in the Reregistration Eligibility Decision document for imazapyr but the citation indicates that the study involved anaerobic soil metabolism (U.S. EPA/OPP 2006a, p. 61). As summarized in Table 1, the reported half-times of imazapyr in soil are highly variable. The aerobic soil metabolism study by Ta (1999a as detailed in U.S. EPA/OPP 2005g, p. A-5) reported half-lives for imazapyr of 296 (247 to 370) days. A somewhat more conservative analysis of this study, including two compounds that may have been artifacts, resulted in an adjusted half-life of 313 days. As summarized in Table 10, the adjusted half-life of 313 days is used as the lower bound of the soil half-life. Most other studies, however, suggest that imazapyr is more persistent in soil. In the soil metabolism study by Tollackson (1988 as also detailed in U.S. EPA/OPP 2005g, p. A-5), very little degradation of imazapyr was noted in sandy loam soil over an incubation period of 365 day. The extrapolated half-life for imazapyr was 5.9 years or about 2150 days and this value is used as a conservative central estimate of the half-life of imazapyr in soil. The longest reported half-life of imazapyr in soil is from the open literature study by Jarvis et al. (2006). The study by Jarvis et al. (2006) is a field study in which imazapyr was applied along a railway embankment and biphasic degradation was noted with an initial half-life of about 123

days and a terminal half-life of about 2,972 days. In field studies, biphasic degradation is commonly noted with the initial more rapid half-life associated with dissipation and the slower terminal half-life associated with degradation. For the Gleams-Driver modeling, terminal half-life of 2,972 days is used as the upper bound of the half-life of imazapyr in soil.

There is modest variability in the reported half-lives on vegetation. For the Gleams-Driver simulations, the central estimate of 30 days is taken from Knisel and Davis (2003) and the lower and upper bounds are taken from Neary and Michael (1993). While imazapyr is chemically and biologically stable in water, it is subject to rapid hydrolysis. The extent to which hydrolysis will impact the degradation of imazapyr in the field, however, is likely to vary substantially with factors such as the intensity of natural sunlight, topography and other factors that may shade the surface of the water, as well as the turbidity of the water. For the Gleams-Driver analyses, the measured photolytic half-life of 19.9 days is used as a lower bound. In the absence of additional information, the upper bound for the half-life of imazapyr in water is judgmentally set to 199 days.

The reported soil K_{oc} and K_d values display substantial variability spanning a factor of about 14 for K_{oc} values [110÷8=13.75] and a factor of about 50 for K_d values [3.4÷0.07≈48.6]. As with many weak acids, this variability reflects the fact that the binding of imazapyr to soil deviates from the simple K_{oc} model in which the K_{oc} should be relatively constant, because, under the K_{oc} model, the extent of soil binding (K_d) is directly proportional to the organic carbon in the soil (e.g., Winegardner 1996). More formally, the relationship of K_d to K_{oc} under the simple K_{oc} model can be expressed as:

$$K_d = K_{oc} \times oc, \qquad \text{(Eq. 5)}$$

where ***oc*** is the proportion of organic carbon in the soil. In other words, for any set of measured K_d values, the K_{oc} should be a constant. As summarized in Table 1, this is clearly not the case for imazapyr. Both the K_{oc} and K_d values for imazapyr based on Table A.2 in U.S. EPA/OPP (2005g, p. A-4), which summarizes studies providing matched estimates of K_d and K_{oc} values for 11 different soils. As discussed by Negre et al. (2001), factors which influence the apparent K_{oc} for imazapyr in soil include the presence of humic acids as well as the soil pH, with increased soil binding as soil pH decreases (i.e., as the soil becomes more acidic). The relationship of soil pH to soil binding is what would be expected for any weak acid—i.e., increasing soil pH will result in greater protonation of the imazapyr molecule which will in turn facilitate binding to organic matter.

Details of the results for the Gleams-Driver runs are provided in Appendix 7. A summary of the results for the Gleams-Driver runs are presented in Table 11, along with a summary of other modeling efforts which are discussed further in the following subsection. The uses of all of the available data in developing the exposure assessments for the current risk assessment are discussed in Section 3.2.3.4.6.

3.2.3.4.4. Other Modeling Efforts

Other efforts to model imazapyr concentrations in surface water are summarized in Table 11, 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, the U.S. EPA

typically uses Tier 1 screening models (e.g., GENEEC, FIRST, and SCIGROW) or PRZM/EXAMS, a more refined 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 11 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 concentrations estimated with Gleams-Driver.

In support of the Reregistration Eligibility Decision on imazapyr (U.S. EPA/OPP 2005c), the U.S. EPA used FIRST to estimate peak concentrations in surface water of about 97.3 µg a.e./L and annual average concentrations of 52.7 µg a.e./L. SCIGROW, a Tier 1 model for estimating concentrations in groundwater, was used to estimate peak concentrations of 24 µg a.e./L. All of these concentrations are higher than the central estimates from Gleams-Drive (i.e., about 11 to 18 µg/L for peak concentrations and from 0.5 to 7 µg a.e./L for longer-term concentrations). Notably, however, the maximum of the upper bound concentrations from Gleams-Driver (i.e., about 255 µg a.e./L for peak exposures and 120 µg a.e./L for longer-term concentrations) are higher than the corresponding concentrations from either FIRST or SCIGROW. This discrepancy is typical of many comparisons of Gleams-Driver to Tier 1 models. Because Gleams-Driver is applied to a large number of 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.

PRZM/EXAMS is a more sophisticated model than Gleams-Driver in that the EXAMS component of PRZM/EXAMS involves detailed subsurface hydrology which is not incorporated into Gleams-Driver. Nonetheless, for peak concentrations, the values from PRZM/EXAMS (i.e., about 12 to 20 µg a.e./L) are strikingly similar to the central estimates of the peak concentrations modeled with Gleams-Driver (i.e., about 11 to 18 µg a.e./L). The longer-term concentrations from PRZM/EXAMS (i.e., 60-day averages of about 10 to 20 µg a.e./L) are higher than the central estimates from the longer-term concentrations modeled with Gleams-Driver (i.e., about 0.5 to 7 µg a.e./L). This, however, is most likely an artifact of the averaging period. For example, the location with moist and temperate weather conditions (Quillayute, WA) with clay soil yielded an annual average concentration of 9.3 µg a.e/L in the pond (Appendix 7, Table 8), close to the average for all sites combined (i.e., 7.24 µg/L). The detailed results of from this site were exported to EXCEL and the average of the maximum 60-day concentrations for the 100 simulations for this site is about 19.8 µg a.e./L, very close to the 20 µg a.e./L concentration modeled using PRZM/EXAMS. In addition and as also summarized in Table 11, the upper bound of the annual averages from Gleams-Driver (i.e., 120 µg a.e./L for ponds) is higher than the 60-day average from PRZM/EXAMS. As discussed in the previous paragraph on the Tier 1 models, this is not an unusual pattern. Given the numerous site/soil combinations and the large number of simulations per combination, Gleams-Driver modeling will often result in upper bound estimates of pesticides in water which exceed those from both Tier 1 models as well as PRZM/EXAMS. This is the case for imazapyr.

3.2.3.4.5. Monitoring Data

Monitoring data regarding imazapyr concentrations in surface water were not identified in the literature. USGS (2003a) provides data on the agricultural uses of imazapyr; however, USGS (2003b) does not include imazapyr in the survey of pesticides in streams and groundwater.

Similarly, no monitoring data on imazapyr were identified in the more recent compendia by USGS (2007) on pesticide concentrations in streams and groundwater. The lack of monitoring data on imazapyr in surface water and groundwater is noted also in the recent EPA ecological risk assessment on imazapyr (U.S. EPA/OPP 2007a, p. 55).

3.2.3.4.6. Concentrations in Water Used for Risk Assessment

3.2.3.4.6.1. Terrestrial Applications

For terrestrial applications, the surface water concentrations of imazapyr used in the current risk assessment are summarized in Table 12. 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.e./acre, converted to units of ppm or mg/L per lb a.e./acre. In Table 11, units of exposure are expressed as ppb or µg/L, as a matter of convenience. In Table 12, however, ppb is converted to ppm because ppm and mg/L are the units of measure used in the EXCEL workbook for contaminated water exposure scenarios in both the human health and ecological risk assessments. The water contamination rates are entered in Worksheet B04Rt in Attachment 1 (the EXCEL workbook for terrestrial applications). The values in Worksheet B04Rt are linked to the appropriate scenario-specific worksheets in the EXCEL workbooks.

As discussed in the previous subsections and summarized in Table 11, the Gleams-Driver simulations of the small pond provide the highest estimates of imazapyr concentrations in surface water. Consequently, the Gleams-Driver simulations serve as the primary basis for the water concentrations of imazapyr used in the current risk assessment. As noted in 3.2.3.4.5, no monitoring data are available on concentrations of imazapyr in surface water. 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.

As summarized in Table 12, the peak concentrations are taken as 0.020 **(**0.000009 to 0.26**)** mg a.e./L. The central estimate of 0.020 mg/L is a composite of the central estimates from Gleams-Driver simulations of ponds (17.9 µg/L) and the PRZM/EXAMS estimate from the California rangeland scenario (22 µg/L). The average of these estimates (19.95 µg/L) is rounded to the nearest significant digit (i.e., 20 µg/L or 0.020 mg/L). The upper bound of 0.255 mg/L is simply a unit conversion of the upper bound concentration of 255 ppb from the Gleams-Driver pond simulations rounded to two significant places. The lower bound of 0.000009 mg/L is based on the lower bound of the peak concentrations in pond for a location with below average temperatures, average rainfall, and loamy soil – i.e., 0.009 µg/L as summarized in Appendix 7, Table 7. Lower concentrations could be selected; however, the selection of lower concentrations would have no impact on the risk assessment.

As also summarized in Table 12, the longer-term concentrations are taken as 0.007 (0.000003 to 0.12) mg a.e./L. The central estimate and upper bound are the central estimate of 7.24 ppb and the upper bound of 120 ppb for a small pond based on the Gleams-Driver modeling (Table 11) converted to units of mg/L and rounded to one significant figure. The lower bound of 0.0000025 mg/L is simply the lower bound of peak (acute) concentration divided by 3. This approach is adopted because the ratio of central estimates of the peak to longer-term concentrations is a factor of about 3 [0.02 mg a.e./L ÷ 0.007 mg a.e./L ≈ 2.86]. As with the lower bound of the peak concentrations, a lower concentration could be selected; however, it would have no impact on the risk assessment.

3.2.3.4.6.2. Aquatic Applications

Generic methods for modeling the peak concentrations resulting from the direct application of imazapyr to water are relatively simple in that the concentration of imazapyr will depend on the application rate and water depth. For the current risk assessment, the unit application rate of 1 lb a.e./acre is used. Water depth is likely to vary according to site conditions. For the current risk assessment the assumption is made that the water depth may range from 1 to 10 feet with a central estimate of 3 feet, the approximate geometric mean of the range. As summarized in Table 12 and detailed in Worksheet B04a of Attachment 2 (Aquatic Applications), these assumptions result in estimated peak concentrations of about 0.12 (0.037 to 0.37) mg a.e./L. These concentrations are substantially greater than concentrations anticipated from terrestrial applications, and this difference is to be expected.

Developing generic estimates of longer-term concentrations of imazapyr in water is much more difficult. As with terrestrial applications, no monitoring studies are available for aquatic applications of imazapyr. As summarized in Table 1, imazapyr is stable in terms of hydrolysis and biological degradation; however, the reported half-lives for the aqueous photolysis of imazapyr range from about 2 to 20 days. Depending on site-specific conditions (e.g., shading by the water edge) and water depth, the impact of photolysis could be diminished. An equally important factor involves dilution and water turnover rates. If applied to a shaded and relatively stagnant body of water in which natural dilution would be minimal, imazapyr might persist near the treatment site for a prolonged period. If applied to rapidly flowing stream, imazapyr would not occur at high concentrations at the treated site, and the concentration of imazapyr in the stream water would be diluted as the compound is transported downstream. These factors are difficult to consider with any precision. For the current risk assessment, the assumption is made that the functional dissipation half-life of imazapyr in water could range from about 2 days to 2 years (730 days). A dissipation half-life of 40 days (the geometric mean of the range) is used as the central estimate. As summarized in Table 12 and detailed in Worksheet B04a of Attachment 2 (Aquatic Applications), these assumptions result in estimated longer-term average concentrations of about 0.06 (0.0011 to 0.35) mg a.e./L. Notably, the upper bound concentration of 0.35 mg a.e./L is based on the half-life of 730 days; thus, the average longer-term concentration is not substantially different from the peak concentration. It seems likely that this upper bound estimate of the longer-term concentration may overestimate exposures, perhaps grossly so, in all but the most extreme situations.

Another mitigating factor that might typically lead to lower concentrations than those used in this risk assessment involves the proportion of the water body to be treated. The product labels for imazapyr formulations labeled for aquatic applications indicate that the entire body of water should not be treated at one time. The intent of this limitation is to allow mobile aquatic organisms to leave the treated area due either to the avoidance of imazapyr or to diminished levels of oxygen in the water as treated vegetation dies and rots. This mitigating factor is not considered quantitatively but is discussed further in the risk characterization for aquatic organisms (Section 4.4.3).

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 imazapyr 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 (2007a).

As part of the registration process, experimental bioconcentration factors are required, and one such study (McAllister et al. 1985) was submitted to U.S. EPA. McAllister et al. (1985) exposed bluegill sunfish to ^{14}C-labeled imazapyr for 28 days and found no indication of bioconcentration. The measured bioconcentration factor was less than 0.5. In other words, the concentration of imazapyr in the fish was less than the concentration of imazapyr in the water. For exposure assessments based on the consumption of contaminated fish, a BCF of 0.5 is used (i.e., the concentration in the fish will be one-half that of the concentration in the water). The EPA reviewed the data on the bioconcentration of imazapyr and confirms that imazapyr does not bioconcentrate in fish (BCF<1 L/kg) (U.S. EPA/OPP (2005b, p. 13; 2007a, p. 33).

The scenarios associated with consumption of contaminated fish are based on the same concentrations of imazapyr 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).

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. To assess the potential risks associated with swimming in contaminated water, an exposure assessment is developed for a young woman swimming in surface water for 1 hour (Worksheet D11). Conceptually and computationally, this exposure scenario is virtually identical to the contaminated gloves scenario used for workers (Section 3.2.2.2)—i.e., a portion of the body is immersed in an aqueous solution of the compound at a fixed concentration for a fixed period of time.

As 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, the exposure and consequently the risk will increase linearly with the duration of exposure, as indicated in Worksheet D11. Thus, a 2-hour exposure would lead to 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 imazapyr, 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 imazapyr 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 imazapyr will involve crop treatment, Forest Service risk assessments typically include standard exposure scenarios for the acute and longer-term consumption of contaminated vegetation. Two sets of exposure scenarios are provided: one for the consumption of contaminated fruit and the other for the consumption of contaminated vegetation. These scenarios, 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 imazapyr (Attachment 1) and are omitted from the EXCEL workbook for aquatic applications of imazapyr (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) after a normalized application rate of 1 lb a.e./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 assessment of imazapyr (U.S. EPA/OPP 2007a, p. 78).

The residue rates recommended by Fletcher et al. (1994) are given in Table 13 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 13 are made under the assumption that the ratio of the central estimate to the upper bound estimate is identical to the ratio of the lower bound estimate to the central estimate (i.e., the variability is log-symmetrical).

For longer-term exposures, the time-weighted-average exposure is estimated using the initial pesticide concentration and its half-life on vegetation (Worksheet D04a and D04b). These worksheets accommodate a central estimate and the lower and upper bounds on the half-life. In these worksheets, the half-lives are identical to those used in the Gleams-Driver modeling—i.e., 30 (15 to 37) days, as summarized in Table 10.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

The dose-response assessment for imazapyr is relatively straightforward, and the toxicity data base is reasonably complete and unambiguous. The U.S. EPA/OPP derived a chronic RfD of 2.5 mg/kg/day using a dog NOAEL of 250 mg/kg/day and an uncertainty factor of 100. The NOAEL selected by the U.S. EPA appears to be the most appropriate and is supported by additional NOAELs in rats and mice as well as a number of studies on potential reproduction and developmental effects. Consistent with the approach taken in U.S. EPA (2005a) in the most recent human health risk assessment, no acute RfD is derived in the current Forest Service risk assessment and the chronic RfD of 2.5 mg/kg/day is used to characterize the risks of both acute

and longer-term exposures. Because doses clearly associated with adverse effects have not been identified and because none of the hazard quotients developed in Section 3.4 (Risk Characterization) exceeds the level of concern, considerations of dose-severity relationships cannot be made and are not necessary.

3.3.2. Chronic RfD

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

The Office of Pesticide Programs of the U.S. EPA derived an RfD of 2.5 mg/kg/day (U.S. EPA 1997). The RfD is based on a study in which groups of male and female dogs were exposed to dietary concentrations of 0, 1000, 5000, or 10,000 ppm imazapyr for 1year (Shellenberger 1987).

As discussed in Section 3.1.3 and detailed further in Appendix 1 (Table 11), no adverse effects attributable to treatment were observed in dogs from any treatment group. As reported in U.S. EPA (1997), the highest dietary concentration corresponds to reported daily doses of 250 mg/kg/day. In deriving the RfD, the EPA used an uncertainty factor of 100 (10 for species-to-species extrapolation and 10 for sensitive subgroups in the human population) [250 mg/kg/day ÷ 100 = 2.5 mg/kg/day] (U.S. EPA 1997). Because the available data on reproductive toxicity and teratogenicity do not indicate that young animals are more sensitive than adults to imazapyr, no additional uncertainty factor for infants or children was applied. This approach and the resulting RfD are maintained in the more recent Reregistration Eligibility Decision for imazapyr (U.S. EPA/OPP 2005a, 2006a).

3.3.3. Acute RfD

The U.S. EPA/OPP sometimes derives acute RfDs for certain pesticides. Typically, acute RfDs are based on developmental studies under the assumption that the endpoint observed in the developmental study could be associated with a single dose of the pesticide. For imazapyr, however, the EPA elected not to derive a reference dose. The rationale for not doing so is as follows:

> *There was no appropriate endpoint attributable to a single dose in the available data base, including the developmental studies. The salivation seen in dams during gestation days 8-15 at 1000 mg/kg (limit dose) in the rat developmental study was not considered to be an appropriate endpoint for risk assessment because it was a transient effect seen only at the limit dose.*
>
> U.S. EPA/OPP (2005a, p. 21)

The study referenced in the above discussion is the study by Salamon et al. (1983c, MRID 131611). As discussed in Section 3.1.6, the current risk assessment offers a somewhat different interpretation of the Salamon et al. (1983c) study in that the dose-response relationship for salivation does appear to be statistically significant, and salivation was also noted in the pilot study by Salamon et al. (1983d).

The failure of the U.S. EPA to derive an acute RfD has little impact on the acute hazard quotients for imazapyr. If the EPA had derived an acute RfD, the NOAEL of 300 mg/kg bw and the likely

uncertainty factor of 100 would have resulted in an acute RfD of 3 mg/kg bw, which is not substantially different from the chronic RfD of 2.5 mg/kg bw (Section 3.3.2). As discussed further in Section 3.4, all of hazard quotients developed in the current risk assessment are based on the chronic RfD, and none of these hazard quotients exceeds the level of concern (HQ=1). Consequently, the use of an acute RfD of 3 mg/kg bw would have no impact on interpretation of the acute hazard quotients.

3.3.4. Dose-Severity Relationships

Most Forest Service risk assessments of pesticides consider dose-severity relationships in an effort to more fully characterize potential risks in exposure scenarios where the doses exceed the RfD. For imazapyr, however, endpoints of concern cannot be identified and dose-severity relationships are not relevant. In addition as noted above, there are no exposure scenarios, including accidental exposure scenarios, which result in dose estimates that exceed the chronic RfD (Section 3.4). Consequently, considerations of dose-severity relationships are not required for an elaboration of the risk characterization.

3.4. RISK CHARACTERIZATION

3.4.1. Overview

An overview of risks to workers, covering both terrestrial and aquatic applications, is given in Table 15. Similar overviews for risks to members of the general public are given in Table 16 for terrestrial applications and Table 17 for aquatic applications. These tables are discussed in the following subsections.

The quantitative risk characterization in both the human health and in the ecological risk assessment is based on the hazard quotient (HQ), which is defined as the anticipated exposure divided by the toxicity value. For both workers and members of the general public, the chronic RfD of 2.5 mg a.e./kg bw/day is used to characterize risks associated with both acute and longer-term exposures. As discussed in the exposure assessment (Section 3.2.2), all exposure assessments for terrestrial applications are based on the unit application rate of 1.0 lb a.e./acre.

In most Forest Service risk assessments, an HQ of 1 is defined as the level of concern. As discussed in the dose-response assessment (Section 3.3), imazapyr is somewhat unusual in that doses of imazapyr which may cause adverse effects have not been determined. Thus, the interpretation of HQs that exceed a value of 1 would be unclear. This is not a practical concern in this risk assessment on imazapyr because none of the HQs exceed a value of 1 at an application rate of 1 lb a.e./acre and no exposures substantially exceed the HQ of 1 at the maximum application rate of 1.5 lb a.e./acre. Consequently, there is no basis for asserting that imazapyr is likely to pose any identifiable risks associated with systemic toxic effects to either workers or members of the general public.

Irritation to the eyes can result from exposure to concentrated solutions of imazapyr. From a practical perspective, eye irritation is likely to be the only overt toxic effect as a consequence of mishandling imazapyr, and these risks are likely to be greatest for workers handling concentrated solutions of imazapyr during cut surface treatments. The potential for eye irritation can be minimized or avoided by prudent industrial hygiene practices, including, exercising care to reduce splashing and wearing goggles, during the handling of the compound.

3.4.2. Workers

The quantitative risk characterization for workers is summarized in Table 15. The HQs given in this table are taken from Worksheets E02 in Attachment 1 (terrestrial applications) and Worksheet E02 in Attachment 2 (aquatic applications).

The risk characterization for workers is simple and unambiguous: there is no basis for asserting that workers are likely to be at risk in applications of imazapyr. The highest HQ for general exposures—i.e., exposure levels anticipated in the normal use of imazapyr —is 0.06, the upper bound of the HQ for workers involved in ground broadcast applications of imazapyr. If the RfD of 2.5 mg/kg bw/day (HQ=1) is taken as the level of concern, this HQ is associated with a dose which is below the level of concern by a factor of about 17. The highest accidental HQ is 0.01, the upper bound of the HQ for a worker wearing contaminated gloves for 1 hour.

Risks are explicitly characterized only for workers involved in ground or aerial broadcast applications or direct applications to water. As discussed in Section 2.4.3, various other

application methods, including various forms of cut surface and basal bark treatments may be used in some Forest Service programs. Exposure assessments for workers involved in these types of treatments have not been developed, because adequate worker exposure studies are not available. As summarized in Table 7, the highest documented worker exposure rates are associated with directed foliar applications. In Forest Service programs considering cut surface and basal bark treatments, it may be reasonable to use worker exposure rates for directed foliar applications with the amount of imazapyr that will be handled to approximate worker exposures.

As also noted in Section 2.4.3, some cut surface applications may involve handling highly concentrated solutions of imazapyr (i.e., up to about 480 mg a.e./L), which are more concentrated than imazapyr solutions used in foliar applications (24 mg a.e./L) by a factor of about 20. As noted above, the highest HQ for workers involved in foliar or aquatic applications is 0.01 associated with wearing contaminated gloves for 1 hour. If a worker involved in hack and squirt applications were to apply a 480 mg a.e./L solution of imazapyr and wear contaminated gloves for 1 hour, the corresponding HQ would be about 0.2, below the level of concern by a factor of 5. Because the exposure period is directly proportional to the HQ, the HQ for gloves contaminated by a 480 mg a.e./L solution of imazapyr would reach a level of concern (HQ=1) at 5 hours. However extreme this exposure scenario may seem, it would seem prudent to caution workers who use highly concentrated solutions of imazapyr to exercise particular caution to prevent prolonged skin contact with the concentrated solutions.

As discussed in Section 3.1.11.3, some formulations of imazapyr may cause eye irritation. From a practical perspective, mild to moderate eye irritation is likely to be the only overt effect as a consequence of mishandling imazapyr. This effect can be minimized or avoided by prudent industrial hygiene practices, including exercising care to reduce splashing and wearing goggles, while handling concentrated solutions of imazapyr. As with skin contact, the risks of eye irritation would probably be greatest for workers handling very concentrated solutions of imazapyr during cut surface applications.

3.4.3. General Public

The quantitative risk characterization for members of the general public is summarized in Table 16 for terrestrial applications and Table 17 for aquatic applications. The HQs given in these tables are taken from Worksheets E04 in Attachment 1 (terrestrial applications) and Attachment 2 (aquatic applications). As with the quantitative risk characterization for workers, the quantitative risk characterization for the general public is expressed as the hazard quotient using the chronic RfD of 2.5 mg/kg/day for both acute and longer-term exposures.

The risk characterization for members of the general public is essentially identical to the risk characterization for workers: there is no basis for asserting that members of the general public are likely to be at risk due to applications of imazapyr. Based on the RfD of 2.5 mg/kg bw/day, the highest HQs are those associated with an accidental spill of imazapyr into a small pond and the subsequent consumption of contaminated water by a small child. For this exposure scenario the HQs are 0.07 (0.002 to 0.8) for both terrestrial and aquatic applications. This accidental spill scenario is used consistently in Forest Service risk assessments simply to serve as a guide in the case of a substantial accidental spill. For imazapyr as well as most other chemicals, a large spill into a small body of water should lead to steps to prevent the consumption of the contaminated water. Nonetheless, the current risk assessment suggests that only very severe accidental spills

would approach a level of concern. As discussed in the dose-response assessment, the dose of imazapyr that might actually pose a risk to humans has not been determined. The RfD of 2.5 mg/kg bw/day may be regarded as a dose that will not lead to adverse effects in humans; however, the same may be said for higher doses of imazapyr. The RfD of 2.5 mg/kg bw/day is used as a convenience to quantitatively illustrate that the use of imazapyr is not likely to pose any identifiable risk to humans.

The highest HQ for members of the general public associated with expected (i.e., non-accidental) exposure scenarios is 0.5, the upper bound of the acute HQ for the consumption of contaminated vegetation. For any pesticide applied directly to vegetation, this is an extraordinarily conservative exposure scenario which typically leads to HQs that exceed the level of concern. For imazapyr, no risks can be identified.

Each of the HQs summarized in Tables 16 and 17 involves a single exposure scenario. In some cases, individuals could be exposed by more than one route. In such cases risks can be approximated simply by adding the HQs for different exposure scenarios. For imazapyr, consideration of multiple exposure scenarios has little impact on the risk assessment. For example, based on the upper bounds of HQs for being directly sprayed on the lower legs (HQ=0.01), staying in contact with contaminated vegetation for 1 hour (HQ=0.003), eating contaminated fruit (HQ=0.5), drinking contaminated surface water (HQ=0.01), and consuming contaminated fish at rates characteristic of subsistence populations (HQ=0.0007) leads to a combined HQ of 0.53 [0.01 + 0.003 + 0.5 + 0.01 + 0.007]. In other words, for imazapyr, the predominant route of exposure will involve the consumption of contaminated vegetation. This pattern is also apparent in most pesticide risk assessments involving foliar applications.

3.4.4. Sensitive Subgroups

No hazards to members of the general population associated with exposure to imazapyr have been identified (Section 3.1). Because no mechanism of toxicity for imazapyr in humans can be identified, subgroups within the human population that might be sensitive to imazapyr cannot be identified.

Notwithstanding the above, imazapyr is a weak acid. As noted in Section 3.1.16, it is likely that imazapyr would influence and be influenced by other weak acids excreted by the kidney; however, this effect would occur only at high doses at which the ability of the kidney to excrete weak acids might be saturated or nearly so. Given the very low HQs for imazapyr, there appears to be no basis for asserting that this or other adverse effects in a specific subgroup are plausible. U.S. EPA (2005a) judges that infants and children are not likely to be more sensitive than adults to imazapyr. Given the number of studies available on reproductive and developmental effects and the unremarkable findings from these studies, this judgement appears appropriate.

3.4.5. Connected Actions

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

justification. Within the context of this risk assessment, "connected actions" include actions or the use of other chemicals which are necessary and occur in close association with use of imazapyr.

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

Adjuvants are a much more difficult issue to address, and it is beyond the scope current risk assessment to address adjuvants in the absence of specific information on the joint action of imazapyr with adjuvants. This is a general issue in many Forest Service risk assessments.

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 imazapyr) and other agents that may cause the same effect or effects by the same or a similar mode of action.

As noted by the U.S. EPA/OPP:

> *FQPA requires the Agency to consider available information concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity" when considering whether to establish, modify, or revoke a tolerance. Unlike other pesticides for which the Agency has followed a cumulative risk approach based on a common mechanism of toxicity, the Agency has not made a common mechanism of toxicity finding for imazapyr with any other substances. Therefore, for the purposes of tolerance reassessment, which was completed in 2003, the Agency did not assume that imazapyr shared a common mechanism of toxicity with any other compound.*
>
> U.S. EPA/OPP (2006a, p. 2).

As noted in Section 2.2 and illustrated in Figure 1, imazapyr is a imidazolinone herbicide and is structurally similar to several other to several other imidazolinone herbicides, including imazapic, imazamox, and imazethapyr. The EPA considers these relationships as follows:

> *Despite imazapyr's structural similarity to imazapic, as well as its similarity to the pesticides, imazethapyr and imazamethabenz-methyl (Assert®), the available data do not support the conclusion that these pesticides share a common mechanism of toxicity such that combined exposure to them would result in cumulative effects. First, as noted, the toxicity data for imazapyr show no adverse effects, including no skeletal muscle effects. Second, the toxic endpoints for the three structurally similar pesticides are quite varied: imazapic (skeletal muscle effects); imazethapyr (an increased incidence of clinical signs during gestation,*

> *ulcerations in the mucosal layer of the stomach and gall bladder, increased abortions, maternal deaths, decrements in body weight gain) and imazamethabenz-methyl (transient decreased body weight, mild liver effects, slight increase in a common kidney lesion). Accordingly, for the purposes of this RED, EPA has not assumed that imazapyr has a common mechanism of toxicity.*
>
> U.S. EPA/OPP (2006a, p. 7).

While Forest Service risk assessments have not been conducted on as many imidazolinone herbicides as the U.S. EPA/OPP has addressed, a recent Forest Service risk assessment has been completed on imazamox (SERA 2010c), and a risk assessment on imazapic was conducted in 2004 (SERA 2004b). Based on this more limited series, the conclusions by the U.S. EPA/OPP noted above appear to be well-reasoned. Imazapyr is strikingly similar to imazamox in that doses that cause clear signs of toxicity have not been determined (SERA 2010c). While this apparent lack of mammalian toxicity is a similarity, this particular similarity is not a basis for enhanced concern for cumulative effects. Imazapic is also relatively nontoxic to most mammalian species, except for canids. Unlike either imazapyr or imazamox, imazapic (as noted above by the U.S. EPA/OPP) causes treatment-related effects on skeletal muscle in dogs after longer-term exposures to relatively low doses—i.e., ≈150 mg/kg bw/day (SERA 2004b). Thus, while structurally similar to both imazapyr and imazamox, imazapic clearly exerts toxic effects on canids not exerted by either imazapyr or imazamox.

Based on the above considerations, the EPA decision not to assume a common mechanism of action in assessing imazapyr relative to other imidazolinone herbicides appears to be a reasonable and justified approach (U.S. EPA/OPP 2006a).

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

In the ecological risk assessment, as in the human health risk assessment, exposure to imazapyr is generally not associated with hazards, except for terrestrial and aquatic macrophytes. U.S. EPA/OPP (2006a) classifies imazapyr as *practically non-toxic* to mammals, birds, honeybees, fish, aquatic invertebrates, and algae. This classification is clearly justified by the available data. As with most ecological risk assessments, the largely benign assessment of the hazards or lack of hazards to most groups of nontarget species is tempered by the fact that toxicity data are available on only a few species, relative to the numerous species which may be exposed to imazapyr. A notable limitation in the hazard identification of imazapyr is the lack of data regarding toxicity to terrestrial-phase or aquatic-phase amphibians.

Imazapyr is an effective herbicide; accordingly, it is hazardous to both terrestrial and aquatic macrophytes. Like other imidazolinone herbicides and sulfonylurea herbicides, imazapyr inhibits acetolactate synthase (ALS), an enzyme that catalyzes the biosynthesis of three branched-chain amino acids, all of which are essential for plant growth. In both pre-emergent and post-emergent exposures, imazapyr is more toxic to dicots than to monocots, but especially so in post-emergent exposures—i.e., foliar applications. While algae are relatively tolerant to imazapyr, imazapyr is highly toxic to aquatic macrophytes. Only two species of aquatic macrophytes have been assayed in standard toxicity studies involving defined concentrations of imazapyr in water. Although these studies suggest only negligible differences in species sensitivity to imazapyr, efficacy studies, in which exposures are defined as application rates in units of lb/acre, suggest that species sensitivity differences to imazapyr may be substantial among different species of aquatic macrophytes. As with many other imidazolinone herbicides, aquatic plant populations may develop resistance to imazapyr, primarily by developing less sensitive forms of acetolactate synthase (ALS).

The toxicity of imazapyr to terrestrial and aquatic plants may cause secondary effects, including alterations to habitats and food availability, on terrestrial and aquatic animals. Secondary effects, which can result from the use of any herbicide as well as from mechanical methods to control vegetation, may be considered detrimental or beneficial, depending on the affected species. Specific examples of secondary effects associated with imazapyr applications are noted below.

4.1.2. Terrestrial Organisms

4.1.2.1. Mammals

The toxicity studies used to assess the potential hazards of imazapyr to humans (Appendix 1) are applicable to the risk assessment for mammalian wildlife. While the toxicity of imazapyr to plants is understood relatively well (Section 4.1.2.5), it is not clear what, if any, specific toxicity imazapyr may cause in mammalian wildlife. As discussed in Section 3.1 and summarized in Appendix 1, acute, subchronic, and chronic toxicity studies on imazapyr do not demonstrate adverse effects that are unequivocally attributable to exposure. This uncertainty or a lack of knowledge has a relatively minor impact on this risk assessment, because the available toxicity studies are relatively complete—chronic studies in three mammalian species (dogs, rats, and

mice) and several reproduction studies in two mammalian species (rats and rabbits)—and indicate that imazapyr is not likely to be associated with adverse effects at relatively high-dose levels.

The toxicity data on imazapyr includes only one relevant field study regarding potential effects on terrestrial mammals. Brooks et al. (1995) examined the impact of imazapyr, picloram, triclopyr, and hexazinone, all used in site preparation, on small mammal and avian communities. The study, located in Georgia, consisted of a 157-ha tract of residual hardwoods. Imazapyr (Arsenal) was applied at 4.1 kg a.e./ha (≈3.7 lb a.e./acre). After herbicide treatment and a prescribed burn, loblolly pine trees were planted. Data collection methods included trapping small mammals and visual surveys of bird populations. The observations made at pre-treatment and three times per year at 1, 2, and 3 years after treatment did not differ remarkably among the herbicides tested. With all herbicides, the number of small animals trapped after treatment was diminished compared with pre-treatment levels. The study did not include untreated sites (i.e., control sites); consequently, observed changes in populations of small mammals or birds cannot be clearly associated with herbicide treatment.

4.1.2.2. Birds

As summarized in Appendix 2, a relatively 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) in both quail and mallards—were submitted to the U.S. EPA/OPP in support of the registration of imazapyr.

Like the acute and chronic studies in mammals (Sections 3.1 and 4.1.2.1), the available avian studies on imazapyr, all of which were conducted up to limit doses, do not report any signs of toxicity. In the acute gavage studies, single oral doses of imazapyr acid cause no signs of toxicity at a dose of 2510 mg a.e./kg bw in either quail or ducks (MRID 00131633 and MRID 00131634 as summarized in U.S. EPA/OPP 2007a, Appendix B). Similarly, the Arsenal herbicide formulation also caused no signs of toxicity at doses of up to 2150 mg formulation/kg bw, equivalent to about 486 mg a.e./kg bw. Clearly, the lower functional acute NOAEL of 486 mg a.e./kg bw for the formulation, relative to the 2510 mg a.e./kg bw for imazapyr acid does not suggest that the formulation is more toxic than the acid. The dose of 486 mg a.e./kg bw is simply the highest dose assayed with the formulation.

Similarly, as summarized in Appendix 2 (Table 3), the longer-term (≈18 week) reproduction studies on imazapyr acid indicate no adverse effects following exposures to dietary concentrations of up to 2000 ppm a.e (Fletcher et al. 1995a,b; Ahmed et al. 1990). While the U.S. EPA/OPP risk assessments designate indefinite dietary LOAELs of > 2000 ppm a.e., the longer-term dietary concentration at which adverse effects might be observed is not defined.

The submission by Ahmed et al. (1990, MRID 45119714) involved two studies, one in quail and the other in mallards. As indicated in Appendix 2 (Table 3), the study in mallards was classified as invalid in the U.S. EPA/OPP Data Evaluation Record (DER) … *due to bacterial contamination and high embryonic mortality in the control group*. While this study is summarized in Appendix 2 for the sake of documentation, this study is not otherwise used or discussed in the current risk assessment.

As discussed in Section 4.1.2.1 (Mammals), the field study by Brooks et al. (1995) reports that no changes in bird populations were observed after imazapyr was applied at about 3.7 lb a.e./acre for site preparation. Based on visual surveys, no impact was noted on bird diversity, relative to sites treated with picloram, triclopyr, or hexazinone. More recently, Welch et al. (2004) indicates that imazapyr can improve bobwhite quail habitat by controlling hardwood invasion in pine stands. Details about direct beneficial effects on quail populations are not discussed in this publication.

The U.S. EPA/OPP (2005k, p. J-1) notes one incident from Aiken County, South Carolina, in which birds were exposed to imazapyr as well as diuron and metsulfuron methyl. The incident is described as follows:

> *Spray on fence row drifted onto adjacent bird nest boxes located from 2-85 feet of application site; runoff into a pond 60 foot away/bird kill of nesting and mature birds and fish and algae kill in pond.*

This incident is described in somewhat greater detail by U.S. EPA/OPP (2007a, Appendix E, p. 1):

> *The same fencerow incident as listed in the aquatic organism section drifted onto adjacent bird nest boxes and caused a bird kill of nestling and mature birds located from 2-85 feet from the application site. Thirty-two bluebirds, 5 Carolina chickadees and 35 unknown birds were affected. Again, this was a mixture of herbicides. The certainty index is rated possible and the legality is undetermined. It cannot be definitively determined whether or not the bird kill was due to exposure to imazapyr.*

In the absence of any additional details, this incident does not provide a compelling or credible basis for asserting that imazapyr caused adverse effects in birds.

4.1.2.3. Reptiles and Amphibians (Terrestrial Phase)

There is no information regarding the toxicity of imazapyr to reptiles or terrestrial-phase amphibians in the open literature or in studies submitted to the EPA (U.S. EPA/OPP 2005b, 2006a, 2007a). Neither the database maintained by Pauli et al. (2000) nor the open literature includes information on the toxicity of imazapyr to reptiles or terrestrial-phase amphibians.

Risks to terrestrial phase amphibians are addressed in the EPA ecological risk assessment prepared by the Environmental Fate and Effects Division (EFED) of U.S. EPA/OPP U.S. (EPA/OPP 2005b) in support of the Reregistration Eligibility Decision for imazapyr (U.S. EPA/OPP 2006a). In this ecological risk assessment as well as many similar ecological risk assessment prepared by U.S. EPA/OPP, birds are used as surrogates for terrestrial phase amphibians and reptiles (U.S. EPA/OPP 2005b, p. 21) in the absence of data on these groups of organisms. The same approach is taken by the Agency in the risk assessment for the California red-legged frog (U.S. EPA/OPP 2007a, p. 14).

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 imazapyr, 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. One registrant-submitted study involving contact exposure (Atkins 1984) is considered in the EPA ecological risk assessment and in the EPA risk assessment for the California red-legged frog (U.S. EPA/OPP 2007a, p. 14). In addition, an oral toxicity study in honeybees (Atkins and Kellum 1983) submitted to EPA is cited but not discussed in the RED for imazapyr (U.S. EPA/OPP 2006a) or in the risk assessment on the California red-legged frog (U.S. EPA/OPP 2007a).

In both the oral and contact toxicity studies, the LD_{50} for imazapyr is >100 µg/bee. 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 comparable to the NOAEL values reported in experimental mammals (Appendix 1) and birds (Appendix 2). This similarity suggests that the toxicity of imazapyr to terrestrial invertebrates may be similar to the toxicity of this compound to terrestrial vertebrates. On the other hand, there are numerous terrestrial invertebrates in any diverse environment. Typically, as with imazapyr, 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 with several sulfonylurea, imidazolinone, and triazolopyrimidine herbicides, imazapyr inhibits acetolactate synthase (ALS; EC 4.1.3.18), an enzyme that catalyzes the biosynthesis of three branched-chain amino acids, all of which are essential for protein synthesis and plant growth (Boutsalis and Powles 1995; Nadler-Hassar et al. 2009; Tan et al. 2005). Although a number of herbicides inhibit acetolactate synthase, the kinetics of inhibition and thus the mechanisms are not necessarily identical. For example, imazapyr acts as an uncompetitive inhibitor of acetolactate synthase in *Arabidopsis thaliana*; whereas, chlorsulfuron acts as a non-competitive inhibitor (Chang and Duggleby 1997).

Several species of weeds have developed resistance to imazapyr. In some plant species, resistance is based on a modified form of acetolactate synthase and/or an alteration of levels of acetolactate synthase in the resistant plant (Boutsalis and Powles 1995; Christopher et al. 1992; Kuk et al. 2003; Osuna and De Prado 2003; Pang et al. 2002; Saari et al. 1992). Based on a comparison of different levels of resistance to various herbicides, including imazapyr, Burnet et al. (1994a) suggest that there is likely to be more than one mechanism involved in the development of resistance to imazapyr and other similarly acting herbicides. The magnitude of resistance to imazapyr appears to be highly variable. Relatively modest resistance factors of about 2 to 10 are reported for *Cyperus difformis* (flatsedge , Kuk et al. 2003), *Amaranthus*

blitoides (prostrate amaranth, Nadler-Hassar and Rubin 2003), and *Helianthus annuus* (a species of sunflower, Vega et al. 2009). Much higher resistance factors are reported for other species, including a factor of about 300 for *Conyza albida* (broadleaf fleabane, Osuna and De Prado 2003) and a factor of about 480 for *Zea mays* (corn, Wright and Penner 1998)

After foliar application, imazapyr as well as other structurally similar herbicides (e.g., picloram, clopyralid, and other imidazolinone herbicides) are transported via the phloem; thus, they are able to control deeply rooted weeds. The efficacy of imazapyr appears to be particularly strongly related to its transport in phloem, which is more rapid than would be expected from simple structure-activity correlations (Chamberlain et al. 1995).

Rapid transport from treated leaves to root systems was also noted by Nissen et al. (1995) using liquid growth cultures of leafy spurge (*Euphorbia esula*) after foliar treatments with ^{14}C-imazapyr. By day 8 after application, 14% of the applied imazapyr remained in the leaf tissue, while 17% was transported to the root system. In terms of total absorption, 62.5% of the applied radioactivity was absorbed by day 2 and 80.0% by day 8. Under the assumption of simple first-order absorption, the absorption rate, k_a, should be constant over time and can be calculated as the natural logarithm of the proportion of the unabsorbed dose divided by the duration of exposure [ka = ln(1- Pa)/t], where *Pa* is the proportion absorbed over the time interval *t*. The k_a values calculated for day 2 and day 8 are 0.49 day^{-1} [ln(1-0.625)/2] and 0.20 day^{-1} [ln(1-0.8)/8], respectively. Thus, at least in this species, the rate of absorption may not be constant with time, and first order absorption kinetics may not apply. Alternatively, these differences may simply reflect random variation in the responses of the plants or the measurements taken during the study. The data reported by Nissen et al. (1995) do not include a sufficient number of time points to evaluate either possibility.

Imazapyr does not appear to be extensively metabolized by plants, although imazapyr metabolites from leafy spurge were detected but not identified after 8 days in the study by Nissen et al. (1995). These authors noted two groups of metabolites, one eluting earlier and one eluting later than imazapyr. Nissen et al. (1995) suggest that the earlier eluting (more polar metabolites) were 2-carbamoylnicotinic acid and 2,3-pyridinedicarboxylic acid. The later eluting metabolite was thought to be a ring closure product, imidazopyrrolopyridine.

The phytotoxicity of imazapyr can be reduced by some compounds such as naphthalic anhydride and BAS 145138 (Davies et al. 1995). Exposure to a mixture of imazapyr and diuron in a soil application, both at rates below those recommended for separated applications of the two herbicides, has been shown to increase the sensitivity of water oak (*Quercus nigra*) to infections from the fungus *Tubakia dryina* (Zhang and Walker 1995). This effect was not seen in plants treated with diuron or imazapyr separately. This effect was associated with an inhibition of stem elongation; however, the mechanism for the apparent interaction is unclear.

Some herbicides may be absorbed by plant foliage, translocated to the roots of plants, and subsequently exuded from the roots to the surrounding soil, posing a risk to neighboring plants. This process, referred to as allelopathy, has been demonstrated for picloram, 2,4-D, and 2,4,5-T (Reid and Hurtt 1970; Webb and Newton 1972). These herbicides, like imazapyr, are weak acids with pK_a values between 1.9 and 2.8 (Willis and McDowell 1987) and are poorly soluble in non-

polar liquids (Bromilow et al. 1990). Although there are no reports of allelopathic effects for imazapyr in field studies, Nissen et al. (1995) found that about 3% of absorbed imazapyr may be exuded from the root system of leafy spurge into a liquid culture medium by day 8 after treatment. This report combined with the fact that herbicides with similar physical and chemical properties generally translocate similarly in plants (Bromilow et al. 1990) suggests that imazapyr has the potential to induce allelopathic effects. Nonetheless, given the relatively rapid movement of imazapyr in soil, the potential for allelopathic effects may not have a practical or substantial impact on potential risk to non-target plants.

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 usual target of 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 3, studies submitted to the EPA in support of the registration of imazapyr include bioassays for vegetative vigor (Appendix 3, Table 1), seedling emergence (Appendix 3, Table 2), and seed germination (Appendix 3, Table 3).

As discussed further in Section 4.3.2.5, the dose-response assessment for terrestrial plants is based on the NOAEC values, because the Forest Service prefers to use NOAECs for risk characterization rather than defined effect levels, like EC_{25} values. Defined effect levels are preferable, however, for comparisons among species; accordingly, the following discussion focuses on EC_{25} values. Imazapyr formulations are labeled for both postemergence and preemergence of both broadleaf vegetation (dicots) and grasses (monocots). Based on the standard toxicity studies submitted to the U.S. EPA in support of the registration of imazapyr, dicots appear to be more sensitive than monocots in assays for both vegetative vigor (foliar applications as summarized in Appendix 3, Table 1) and seedling emergence (foliar applications as summarized in Appendix 3, Table 1).

For foliar applications with technical grade imazapyr (American Cyanamid 1988b), the differences in sensitivity between monocots and dicots are substantial. Based on EC_{25} values, the most sensitive dicot is cucumber with an EC_{25} of 0.0009 lb a.e./acre. This EC_{25} is about a factor of 13 below that for the most sensitive monocot—i.e., wheat with an EC_{25} of 0.012 lb a.e./acre [0.012 lb a.e./acre ÷ 0.0009 lb a.e./acre ≈ 13.33]. In seedling emergence assays, the differences between monocots and dicots are much less remarkable. The most sensitive dicot is the sugar beet with an EC_{25} of 0.0024 lb a.e./acre, which is a factor of only about 2 below the most sensitive monocot—i.e., wheat with an EC_{25} of 0.0046 lb a.e./acre [0.0046 lb a.e./acre ÷ 0.0024 lb a.e./acre ≈ 1.92]. These differences in the sensitivity of monocots and dicots reflect differences in the relative sensitivity of monocots and dicots to foliar and soil exposures. Based on EC_{25} values for the most sensitive species of dicot, foliar applications (vegetative vigor) are more toxic than soil exposures (seedling emergence) by about a factor of about 2.6 [0.0024 lb /acre ÷ 0.0009 lb a.e./acre ≈ 2.666]. Based on EC_{25} values for the most sensitive species of

monocots, the opposite trend is apparent with soil exposures being more effective than foliar exposures by a factor of about 2.6 [0.012 lb a.e./acre ÷ 0.0046 lb a.e./acre ≈ 2.609].

As noted in Section 2.2, imazapyr has been used as a herbicide for more than 25 years; accordingly, there is an immense body of open literature regarding its effects on terrestrial plants, including numerous efficacy studies (e.g., Charles 1997; Creager 1990; Harrington et al. 1998; Kuhns and Kaps 1986; Masters et al. 1994). Although efficacy is an important component in the assessment of the use of imazapyr, it is not a primary concern in the current risk assessment. On the other hand, in terms of Forest Service programs, it is worth pointing out that the studies by Harrington et al. (1998) and Kuhns and Kaps (1986) specifically note that imazapyr is useful in the cultivation of pine. Along with efficacy studies, open literature studies regarding the toxicity of imazapyr to nontarget species are summarized in Appendix 3 (Table 4).

Consistent with the assessment by U.S. EPA/OPP (2007a, Appendices G and H), some of the open literature studies on imazapyr do not have a quantitative impact on the current risk assessment, because the toxicity values identified in the open literature are less sensitive than the toxicity values from the registrant-submitted studies (i.e., Appendix 3, Tables 1 and 2). In addition, as noted in Appendix 3 (Table 4), the design and reporting in most of the studies from the open literature are less complete than the studies submitted to U.S. EPA/OPP. For example, Lawrie and Clay (1989) assayed the toxicity of imazapyr as well as several other herbicides to several species of trees at application rates of about 0.15, 0.8, and 2.3 lb a.e./acre. Although the topic of the publication is highly relevant, the application method (soil drench) will not be employed in Forest Service programs. In addition and more significant, Lawrie and Clay (1989) report results for the different species of trees only as averages for the three applications rates combined. Though useful for assessing the relative sensitivities among species (i.e., willows and rap are much more sensitive than beech, birch, or oak), in the absence of data on individual application rates, this study cannot be used quantitatively in the current risk assessment.

The open literature study by Bovey and Senseman (1998), however, is well documented and provides dose-response data for an application method (foliar spray) that is relevant to the current risk assessment. As summarized in Appendix 3 (Table 4) and detailed further in a supplemental table at the end of Appendix 3, Bovey and Senseman (1998) treated one species of grass (monocot) and four dicots at application rates ranging from about 0.015 to 0.81 lb a.e./acre. The dose-response data from this study are illustrated in Figure 5. The most sensitive species in this study was cabbage. Although Bovey and Senseman (1998) do not provide a statistical analysis, the EC_{25} for cabbage appears to be about 0.025 lb a.e./acre. This response is similar to that of tomatoes in the study by American Cyanamid (1988b) in which the EC_{25} is reported as >0.0156 lb a.e./acre. More significantly and as illustrated in Figure 5, a species of pumpkin was far more tolerant, evidencing no significant effect on dry weight following application rates of up to 0.4 lb a.e./acre. This apparent insensitivity to imazapyr is discussed further in the dose-response assessment (Section 4.3.2.5). Anecdotal reports suggest that blackberries may also be relatively tolerant to imazapyr (Duryea and Dougherty 1991).

4.1.2.6. Terrestrial Microorganisms

Relatively little information is available on the toxicity of imazapyr to terrestrial microorganisms. In pure culture laboratory assays, imazapyr inhibited the growth of two strains of plant-associated bacteria, *Bacillus subtilis* and *Bacillus circulans*, both isolated from wheat.

LC_{50} values ranged from about 10 to 100 µM, equivalent to about 2.6 to 26 mg/L (see Forlani et al. 1995, Figure 1, p. 248). Three other species of *Bacillus* as well as several additional soil bacteria were not affected at concentrations up to 1000 µM or about 260 mg/L (Forlani et al. 1995). Thus, effects on bacteria appear to be highly species specific with variations in sensitivity of up to a factor of 100. Using mixed cultures of soil microorganisms, Xuedong et al. (2005) noted an inverse relationship between the degradation of imazapyr and the concentration of imazapyr in bacteria cultures over a range of 50 to 400 mg/L. At 400 mg/L, no degradation of imazapyr was apparent. It is unclear whether these cell culture studies conducted at very high concentrations of imazapyr portend potential adverse effects on field populations of microorganisms is not clear.

In peak soil concentrations, imazapyr inhibited cellulose decomposition and carboxymethyl cellulase activity when applied at 0.25 to 1 kg/ha, equivalent to about 0.22 to 0.9 lb/acre, to a predominantly peat soil (Ismail and Wong 1994). These investigators speculate that *"the reduction in cellulose degradation is likely to be only a temporary effect"* (Ismail and Wong 1994, p. 122) and that the activity of imazapyr on terrestrial microorganisms may decline as the herbicide is adsorbed to soil and thereby becomes less bioavailable to microorganisms. On the other hand, imazapyr may persist in soil for a prolonged period of time, particularly in relatively arid regions, and will not bind tightly to alkaline soils with low organic matter. Thus, in at least some areas, a potential for longer-term effects on soil microorganisms seems possible. This effect, however, has not been demonstrated in field studies. In a greenhouse study, Busse et al. (2004) noted no effects on the infectivity of mycorrhizal fungi to pine seedlings following application of imazapyr at rates of 0.82 to 1.6 lb a.e./acre (i.e., rates that caused clear signs of toxicity in the pine seedlings).

Studies on terrestrial microorganisms are not required for pesticide registration in the United States, and the EPA ecological risk assessments on imazapyr (U.S. EPA/OPP 2005b, 2007a) do not address effects on terrestrial microorganisms.

4.1.3. Aquatic Organisms

4.1.3.1. Fish

4.1.3.1.1. Acute Toxicity

Data on the acute toxicity of imazapyr to fish are summarized in Appendix 4 (Table 1). Based on LC_{50} values of >100 mg a.e./L, imazapyr acid is classified as *practically non-toxic* to fish (U.S. EPA/OPP 2005b, p. 45; U.S. EPA/OPP 2007a, p. 87). Based on acute bioassays in both bluegills (Cohle and McAllister 1984a) and trout (Drotter et al. 1995), the isopropylamine salt of imazapyr is also practically non-toxic to fish.

Toxicity data are also available on one formulation of imazapyr, Arsenal Herbicide. As summarized in Table 2, this formulation consists of the isopropylamine salt of imazapyr (27.8% a.i, 22.6% a.e.) and 72.2% inerts which include an unspecified solvent. The 96-hour LC_{50} of Arsenal Herbicide is about 41 mg a.e./L in bluegills (Cohle and McAllister 1984b) and 21 mg a.e./L in trout (Cohle and McAllister 1984c). The study by Cohle and McAllister (1984b) is not discussed in the EPA ecological risk assessments (U.S. EPA/OPP 2005b, 2007a). The study in trout (Cohle and McAllister 1984c) is discussed in U.S. EPA/OPP (2007a), which notes the

higher toxicity of the formulation relative to imazapyr and isopropylamine salt of imazapyr. The substantially lower LC_{50} values of Arsenal Herbicide, expressed in acid equivalents, suggests that the inerts in the formulation contribute to its greater toxicity, as discussed further in the dose-response assessment (Section 4.3.3.1).

As summarized in Appendix 4, a study from the open literature, Supamataya et al. (1987), reports LC_{50} values for Nile tilapia and the silver barb that are much lower than those reported in registrant-submitted studies (i.e., about 2.7 to 4.5 mg/L). This study is published in Thai with an English abstract. In the previous Forest Service risk assessment on imazapyr (SERA 2004a), information from the study by Supamataya et al. (1987), which was taken from the English abstract, is used in the dose-response assessment. In the recent EPA risk assessment for the California red-legged frog, U.S. EPA/OPP (2007a, Appendix H) rejects this study with a notation of "NO FOREIGN".

In SERA (2004a), the study by Supamataya et al. (1987) is used in the dose-response assessment to characterize risks associated with potentially sensitive species, even though the test species in the study are not native to the United States. In retrospect, using the data from Supamataya et al. (1987) data does not seem justified. While information on non-native fish may arguably be viewed as relevant in assessing impacts on potentially sensitive fish species in the United States, a major limitation with the Supamataya et al. (1987) study is the lack of documentation. As discussed above, formulations of imazapyr may be more toxic than imazapyr itself. It is reasonable to suggest that atypical results from the Thai study could be associated with the use of a formulation that is not typical of formulations used in the United States. Any number of other experimental variables could also have contributed to the atypical results reported by Supamataya et al. (1987). Given the well-documented studies that are available on imazapyr and a relevant U.S. formulation of imazapyr, the data from Supamataya et al. (1987) are not used quantitatively in the current risk assessment.

Tilapia rendalli, a herbivorous fish native to Africa, evidenced positive activity in a micronucleus assay, a screening test for mutagenic activity (Grisolia 2002). After intra-abdominal injections of imazapyr at 20, 40, or 80 mg/kg, a statistically significant increase was seen in erythrocyte micronuclei in the 80 mg/kg dose groups but not in the two lower dose groups. As noted in Section 3.1.11.1, imazapyr does not appear to be mutagenic or carcinogenic in mammals. Because of the atypical route of exposure and because a positive response was seen only at the maximum tolerated dose of 80 mg/kg, this report does not have a substantial impact on the hazard identification for fish.

No field studies have been encountered on the toxicity of imazapyr to fish or the impact of imazapyr on populations of fish. The U.S. EPA/OPP, however, tracks reports of incidents involving the exposure of wildlife to pesticides. As noted in Section 4.1.2.2, one incident has been reported involving exposures to birds and fish. This incident as well as a second incident involving only fish are summarized in the recent U.S. EPA/OPP risk assessment for the California red-legged frog:

> *One incident was reported in which a mixed herbicidal spray, containing a mixture of the isopropylamine salt of imazapyr, diuron and metsulfuron methyl was sprayed onto a fence row and either drifted or ran-off into a pond 60 feet away and caused a*

fish and algae kill (species unknown). The certainty index is rated possible and the legality is undetermined. It cannot be definitively determined whether or not the fish and algae kill was due to exposure to imazapyr.

A second incident was reported which involved a goldfish kill. There was suspected runoff of drift into the pond following an aerial application of an imazapyr formulation to a nearby 145 acres. The NCDA could not determine the cause of the kill.

U.S. EPA/OPP (2007a, Appendix E, p. 1)

As summarized in Table 11and detailed in Attachment 1 (Worksheet 10a), the direct spray of a 1-meter deep pond (or any 1-meter deep column of water) at an application rate of 1 lb a.e./acre will result in a concentration of about 0.112 mg a.e./L, assuming complete mixing. As discussed above, the lowest reported LC_{50} (trout) for the Arsenal Herbicide formulation is 21 mg a.e./L in trout (Cohle and McAllister 1984c), a factor of over 180 higher than the concentration in a 1-meter deep pond at an application rate of 1 lb a.e./acre [21 mg a.e./L ÷ 0.112 mg a.e./L = 187.5]. Thus, to reach the concentration of 21 mg a.e./L (at which substantial mortality would be expected), the application rate would need to be over 180 lb a.e./acre or the depth of the water column would need to about [1 meter ÷ 187.5 ≈ 0.0053 meters ≈ 0.2 inches]. If the latter incident reported by U.S. EPA/OPP (2007a) was associated with an imazapyr application, oxygen depletion (secondary to decaying vegetation) would appear to be a more likely factor than direct toxicity.

As noted in Section 3.2.3.4.6.2, effective aquatic applications of imazapyr will cause oxygen depletion in the water column secondary to rotting vegetation. The event will occur after the application of any effective aquatic herbicide and may kill fish as well as other aquatic organism. While hypoxia in fish due to oxygen depletion in water is identified as an endpoint of concern for fish and other aquatic organisms, potential hazards to fish associated with hypoxia should be minimal, if label directions are followed and only partial sections of standing bodies of water are treated at one time.

4.1.3.1.2. Longer-Term Toxicity

As summarized in Appendix 4 (Table 2), the longer-term toxicity of imazapyr acid to fathead minnows has been assayed in an early life-stage study (Drotter et al. 1998) and a full life cycle study (Drotter et al. 1999). Neither study detected adverse effects at concentrations of up to about 120 mg a.e./L.

Consistent with the acute toxicity studies in fish (Section 4.1.3.1.1), trout appear to be the most sensitive species. In an early life-stage study in rainbow trout (Manning 1989b), a concentration of 92.4 mg a.e./L resulted in reduced hatch and reduced fry survival. No effects, however, were noted at a concentration of 43.1 mg a.e./L. It is worth noting that Manning (1989b) judged the effects at 92.4 mg a.e./L only as a "…*nearly significant effect on hatching.*" Consistent with the approach taken in the previous Forest Service risk assessment (SERA 2004a), the EPA judged that the 92.4 mg a.e./L concentration is a LOAEC rather than a NOAEC (U.S. EPA/OPP 2005h).

No longer-term studies on imazapyr formulations have been conducted. This is not an atypical situation. To support pesticide registration, longer-term studies in fish and most other organisms

are required typically for the active ingredient but are not required on pesticide formulations. For imazapyr, the lack of a longer-term study on a formulation is somewhat problematic. As discussed in Section 4.1.3.1.1, the acute NOAEC of the isopropylamine salt of imazapyr in rainbow trout is 110 mg a.e./L (Drotter et al. 1995), above the longer-term NOAEC of 43.1 mg a.e./L. The acute NOAEC for the Arsenal Herbicide formulation in rainbow trout, however, is 10 .4 mg a.e./L, below the longer-term NOAEC for imazapyr acid by a factor of about 4 [43.1 mg a.e./L ÷ 10 .4 mg a.e./L ≈ 4.14]. This matter is discussed further in the dose-response assessment for fish (Section 4.3.3.1).

4.1.3.2. Amphibians (Aquatic Phase)

As is the case for reptiles and terrestrial-stage amphibians (Section 4.1.2.3), there is no information regarding the toxicity of imazapyr to aquatic-phase amphibians. In view of this lack of data, U.S. EPA/OPP (2005b, 2007a) follows a standard EPA approach: … *Also, it was assumed that fish are approximately as sensitive as aquatic phase amphibians … However, no data are available to support these conclusions* (U.S. EPA/OPP 2005b, p. 24).

4.1.3.3. Aquatic Invertebrates

4.1.3.3.1. Acute Toxicity

The acute toxicity data on aquatic invertebrates are similar to the data on fish. Both imazapyr acid and isopropylamine salt of imazapyr are classified as practically non-toxic to *Daphnia magna* (U.S. EPA/OPP 2005a, p. 8; U.S. EPA/OPP 2007a, p. 88) as well as saltwater invertebrates—i.e., oysters and pink shrimp (U.S. EPA/OPP 2005b, p. 46).

Also as with fish, bioassays in *Daphnia magna* indicate that the Arsenal Herbicide formulation of imazapyr is more toxic than either imazapyr acid or the isopropylamine salt of imazapyr. While a definite EC_{50} for imazapyr acid is not available in *Daphnia magna* (EC_{50} >100 mg a.e./L, Kintner and Forbis, 1983b), the EC_{50} for isopropylamine salt of imazapyr is 614 mg a.e./L (Forbis et al. 1984a), which is a factor of about 9.5 higher than the EC_{50} of 64.9 mg a.e./L reported in U.S. EPA/OPP (2007a) for Arsenal Herbicide from the study by Forbis et al. (1984b) [614 mg a.e./L ÷ 64.9 mg a.e./L ≈ 9.46]. As detailed in Appendix 5 and discussed further in Section 3.3.3.3, the EC_{50} of 64.9 mg a.e./L appears to involve a double correction for going from a.i. to a.e. A more reasonable estimate of the EC_{50} for Arsenal to *Daphnia magna* is about 79 mg a.e./L. Nonetheless, this corrected EC_{50} is still substantially less than those for imazapyr or the salt of imazapyr.

Toxicity studies on the Arsenal Herbicide formulation or other formulations of imazapyr have not been conducted on other species of aquatic invertebrates.

4.1.3.3.2. Longer-Term Toxicity

As summarized in Appendix 5 (Table 2), only one longer-term toxicity study has been conducted on imazapyr, a standard life cycle study in *Daphnia magna* in which no effects were noted at concentrations of up to 97.1 mg a.e./L (Manning 1989c).

Also as with fish, this chronic NOAEC in daphnids is above the acute NOAEC of 59.3 mg a.e./L for Arsenal Herbicide. Concern for longer-term effects of exposures of aquatic invertebrates is at least somewhat diminished by the mesocosm study by Fowlkes et al. (2003). As summarized

in Appendix 5 (Table 4), the study involved exposures of mixed macroinvertebrates to mesocosms treated with Arsenal Applicators Concentrate at concentrations of 0.184, 1.84, or 18.4 mg a.e./L. No impacts were noted on species richness or abundance after a 2-week exposure period, which is comparable to the exposure period in chronic daphnid studies. The apparent NOAEC of 18.4 mg a.e./L is consistent with the acute NOAEC of 59.3 mg a.e./L for Arsenal Herbicide (Forbis et al. 1984b) as well as the chronic NOAEC of 97.1 mg a.e./L in daphnids (Manning 1989c).

U.S. EPA/OPP reviewed the mesocosm study by Fowlkes et al. (2003) as part of the EPA risk assessment for the California red-legged frog and offers the following critique:

> *These results are of limited value because potential effects at the species level were not examined. Individual species could have been affected and the results may not have picked it up because the analysis was conducted at higher taxonomic levels. In addition, effects on aquatic plants were not examined.*
>
> U.S. EPA/OPP (2007a, Appendix B, p. 15)

While this critique is factually correct and has merit, the study by Fowlkes et al. (2003) appears to have been well conducted, is reasonably well documented, and provides useful information on the longer-term effects of a formulation which will be used in Forest Service programs. This study is discussed further in the dose-response assessment for aquatic invertebrates (Section 4.3.3.3).

4.1.3.4. Aquatic Plants

4.1.3.4. Aquatic Plants

As summarized in Table 2, several formulations of imazapyr are labeled for the control of emergent or floating aquatic vegetation. No formulations of imazapyr, however, are labeled for the control of algae. The limitations on the types of target aquatic vegetation specified on the product labels for imazapyr formulations reflect the differential toxicity of imazapyr to different types of aquatic vegetation.

As with imazamox (SERA 2010c) and imazapic (SERA 2004b), imazapyr appears to be less toxic to algae than to aquatic macrophytes. An overview of the EC_{50} values for growth inhibition by imazapyr in algae and aquatic macrophytes is given in Table 18 and illustrated in Figure 6. Based on the geometric means of the EC_{50} values in algae and aquatic macrophytes, imazapyr is more toxic to aquatic macrophytes than to algae by a factor of over 1600 [37.2 mg a.e./L ÷ 0.023 mg a.e./L ≈ 1617.39]. Additional details of these studies are summarized in Appendix 6 and discussed in the following subsections.

4.1.3.4.1. Algae

The toxicity data on algae are summarized in Appendix 6, Table 1. Most of the data on algae are from standard registrant-submitted studies involving an exposure period of 7 days. These data come from a single study by Hughes (1987) which provides both EC_{50} values and NOAECs. The NOAECs are discussed further in the dose-response assessment for algae (Section 4.3.3.4.1). As illustrated in Figure 6 and summarized in Table 18, the differences in EC_{50} values for imazapyr

acid among different species of algae span a factor of about 8, ranging from 12.2 to 92 mg a.e./L [12.2 mg a.e./L ÷ 92 mg a.e./L ≈ 7.54]. Based on the matched bioassays conducted by Hughes (1987) in *Selenastrum capricornutum* (a green algae), the isopropylamine salt of imazapyr is more toxic than imazapyr acid by a factor of about 6 [71 mg a.e./L ÷ 11.5 mg a.e./L ≈ 6.174].

Two studies from Appendix 6, Herrick (1986) and Landstein et al. (1993) are not included in the overview given in Table 18 and illustrated in Figure 6. The study by Herrick (1986) on filamentous algae involved Petri dish exposures expressed in units of lb/acre rather than concentration; thus, the study is not comparable to the studies summarized in Table 18. Moreover, this study is classified as Invalid in the U.S. EPA/OPP data evaluation record (DER) available at http://www.epa.gov/pesticides/foia/reviews.htm, on that basis that no raw data were included in the study submitted to the EPA. The study by Landstein et al. (1993) suggests that *Chlorella emersonii*, a species of single-celled green algae, may be atypically sensitive to imazapyr. Landstein et al. (1993) report an EC_{50} for inhibition of acetolactate synthase (referenced in the publication as acetohydroxy acid synthase or AHAS) of about 0.2 mg a.e./L. This publication, however, does not specify the form of imazapyr used in the bioassay and did not assay endpoints such as cell density that are typically used in studies submitted to the U.S. EPA/OPP. Thus, the study by Landstein et al. (1993) is not comparable to the study by Hughes (1987).

4.1.3.4.2. Aquatic Macrophytes

Appendix 6, Table 2, summarizes the standard toxicity studies on aquatic macrophytes in which exposures are characterized as concentrations of imazapyr in water. Appendix 6, Table 3, summarizes field or field simulation studies in which exposures are characterized as application rates in units of lb a.e./acre. The former set of studies is used directly in the dose-response assessment for aquatic macrophytes (Section 4.3.3.4.2). The latter set of studies is analogous to efficacy studies and provides information on the sensitivity of additional species of aquatic macrophytes to imazapyr.

Standard toxicity studies are available only in one species of duckweed (*Lemna gibba*) and water milfoil (*Myriophyllum sibiricum*). The studies on duckweed are registrant-submitted studies conducted with imazapyr acid (Hughes 1987) and Arsenal (Hughes et al. 1995), a formulation of the isopropylamine salt of imazapyr. The toxicity study in water milfoil is a bioassay from the open literature using Arsenal (Roshon et al. 1999). As summarized in Table 18, these three studies yield remarkably similar EC_{50} values for growth inhibition ranging from 0.018 mg a.e./L for the salt of imazapyr in duckweed (Hughes 1995) to 0.029 mg a.e./L for the Arsenal formulation in water milfoil (Roshon et al. 1999).

While the standard bioassays in aquatic macrophytes suggest little variability in the sensitivity of aquatic macrophytes to imazapyr, the efficacy studies (Appendix 6, Table 3) suggest that some species of aquatic macrophytes may be tolerant to imazapyr. At relatively low application rates of 0.5 lb a.e./acre, aquatic macrophytes, including duckweed, water hyacinth, and water lettuce appear to be well controlled by imazapyr (Herrick 1986), as is consistent with the results of the standard toxicity studies. At the maximum labeled rate of 1.5 lbs a.e./acre, however, Giant Salvinia is not well controlled (Nelson et al. 2001). Other species that appear to be tolerant to imazapyr include lemon bacopa (at 0.75 lb a.e./acre), fanwort, coontail, and water milfoil (at 0.5 lb a.e./acre) (Herrick 1986).

Note that the efficacy study by Herrick (1986) is not consistent with the standard toxicity studies in that it reports limited efficacy in the control of water milfoil, which appears to be a sensitive species in the standard toxicity study by Roshon et al. (1999).

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 imazapyr formulations. It is beyond the scope of the current risk assessment on imazapyr to review the toxicity of all the adjuvants recommended for use with imazapyr or the potential impact of these adjuvants on aquatic organisms.

As discussed above, imazapyr is relatively nontoxic to aquatic animals. At least some of the recommended nonionic surfactants may be more toxic than imazapyr 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 imazapyr formulations, the recommended concentration of a nonionic surfactants ranges from 0.25 to 1% v/v. Assuming a surfactant density of 1 g/mL for illustration, 0.25% w/v corresponds to a concentration of 2500 mg/L and 1% corresponds to 10,000 mg/L. Given the low toxicity of imazapyr to both fish and aquatic invertebrates—i.e., defined LC_{50} values ranging from about 20 mg/L (rainbow trout, Cohle and McAllister 1984c) to about 600 mg/L (*Daphnia magna*, Forbis et al. 1984a)—the use of a relatively toxic nonionic surfactant in an aquatic application of imazapyr may be viewed as posing a greater risk to aquatic animals than would be anticipated from exposure to imazapyr alone.

Notwithstanding the above discussion, there is no basis for asserting that the risks posed by the surfactants would be substantial. The aquatic application of imazapyr to water may serve as a worst-case example. As detailed in Attachment 2 (Worksheet B04a), the concentration of imazapyr in water following an aquatic application would be less than 0.4 mg a.e./L for a representative formulation containing about 22.6% a.e. If 1% surfactant is added to the formulation, the concentration of the surfactant in water would be about 0.04 mg/L [0.4 mg a.e./L x 1% ÷ 22.6% a.e. ≈ 0.04425 mg/L]. As discussed in the EPA ecological risk assessments on imazapyr (U.S. EPA/OPP 2007a, Appendix F), the standard criteria used by U.S. EPA/OPP is a level of concern for endangered species of 0.05 – i.e., 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 in aquatic applications of imazapyr would result in peak exposures 0.04 mg/L and a corresponding ratio of the concentration to the LC_{50} of 0.04—i.e., below the U.S. EPA/OPP level of concern for endangered species [LOC=0.05]. Thus, there is no basis for asserting that the use of surfactants with imazapyr 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., 0.00004), below the level of concern by a factor of about 25,000.

The above discussion applies only to potential acute risks. A useful compendium on the longer-term toxicity of nonionic surfactants to aquatic organisms has not been identified; thus, 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 Attachment 1 for terrestrial applications made at the unit application rate of 1 lb a.e./acre. 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 and birds are summarized in Worksheet G01 of the EXCEL workbooks that accompany this risk assessment—i.e., Attachment 1 for terrestrial applications and Attachment 2 for aquatic applications. For terrestrial applications, the highest short-term exposures are associated with the consumption of contaminated insects by a small bird (224 mg a.e./kg bw) and the consumption of contaminated grasses by a small bird (1710 mg a.e./kg bw). For both acute and chronic exposures, consumption of contaminated water leads to dose estimates far below those associated with consumption of contaminated vegetation. This common pattern in many herbicide exposure assessments reflects the consequences of direct applications to vegetation. For aquatic applications, anticipated exposures to mammals and birds are far lower than those associated with terrestrial applications. The maximum expected acute dose is about 0.01 mg a.e./kg bw—i.e., the consumption of contaminated water by 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. Unintended direct spray is expressed simply as the application rate. As with terrestrial animals, all exposure assessments used in the workbooks that accompany this risk assessment are based on the unit application rate of 1 lb a.e./acre. The consequences of using other application rates are discussed in the risk characterization.

Exposures of aquatic plants and animals to imazapyr 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 workbook for imazapyr that accompanies this risk assessment (Attachment 1). An overview of the mammalian and avian receptors considered in the current risk assessment is given in Table 19. 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, small animals will generally receive a higher dose, in terms of mg/kg body weight, relative to large animals, for a given type of exposure. 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 for terrestrial applications. The first spray scenario (Worksheet F01a) concerns the direct spray of half of the body surface of a 20 g mammal during pesticide application. This exposure assessment assumes first-order dermal absorption using the first-order dermal absorption rate coefficient discussed in Section 3.1.3.2. 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 only approach for estimating the potential significance of dermal contact with contaminated vegetation is to assume a relationship between the application rate and dislodgeable foliar residue. Unlike the human health risk assessment 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 imazapyr, 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, which is addressed in the following subsection.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey

In foliar applications, the consumption of contaminated vegetation is an obvious concern. Exposure assessments for the consumption of contaminated vegetation are developed for all mammals and birds listed in Table 29, except for the large carnivorous mammal and the predatory bird. Both acute and chronic exposure scenarios are developed for the consumption of contaminated fruit (Worksheets F04a-e for acute and Worksheets F10a-e for chronic) and the consumption of short grass (Worksheets F05a-e for acute and Worksheets F11a-e for chronic).

As summarized in Table 13, fruit and short grass are the food items which comprise the commodities with the lowest pesticide residue rates (fruit) and the highest pesticide residue rates (short grass). Fruit and short grass are selected to represent the types of vegetation likely to be

consumed by various mammals and birds and which encompass the range of plausible imazapyr concentrations on vegetation.

For both the acute and chronic exposure scenarios, the assumption is made that 100% of the diet is contaminated. This may not be a realistic assumption for some acute exposures and will probably be a rare event in chronic exposures—i.e., animals may move in and out of the treated areas. 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 initial concentrations of imazapyr on contaminated food items are based on the U.S. EPA/OPP (2001) adaptation of the residue rates from Fletcher et al. (1997), as summarized in Table 13. The methods of estimating the peak and time-weighted average concentrations of imazapyr are identical to those used in the human health risk assessment (Section 3.2.3.7).

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/OPP (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 (Nagy 1987, Table 3). As discussed further 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 27. Most of the specific values in Table 27 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 F08a) or a predatory bird (Worksheet F08b) as well as the consumption of contaminated insects by a small mammal, a larger (400 g) mammal, and a small bird (Worksheets F07a-c).

4.2.2.4. Ingestion of Contaminated Water

The methods for estimating imazapyr concentrations in water are identical to those used in the human health risk assessment (Section 3.2.3.4). The only major differences in the estimates of exposure involve the weight of the animal and the amount of water consumed. As with the estimates of food consumption, water consumption rates are well characterized in terrestrial vertebrates. The water consumption rates are based on allometric relationships in mammals and birds, as summarized in Table 19. Based on these estimates, exposure scenarios involving the consumption of contaminated water are developed for mammals and birds for accidental spills

(Worksheets F02a-e), expected peak expected concentrations (Worksheets F06a-e), and expected longer-term concentrations (Worksheets F12a-e).

As with food consumption, water consumption in birds and mammals will vary substantially with diet, season, and many other factors; however, there are no well-documented quantitative estimates regarding the variability of water consumption by birds and mammals in the available literature. Accordingly, the variability in water consumption rates of birds and mammals is not considered in the exposure assessments. As summarized in Table 12, however, the upper and lower bound estimates of imazapyr concentrations in surface water vary substantially. Given this variability in the concentrations of imazapyr 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); moreover, even extreme variations on the consumption of contaminated water by mammals and birds would have no impact on the risk characterization.

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 imazapyr; accordingly, sets of exposure scenarios are developed for an accidental spill (Worksheets F03a-b), expected peak exposures (Worksheets F09a-c), and estimated longer-term concentrations (Worksheets F13a-c). These exposure scenarios are applied to 5 and 70 kg carnivorous mammals as well as a piscivorous bird. The 70 kg carnivorous mammal would be typical of a black bear (which does not actively hunt fish) but could be representative of a small or immature Great Plains Grizzly Bear (*Ursus arctos horribilis*), which is an endangered species that actively feeds on fish (Reid 2006).

Exposures to imazapyr from the consumption of contaminated fish are dependent not only on the concentration of imazapyr in water but also on the bioconcentration factor for imazapyr in fish. The concentrations of imazapyr in water are identical to those discussed in Section 4.2.2.4. As discussed in Section 3.2.3.5, imazapyr does not bioconcentrate in fish. Consequently and as in the human health risk assessment, the bioconcentration factor for fish is taken as 0.5 L/kg for all exposure scenarios involving mammals and birds.

4.2.3. Terrestrial Invertebrates

4.2.3.1. Direct Spray and Drift

Estimated levels of exposure associated with broadcast terrestrial applications of imazapyr are detailed in Worksheet G09 of Attachment 1 (terrestrial applications of imazapyr). This is a custom worksheet which includes aerial, ground broadcast (high boom and low boom), and backpack applications.

Honeybees are used as a surrogate for other terrestrial insects, and honeybee exposure levels associated with broadcast applications are modeled as a simple physical process based on the application rate and surface area of the bee. The surface area of the honeybee (1.42 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. As in the recent EPA ecological risk assessment of imazapyr (U.S. EPA/OPP 2007a), the honeybee is used as a surrogate for other insect species.

4.2.3.2. Ingestion of Contaminated Vegetation or Prey

Like terrestrial mammals and birds, terrestrial invertebrates may be exposed to imazapyr through the consumption of contaminated vegetation or contaminated prey. For broadcast foliar applications, estimates of residues on contaminated vegetation or prey are based on estimated residue rates (i.e., mg/kg residues per lb applied) from Fletcher et al. (1994), as summarized in Table 13.

An estimate of food consumption is necessary to calculate a dose level for a foraging herbivorous insect. Insect food consumption varies greatly, depending on the caloric requirements in a given life stage or activity of the insect and the caloric value of the food to be consumed. The derivation of consumption values for specific species, life stages, activities, and food items is beyond the scope of the current analysis. Nevertheless, general food consumption values, based on estimated food consumption per unit body weight, are readily available.

Reichle et al. (1973) studied the food consumption patterns of insect herbivores in a forest canopy and estimated that insect herbivores may consume vegetation at a rate of about 0.6 of their body weight per day (Reichle et al. 1973, pp. 1082 to 1083). Higher values (i.e., 1.28-2.22 in terms of fresh weight) are provided by Waldbauer (1968) for the consumption of various types of vegetation by the tobacco hornworm (Waldbauer 1968, Table II, p. 247). The current risk assessment uses food consumption factors of 1.3 (0.6 to 2.2) kg food /kg bw. The lower bound of 0.6 is taken from Reichle et al. (1973), and the central estimate and upper bound are taken from the range of values provided by Waldbauer (1968).

A summary of the estimated exposures in terrestrial herbivorous insects is given in Worksheet G08a and details of the calculations for these scenarios are provided in Worksheets G07a, G07b, G07c, and G07d of the EXCEL workbook for terrestrial foliar applications of imazapyr (Attachment 1). These levels pertain to the four food items included in the standard residue rates provided by Fletcher et al. (1994).

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 imazapyr 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 (Attachment 1).

4.2.4.1. Direct Spray

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

4.2.4.2. Off-Site Drift

Because off-site drift is more or less a physical process that depends primarily on droplet size and meteorological conditions rather than specific properties of the compound being sprayed, estimates of off-site drift can be modeled using AgDRIFT. These estimates are summarized in Worksheet G05 of the EXCEL workbook for terrestrial applications of imazapyr (Attachment 1). This custom worksheet includes 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. Aerial drift estimates are based on Tier 1 using ASAE Fine to Medium drop size distributions. Tier 1 estimates of drift for ground broadcast applications are modeled using both low boom and high boom options in AgDRIFT. For both types of applications, the values are based on Very Fine to Fine drop size distributions and the 90th percentile values from AgDRIFT.

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

4.2.4.3. Runoff and Soil Mobility

Exposures to terrestrial plants associated with runoff and sediment losses from the treated site to an adjacent untreated site are summarized in Worksheet G04 of the EXCEL workbook for terrestrial applications of imazapyr (Attachments 1).

Any pesticide can be transported from the soil at the application site by runoff, sediment loss, or percolation. Runoff, sediment loss, and percolation are considered in estimating contamination of ambient water. Only runoff and sediment loss are considered in assessing off-site soil contamination. This approach is reasonable because off-site runoff and sediment transport will contaminate the off-site soil surface and could 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. GLEAMS modeling provides data on pesticide loss by runoff. As with the estimates of imazapyr in surface water, runoff estimates are modeled for clay, loam, and sand at nine sites which are representative of different temperatures and rainfall patterns (Table 9).

For imazapyr, the results of the standard GLEAMS modeling of runoff and sediment losses are summarized in Appendix 7, Table A7-1. Note that the proportion of runoff as a fraction of the application rate 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 are identical to those used in the Gleams-Driver modeling for concentrations of imazapyr in surface water as discussed in Section 3.2.3.4 and summarized in Tables 8, 9 and 10.

The runoff for imazapyr as a proportion of the application rate is taken as 0.0056 (0.0000034 to 0.227). The central estimate and upper bound is taken directly from the Gleams-Driver modeling—i.e., the median and empirical upper 95% bound, as detailed in Appendix 7 (Table 1). The lower bound is effectively zero—i.e., for sandy soils regardless of temperature and rainfall rates. The lower bound value of 3.4×10^{-6} is based on the lowest non-zero central estimate—i.e., loam soils in cool locations and average rainfall. 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).

4.2.4.4. Contaminated Irrigation Water

Forest Service risk assessments include this standard scenario for the use of contaminated water for irrigation. Nonetheless and as discussed further in Section 4.4.2.5, the Reregistration Eligibility Decision for imazapyr notes that water which may contain imazapyr residues should not be used for irrigation:

> *Data on irrigated crops or label restrictions that prohibit the irrigation of crops with imazapyr treated water for 120 days following application and/or demonstrates non-detectable residue levels of imazapyr in irrigation water by laboratory analysis prior to use are required for reregistration.*
>
> U.S. EPA/OPP (2006a, p. 27)

All product labels for the formulations listed in Table 2 include restrictions to limit the use of water which may contain imazapyr residues for crop irrigation. Representative language from the product label for Arsenal is given below:

> *Application to water used for irrigation that results in Arsenal® herbicide residues greater than 1.0 ppb MUST NOT be used for irrigation purposes for 120 days after application or until Arsenal residue levels are determined by laboratory analysis or other appropriate means of analysis to be 1.0 ppb or less.*
>
> BASF Product Label for Arsenal Herbicide,
> Label 000241-00346.20101216b.NVA 2010-04-104-0192 dated 2011

Consequently, this standard exposure scenario, which is included in all herbicide risk assessments conducted for the Forest Service, may not be relevant to imazapyr. Nonetheless, this exposure assessment is included both for consistency with other herbicide risk assessments as well as to allow for the assessment of the consequences of disregarding the labeled use restrictions.

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

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 terrestrial applications (Attachment 1) and aquatic applications (Attachment 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 imazapyr 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 imazapyr would be transported by wind.

For this risk assessment, the potential effects of wind erosion are estimated in Worksheet G06b. In this worksheet, it is assumed that imazapyr is incorporated into the top 1 cm of soil, which is identical to the depth of incorporation used in GLEAMS modeling (Table 10). Average soil losses are estimated to range from 1 to 10 tons/ha/year with a typical value of 5 tons/ha/year. These estimates are based on 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 G07b, 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 a 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 herbicide applications are rarely made to fallow areas. In any event, the higher offsite losses reported by Larney et al. (1999) are comparable to exposures associated with offsite drift at distances of about 50 feet from the application site following low boom (0.017) and high boom (0.05) 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 imazapyr 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 and summarized in the upper portion of Table 12.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

Table 21 summarizes the toxicity values used in this risk assessment. 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 21 are expressed as acid equivalents (a.e.). Where necessary, the conversion factor of 0.8155 a.e./a.i., derived in Table 2, is used to convert experimental exposures expressed as a.i. to a.e., based on the ratio of the molecular weight of imazapyr acid to the isopropylamine salt of imazapyr.

For imazapyr, as for most herbicides labeled for terrestrial and aquatic applications, the toxicity studies on plants are reasonably complete and adequate for deriving toxicity values for sensitive and tolerant species. Like other imidazolinone herbicides, imazapyr appears to be more toxic to aquatic macrophytes than to algae and more toxic to terrestrial monocots than to dicots.

As is the dose-response assessment for human health effects, the dose-response assessments for terrestrial and aquatic animals are limited, primarily because imazapyr is relatively nontoxic to animals and the number of animal species tested is so few. Consequently, sensitive and tolerant species are not defined for either terrestrial animals or for most groups of aquatic animals. For fish and aquatic invertebrates, studies consistently indicate that Arsenal, the only formulation on which toxicity data are available, is more toxic than imazapyr acid or the isopropylamine salt of imazapyr. To the extent possible, the limited data on Arsenal are used in or incorporated into the dose-response assessment for fish and aquatic invertebrates. No toxicity data are available on terrestrial phase or aquatic phase amphibians. Consequently, no dose-response assessments for amphibians are developed.

4.3.2. Toxicity to Terrestrial Organisms

4.3.2.1. Mammals

In characterizing risk to mammalian wildlife, Forest Service risk assessments generally consider the NOAELs on which the acute and chronic RfDs used in the human health risk assessment are based. As summarized in the hazard identification for both human health (Section 3.1) and mammalian wildlife (Section 4.1.2.1), the standard array of studies used to assess the acute, subchronic, and chronic toxicity of pesticides, including effects on reproduction and development, indicate that imazapyr causes adverse effects in mammals only at doses of 1000 mg a.e./kg or more (Appendix 1, Tables 2 and 8). As summarized in Table 14, the EPA human health risk assessment (U.S. EPA/OPP 2005a) uses a chronic RfD of 2.5 mg/kg bw/day, which is based on a NOAEL of 250 mg a.e./kg bw/day from the chronic study in dogs by Shellenberger (1987). The chronic dog study failed to define an adverse effect level. As also summarized in Table 14, the EPA did not derive an acute RfD but considered the rat NOAEL of 300 mg/kg bw/day with a corresponding, but questionable, LOAEL for salivation of 1000 mg a.e./kg bw/day from the developmental study in rats by Salamon et al. (1983c). For the current Forest

Service risk assessment, the NOAEL of 250 mg a.e./kg bw/day from the chronic study in dogs is applied to canids.

The use of a NOAEL in dogs to characterize risks for all terrestrial mammals, however, may be overly conservative. Imazapyr is a weak acid, and, like most weak acids, is excreted primarily in the urine (Section 3.1.3.1). Because dogs have a limited capacity to excrete weak acids, they are more sensitive than other mammals to certain weak acids, like triclopyr (e.g., SERA 2011c). For imazapyr, the low order of the mammalian toxicity does not permit a rigorous assessment of species sensitivity differences. Nonetheless, as detailed in Appendix 1 (Table 11), higher chronic NOAELs are available in mice (e.g., over 1000 mg/kg/day from the study by Auletta 1988) and rats (e.g., over up to 738 mg/kg/day from the study by Robinson 1987). For the current risk assessment, the NOAELs in mice that exceed 1000 mg/kg bw/day are not used because of marginal concerns with the rat study by Salamon et al. (1983c) in which salivation was observed at 1000 mg/kg bw/day. Thus, the rat NOAEL of 738 mg/kg/day (Robinson 1987) is used to characterize risks to non-canid mammalian species. This NOAEL is identical to the NOAEL used for mammals in the most recent EPA ecological risk assessment (U.S. EPA/OPP 2007a, Table 4.2.a, p. 93).

4.3.2.2. Birds

As discussed in Section 4.1.2.2 and detailed in Appendix 2, imazapyr has a low order of acute toxicity in birds. After 5-day dietary exposures, no mortality or signs of toxicity were observed at doses of up to 647 mg a.e./kg/day (5000 ppm dietary concentrations) in bobwhite quail (Fletcher 1983a) and 1419 mg a.e./kg (5000 ppm dietary concentration) in mallard ducks (Fletcher 1983b). As discussed in Section 4.1.3, studies in aquatic organisms suggest that Arsenal formulations are more toxic than imazapyr itself to aquatic organisms. In dietary studies conducted with Arsenal Herbicide in both quail (Fletcher et al. 1984c) and mallards (Fletcher et al. 1984d), there is no indication that the formulation is more toxic than imazapyr on either an acid equivalent or mass basis. As detailed in Appendix 2 (Table 1), the dietary NOAELs are supported by single dose gavage NOAELs of 2150 mg Arsenal/kg bw, equivalent to 486 mg a.e./kg bw, in both quail (Fletcher et al. 1984a) and mallards (Fletcher et al. 1984b) and NOAELs of 2510 mg a.e./kg bw in quail (MRID 00131633) and mallards (MRID 00131635).

Gavage dosing is more stressful to the animal than dietary exposure; therefore, NOAELS for gavage administration are generally lower those for short-term dietary exposures. This is not the case for imazapyr. Consequently, while the use of the acute dietary NOAEL of 674 a.e. mg/kg/day in bobwhite quail (Fletcher 1983a) would be the most conservative approach, the current Forest Service risk assessment adopts the approach taken in U.S. EPA/OPP (2007a) and uses the gavage NOAEL of 2510 mg a.e./kg bw in quail and mallards to characterize risks associated with acute exposures to imazapyr.

For chronic toxicity, the147-day dietary NOAEL of 1670 ppm a.e. is based on reproductive endpoints (i.e., egg production, hatchability, survival of hatchlings) in bobwhite quail (Ahmed et al. 1969). This study is used also in the most recent EPA ecological risk assessment on imazapyr (U.S. EPA/OPP 2007a, Table 4.2.a, p. 92) to characterize risk in birds. The dietary NOAEL of 1670 ppm a.e. in quail from Ahmed et al. (1969) is supported by dietary NOAELs of 2000 ppm a.e. in quail (Fletcher et al. 1995a) and mallard ducks (Fletcher et al. 1995b). As detailed in

Appendix 2 (Table 3), the dietary NOAEL of 1670 ppm a.e. corresponds to a dose of about 610 mg a.e./kg bw/day, based on measured food consumption and body weights.

The longer-term NOAEL of 610 mg a.e./kg bw/day is not substantially different from the acute NOAEL of 674 a.e. mg/kg/day, also from a study in quail. While pharmacokinetic studies in birds are not available, the similarity between the acute and chronic NOAELs is consistent with a compound that is rapidly excreted.

Both of the acute and chronic NOAELs are free-standing—i.e., adverse effects may occur at higher, but as yet undetermined, doses.

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

4.3.2.4.2. Contact Toxicity Value (for Direct Spray)

The U.S. EPA/OPP (2005b, 2007a) reviewed and accepted the standard contact toxicity study in honeybees (Atkins 1984). As discussed in Section 4.1.2.4, the only information available on this study is that the acute contact LD_{50} in the honey bee is greater than 100 µg/bee, which is equivalent to about 860 mg/kg bw. This apparently low acute toxicity is consistent with the toxicity data on mammals and birds. No quantitative consideration can be given to other potential subchronic or non-lethal effects, and there is no information available on other invertebrate species. Given the numerous species of terrestrial invertebrates, the use of this single acute toxicity value on a single species obviously leads to uncertainty in the risk assessment. While an indefinite LD_{50} is not a preferred endpoint, it is the only piece of relevant information, and is, therefore, used to characterize risks in honeybees. As discussed further in Section 4.4.2.4, exposure levels for honeybees are far below 860 mg/kg bw; consequently, using this dose for risk characterization does not have a substantial impact on the risk assessment.

4.3.2.4.1. Oral Toxicity Value

Forest Service risk assessments also attempt to characterize risks to terrestrial invertebrates from the consumption of contaminated vegetation following broadcast applications (Section 4.2.3.2). The results of oral toxicity studies in honeybees are typically used to assess risks associated with this scenario. As with contact toxicity, the only information available on the oral toxicity of imazapyr to honeybees is the oral LD_{50} is >100 µg/bee, again equivalent to about >860 mg a.e./kg bw (Atkins and Kellum 1983). Consequently, the indefinite LD_{50} of >860 mg a.e./kg bw is used as a surrogate toxicity value to characterize risks to herbivorous insects from the consumption of vegetation contaminated with imazapyr.

The apparently low acute toxicity of imazapyr to terrestrial invertebrates is consistent with the toxicity data on mammals and birds. No quantitative consideration can be given to other potential subchronic or non-lethal effects, and no information is available on other invertebrate species.

4.3.2.5. Terrestrial Plants (Macrophytes)

As with most herbicides, there are adequate data for developing toxicity values for both sensitive and tolerant plant species involving soil exposures (i.e., herbicide runoff to an untreated field) and foliar exposures (direct spray, wind erosion, or drift). The available studies are discussed in Section 4.1.2.5 and summarized in Appendix 3. Studies on seedling emergence are used to assess risks associated with exposures to residues of imazapyr in soil. Studies on vegetative vigor are used to assess risks associated with the deposition of imazapyr onto plants as a result of direct spray or spray drift.

The study by American Cyanamid (1988b, MRID 40811801) is the only study on seedling emergence used quantitatively in U.S. EPA/OPP (2005b, 2007a). This study involved technical grade imazapyr. An earlier Tier 1 study on an Arsenal formulation (Malefyt 1986) involved only a single exposure level, and detailed supporting data on observations were not provided in the submission to the U.S. EPA/OPP (2005h, E-8). Consistent with the approach taken in (U.S. EPA/OPP 2007a), the data on sugar beets (a dicot) is used to assess risks to sensitive plant species, using the NOAEL of 0.00017 lb a.e./acre. Risks to tolerant species are based on the NOAEL of 0.0156 lb a.e./acre for growth (height) in oats (a monocot).

In the registrant-submitted studies on vegetative vigor (i.e., foliar exposures), the most sensitive species is clearly cucumber (a dicot) with an NOAEL of 0.000064 lb a.e./acre (American Cyanamid 1988b). The least sensitive species from the registrant-submitted studies is soybean (also a dicot), with a NOAEL of 0.008 lb a.e./acre from the study by Christensen et al. (1995). This NOAEL is supported by very similar NOAELs in monocots—i.e., 0.0078 lb a.e./acre for corn (American Cyanamid 1988b) and 0.005 lb a.e./acre for onion (Christensen et al. 1995).

As illustrated in Figure 5, the open literature study by Bovey and Senseman (1998) suggests that pumpkin (a dicot) is very tolerant to imazapyr with an NOAEL of 0.4 lb a.e./acre—i.e., a factor of about 50 higher than the highest reported NOAEL from the registrant-submitted studies [0.4 lb a.e./acre ÷ 0.0078 lb a.e./acre ≈ 51.28]. The study by Bovey and Senseman (1998) did not use a protocol that is closely related to those used in registrant-submitted studies. Nonetheless, as discussed in Section 4.1.2.5.2, the approximate EC_{25} for sensitive dicots (Bovey and Senseman 1998) is comparable to toxicity data on dicots from the registrant-submitted studies. Furthermore, as discussed in Section 4.3.2.5.1, plant populations may develop resistance to imazapyr. Wright and Penner (1998) report resistance factors of up to about 500 in corn. While the development of resistant populations is not considered quantitatively in the dose-response assessment, the NOAEL of 0.4 lb a.e./acre for pumpkin appears to be a credible value which may represent a very tolerant species or perhaps a resistant subpopulation. Consequently, the NOAEL of 0.4 lb a.e./acre is used to assess risks in species of plants that are tolerant and perhaps resistant to imazapyr.

Figure 5 also illustrates an apparent hormetic response in grass in which the lower doses of imazapyr lead to an increase rather than decrease in dry weight. Hormetic responses to herbicides are common in plants (Calabrese and Blain 2009).

4.3.2.6. Terrestrial Microorganisms

As summarized in Section 4.1.2.6, liquid culture solutions of imazapyr were toxic to various soil bacteria, with LC_{50} values ranging from about 10 to 1000 μM (Forlani et al. 1995, Figure 1,

p. 248). These concentrations correspond to about 2.61 to 261 mg/L (ppm) [1 μM = 1 μM/L, MW of acid = 261 g/mole]. Because these concentrations involve liquid cultures and because bioavailability of imazapyr is likely to be substantially less in a soil matrix, these values are not appropriate for direct use analogous to other NOAEL and NOAEC values discussed in this risk assessment. Ismail and Wong (1994) note that imazapyr had only a slight effect on the breakdown of cellulose at a concentration in soil of 20 mg/kg but had a substantial impact at a concentration in soil of 150 mg/kg. These values are relevant to the functional effect of imazapyr on soil microorganisms, as discussed in the risk characterization (Section 4.4.2.6).

4.3.3. Aquatic Organisms

4.3.3.1. Fish

For assessing risks to fish, the most recent EPA ecological risk assessment uses a 96-hour LC_{50} of >100 mg a.e./L in trout for acute exposures and an NOAEC of 43.1 mg a.e./L in trout for longer-term exposures (U.S. EPA/OPP 2007a, p. 85, Table 4.1a). These toxicity values are also used in the ecological risk assessment prepared by the Environmental Fate and Effects Division (EFED) of U.S. EPA/OPP U.S. (EPA/OPP 2005b) in support of the Reregistration Eligibility Decision for imazapyr (U.S. EPA/OPP 2006a).

As summarized in Appendix 4, the 96-hour LC_{50} of >100 mg a.e./L for trout is from MRID 131629 and is supported by several additional acute bioassays of either imazapyr acid or the isopropylamine salt of imazapyr in other species of fish that yield indefinite 96-hour LC_{50} values of >100 mg a.e./L. The longer-term NOAEC of 43.1 mg a.e./L is from the early life-stage study in trout using imazapyr acid (Manning 1989b) and is supported by higher NOAECs in fathead minnows from both an early life-stage study (Drotter et al. 1998) and a full life cycle study (Drotter et al. 1999).

A concern with the EPA dose-response assessment for fish involves the greater toxicity of the Arsenal formulation, relative to imazapyr acid and the isopropylamine salt of imazapyr. As detailed in Appendix 4 and discussed in Section 4.1.3.1.1, definitive 96-hour LC_{50} values for Arsenal are 20.8 mg a.e./L in trout (Cohle and McAllister 1984c) and about 40.7 mg a.e./L in bluegill sunfish (Cohle and McAllister 1984b). The greater toxicity of the formulation, relative to the acid and salt, is noted by U.S. EPA/OPP (2007a, p. 118). The formulation data, however, are not used in the EPA dose-response assessment because the lowest LC_{50} of 20.8 mg a.e./L is *…248 times higher than the aquatic EEC* [Expected Environmental Concentration]. In other words, U.S. EPA/OPP (2007a) appears to decline to use the lower toxicity values because they would not have an impact on the risk characterization.

While Forest Service risk assessments typically defer to the U.S. EPA/OPP, it does not seem sensible to use the toxicity data on imazapyr acid instead of the available information on the Arsenal formulation. As discussed in Section 2 and summarized in Table 2, all formulations of imazapyr considered in the current risk assessment either contain surfactants and other ingredients or surfactants are recommended as adjuvants. Consequently, in the current Forest Service risk assessment, the NOAEC of 10.4 mg a.e./L in trout (Cohle and McAllister 1984c) is used to characterize risks associated with acute/peak exposure to imazapyr in surface water.

The available information on the acute toxicity of imazapyr formulations to fish is limited to only two acute bioassays on a single formulation. These limited acute data cannot be used with confidence to define variations in sensitivity among species or differences in toxicity among formulations. Nonetheless, the available acute and chronic toxicity data suggest that trout are more sensitive than other species. Consequently, the NOAEC of 10.4 mg a.e./L is applied to sensitive species of fish. Uncertainties associated with the limited information on different species of fish and different formulations of imazapyr are discussed further in the risk characterization.

The dose-response assessment for longer-term exposures of fish is complicated by concerns regarding the greater toxicity of imazapyr formulations, relative to imazapyr acid. As noted above, the chronic NOAECs for imazapyr acid in fish range from 43.1 to 120 mg a.e./L. Given the information on greater acute toxicity of one imazapyr formulation to fish, there is a concern that the chronic NOAECs for imazapyr acid might not be sufficiently protective. In the absence of chronic studies on imazapyr formulations, the concern for the effects of chronic exposures in fish following applications of imazapyr formulations cannot be adequately addressed.

Many surfactants are essentially soaps and may degrade more rapidly than imazapyr. In this respect, the impact of surfactants in longer-term exposures to imazapyr/surfactant combinations could be less than the impact of surfactants immediately following applications. The identity of the surfactants, however, is proprietary. In the absence of explicit information, assumptions concerning the possibly rapid degradation of surfactants and other ingredients in the formulations are not supportable.

The available information suggests that the one tested formulation of imazapyr (Arsenal) is more toxic than imazapyr acid by a factor of at least 5 (i.e., >100 mg a.e./L ÷ 20.8 mg a.e./L ≈ 4.81). In the absence of additional information, the chronic NOAEC in trout of 43.1 mg a.e./L is divided by a factor of 10 and rounded to one significant digit to yield an adjusted NOAEC of 4 mg a.e./L, which is used to characterize risks associated with longer-term exposures of fish to imazapyr and other ingredients in imazapyr formulations. A factor of 10 rather than 5 is used to account for the uncertainty in dealing with the indefinite LC_{50} of >100 mg a.e./L for imazapyr acid. This NOAEC is applied to sensitive species of fish. Similarly, the full life cycle NOAEC of 118 mg a.e./L in fathead minnows is divided by 10 and rounded to 1 significant digit to yield an estimated longer-term NOAEC of 12 mg a.e./L, which is used to assess longer-term risks for tolerant species of fish.

4.3.3.2. Amphibians

As noted in Section 4.1.3.2, no information is available on the toxicity of imazapyr to aquatic phase amphibians. Consequently, no dose-response assessment is given for this group. U.S. EPA/OPP (2005b, 2007a) uses the toxicity values in fish in the risk characterization of aquatic phase amphibians.

4.3.3.3. Aquatic Invertebrates

In many respects, the dose-response assessment for aquatic invertebrates parallels the dose-response assessment for fish. The most recent EPA ecological risk assessment uses a 48-hour EC_{50} of >100 mg a.e./L to assess acute risks to aquatic invertebrates and a chronic NOAEC of 97.1 mg a.e./L to assess longer-term risks (U.S. EPA/OPP 2007a , p. 61). These toxicity values

for aquatic invertebrates are also used in the ecological risk assessment prepared by the Environmental Fate and Effects Division (EFED) of U.S. EPA/OPP U.S. (EPA/OPP 2005b, p. 66) in support of the Reregistration Eligibility Decision for imazapyr (U.S. EPA/OPP 2006a).

As summarized in Appendix 5, the 48-hour EC_{50} of >100 mg a.e./L for imazapyr in *Daphnia magna* is from the study by Kintner and Forbis (1983b) and the chronic NOAEC of 97.1 mg a.e./L for imazapyr acid, also in *Daphnia magna*, is from the study by Manning (1989c). The acute toxicity value is supported by several studies conducted with imazapyr acid and the isopropylamine salt of imazapyr which provide definitive EC_{50} values—i.e., up to an EC_{50} of 614 mg a.e./L in *Daphnia magna* for the salt (Forbis et al. 1984a)—and NOAECs of up to 132 mg a.e./L for imazapyr acid in oysters (Drotter et al. 1997).

As with fish, the concern with using the above acute toxicity values is that they all involve imazapyr acid or salt rather than an imazapyr formulation. The U.S. EPA/OPP (2007a) reports an EC_{50} of 64.9 mg a.e./L for Arsenal in *Daphnia magna* from the study by Forbis et al. (1984b). As detailed in Appendix 5, a review of the U.S. EPA/OPP data evaluation record (DER) for this study indicates that the reported EC_{50} of 64.9 mg a.e./L may be lower than the actual EC_{50}. It appears that U.S. EPA/OPP (2007a) may have double corrected for the a.i. to a.e. conversion. Based on the EPA analysis in the DER, the EC_{50} is about 350 mg Arsenal/L. As summarized in Table 2, Arsenal herbicide contains 22.6% a.e. Thus, the EC_{50} of 350 mg Arsenal/L corresponds to about 79 mg a.e./L [350 mg Arsenal/L x $0.226_{a.e./form}$ = 79.1 mg a.e./L]. Based on the raw data for Arsenal from Forbis et al. (1984b), the EC_{50} of 350 mg Arsenal/L was verified in the conduct of the current risk assessment using the U.S. EPA's Benchmark Dose Software (U.S. EPA/NCEA 2011b).

By comparison to the matched study by Forbis et al. (1984a) with the isopropylamine salt of imazapyr which yielded a definitive LC_{50} of 614 mg a.e./L, the Arsenal formulation (with a definitive LC_{50} of 79 mg a.e./L) appears to be more toxic than the isopropylamine salt of imazapyr by a factor of about 8 [614 mg a.e./L ÷ 79 mg a.e./L ≈ 7.77]. In the study conducted with Arsenal, the NOAEC is 180 mg formulation/L or about 41 mg a.e./L (i.e., no mortality or signs of sublethal toxicity were observed). The EPA DER classifies the 320 mg formulation/L concentration (≈72.3 mg a.e./L) as the LOAEC. While this concentration is literally the Lowest Observed Adverse Effect Concentration, 45% of the daphnids died at this concentration; accordingly, 72.3 mg a.e./L can be viewed as a Frank Effect Concentration.

For assessing acute risks to aquatic invertebrates, the concentration of 41 mg a.e./L from the Forbis et al. (1984b) study conducted with Arsenal is used as a NOAEC. As discussed further in Section 4.4.3.4, the proximity of the Frank Effect Concentration to the NOAEC has no impact on the risk assessment, because peak concentrations of imazapyr in water, including those associated with an accidental spill, are below the NOAEC.

The limited information on the toxicity of imazapyr and imazapyr formulations to aquatic invertebrates does not support an assessment of the sensitivity of daphnids, relative to other aquatic invertebrates. For the current risk assessment, the conservative assumption is made that daphnids may be representative of relatively tolerant species, and the NOAEC of 41 mg a.e./L is

applied to presumably tolerant species. No toxicity value is proposed for sensitive species, and this limitation is discussed further in the risk characterization (Section 4.4.3.4).

The only longer-term toxicity study in aquatic invertebrates is the life cycle study in *Daphnia magna* by Manning (1989c), which reports an NOAEC of 97.1 mg a.e./L for imazapyr acid. As discussed above, the acute toxicity data in *Daphnia magna* indicate that the Arsenal formulation is about 8 times more toxic than the isopropylamine salt of imazapyr. In the absence of other information, the experimental NOAEC of 97.1 mg a.e./L is divided by 8 to account for the potentially greater longer-term toxicity of imazapyr formulations, and similarly, the adjusted longer-term NOAEC of 12 mg a.e./L [97.1 mg a.e./L ÷ 8] is used to assess longer-term risks in presumably tolerant species of aquatic invertebrates. As with the dose-response assessment for acute risks, no longer-term dose-response assessment is offered for potentially sensitive species of aquatic invertebrates.

4.3.3.4. Aquatic Plants

4.3.3.4.1. Algae

Based on the well-documented registrant study by Hughes (1987) conducted with imazapyr acid, variability in the response of algae is less than an order of magnitude, with EC_{50} values ranging from about 11.5 to 92 mg a.e./L and NOAECs ranging from 7.6 to 50.9 mg a.e./L. Based on both endpoints, the most sensitive species is *Selenastrum capricornutum* and the most tolerant species is *Skeletonema costatum*. The open literature study by Landstein et al. (1993) reports a much lower EC_{50} of about 0.2 mg a.e./L for acetohydroxy acid synthase activity. This study, however, is not comparable to the more directly relevant ecological endpoints relating to growth inhibition, which are typically used in Forest Service and U.S. EPA/OPP risk assessments.

For the current risk assessment, the NOAECs of 7.6 and 50.9 mg a.e./L are applied directly to potentially sensitive and tolerant species of aquatic algae, respectively. For sensitive species, this approach is identical to that taken in U.S. EPA/OPP (2007a, p. 58), except that the EPA uses EC_{50} values rather than NOAECs for risk characterization. The Forest Service, however, prefers to use NOAECs for risk characterization, as detailed in SERA (2007a). Because of the short lifespan of algae, the NOAECs are applied to both acute and longer-term exposures.

No data are available on the toxicity of imazapyr formulations to algae. As discussed in the following section, the available data on aquatic macrophytes do not suggest a substantial difference between the toxicity of imazapyr acid and Arsenal formulations to *Lemna gibba*. In the absence of additional information, the assumption is made that algae are equally sensitive, or nearly so, to both imazapyr acid and imazapyr formulations.

4.3.3.4.2. Macrophytes

As discussed in Section 4.1.3.4 and illustrated in Figure 6, standard toxicity studies in which exposure levels are characterized in terms of imazapyr concentration in water suggest that aquatic macrophytes are much more sensitive than algae to imazapyr. Based on the studies in *Lemna gibba* (duckweed) using imazapyr acid (Hughes 1987) and Arsenal (Hughes 1995), there are no substantial or significant differences regarding the potency of the acid or the formulation—i.e., and EC_{50} of 0.024 mg a.e./L for the acid and of 0.018 mg a.e./L for the formulation. As detailed in Appendix 6 (Table 2), U.S. EPA/OPP (2007a) gives an EC_{50} of

0.018 mg a.e./L for the formulation, while the study author reports a somewhat higher EC_{50} of 0.0228 mg a.e./L. This situation is not unusual. There are many different ways of calculating EC_{50} values, and modest differences in results among the different methods are common. These differences are trivial, and the values from U.S. EPA/OPP are adopted in the current risk assessment for the sake of consistency.

Standard bioassays are available on only two types of aquatic plants, duckweed (a common test species) and water milfoil (a target species). For the Arsenal formulation, the most sensitive EC_{50} for water milfoil is 0.008 mg a.e./L (based on root growth), about a factor of 2 below the EC_{50} of 0.018 mg a.e./L for duckweed. While Roshon et al. (1999) do not report an NOAEC for root growth in water milfoil, visual examination of Figure 1 in the publication (Roshon et al., 1999, p. 1162) indicates an NOAEC of about 0.003 mg a.e./L. This concentration is about a factor of 4 below the NOAEC of 0.011 mg a.e./L in duckweed (Hughes et al. 1995) [0.011 mg a.e/L ÷ 0.003 mg a.e./L ≈ 3.66].

For the current risk assessment, the NOAEC of 0.003 mg a.e./L in water milfoil is applied directly to sensitive species of aquatic macrophytes. The modestly higher NOAEC of 0.011 mg a.e./L in duckweed, however, may not adequately encompass the susceptibility of tolerant species. Field simulation studies in which exposure levels are characterized as application rates in lb a.e./acre, suggest that at least some species of aquatic macrophytes may be relatively tolerant to imazapyr. As summarized in Appendix 6 (Table 3), Herrick (1986) suggests that water milfoil as well as duckweed are similarly sensitive to the Arsenal formulation of imazapyr at an application rate of 0.5 lbs a.e./acre. Other species, such as lemon bacopa, are insensitive at an application rate of 0.75 lbs a.e./acre. In addition, the field simulation study by Nelson et al. (2001) suggest that giant salvinia is relatively tolerant to application rates of up to 1.5 lbs a.e./acre (i.e., the maximum labeled application rate).

Nelson et al. (2001) do not specify the target concentration associated with the simulated application rate of 1.5 lbs a.e./acre. They do, however, indicate that the study was conducted using 80-liter trash cans. Assuming 30 inches as the approximate diameter of the trash can, the lateral surface area would be about 479 cm^2. An application rate of 1.5 lbs a.e/acre is equivalent to about 0.0168 mg/cm^2 [1 lb/acre = 112.1 mg/m^2 ÷ (10,000 cm^2/m^2) = 0.01121 mg/cm^2]. The amount applied to a 479 cm^2 surface area would be about 8 mg [0.0168 mg/cm^2 x 479 cm^2 ≈ 8.0472 mg], and the concentration in 80 liters of water would be about 0.1 mg a.e./L.

While the above calculations of the approximate target concentration used by Nelson et al. (2001) on giant salvinia may be somewhat tenuous, the estimated concentration of 0.1 mg a.e./L may provide a better approximation of an NOAEC for tolerant species, compared with the nearly 10-fold lower NOAEC of 0.011 mg a.e/L in duckweed (Hughes et al. 1995). Thus, in the current risk assessment, the estimated NOAEC of 0.1 mg a.e./L is used to assess risks in sensitive species of aquatic macrophytes.

4.4. RISK CHARACTERIZATION

4.4.1. Overview

Imazapyr is an effective herbicide for the control of both terrestrial and aquatic vegetation. Under some conditions, the terrestrial application of imazapyr could damage nontarget terrestrial vegetation. Effective aquatic applications of imazapyr will most certainly damage aquatic macrophytes and perhaps some sensitive species of algae. While adverse effects on plants may be anticipated, there is no basis for asserting that applications of imazapyr will lead to significant or even detectable signs of toxicity in terrestrial or aquatic animals. The risk characterization for imazapyr, however, must be qualified with respect to the likelihood of adverse effects in nontarget terrestrial plants as well as data limitations in the risk characterization for terrestrial and aquatic animals and plants.

While imazapyr is an effective terrestrial herbicide, the exposure scenarios developed for terrestrial plants in the current risk assessment lead to an extremely wide range of HQs, some of which are far below the level of concern and others substantially above the level of concern. This apparent ambiguity relates to the attempt made in the exposure assessments to encompass a wide range of potential exposures associated with different weather patterns and other regional or site-specific variables. Thus, for applications of imazapyr to areas in which potential effects on nontarget plants are a substantial concern, refinements to the exposure scenarios for nontarget plants should be considered based on site or region specific factors.

The risk characterization for both aquatic and terrestrial animals must be qualified in terms of the small number of species on which data are available, relative to the numerous species which could be exposed to imazapyr. This type of reservation is common to many pesticide risk assessments. For mammals and birds, however, the reservations are modest. Imazapyr has been subject to a standard and relatively extensive series of acute, subacute, and chronic studies in mammals. There is little doubt that imazapyr is *practically non-toxic* (the classification assigned by the U.S. EPA/OPP) to mammals, birds, honeybees, fish, and aquatic invertebrates. None of the expected (non-accidental) exposures to these groups of animals raise substantial concern. The major uncertainties regarding toxic effects in animals are associated with the lack of toxicity data on either reptiles or amphibians. While the available studies on other groups of organisms fail to suggest hazards associated with exposure to imazapyr, confidence in extending this risk characterization to reptiles and amphibians is limited.

While the risk characterization for imazapyr focuses on the potential for direct toxic effects, the potential for secondary effects is evident for virtually all groups of nontarget organisms. Terrestrial or aquatic applications of any effective herbicide, including imazapyr, are likely to alter vegetation within the treatment area. This alteration is likely to have secondary effects on terrestrial or aquatic animals including changes in food availability and habitat quality. Secondary effects on nontarget vegetation are also likely. 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 imazapyr or herbicide applications in general. Any effective method for vegetation management, including mechanical methods which do not involve imazapyr or any other chemical, is likely to lead to secondary effects on both nontarget animals and vegetation.

4.4.2. Terrestrial Organisms

4.4.2.1. Mammals

The risk characterization for mammals and birds is summarized in Worksheet G02 of the EXCEL workbooks that accompany this risk assessment, Attachment 1 for terrestrial applications and Attachment 2 for aquatic applications. Both workbooks are based on the unit application rate of 1 lb a.e./acre for terrestrial directed and broadcast foliar applications and aquatic applications to emergent vegetation.

For aquatic applications, none of the HQs approaches a level of concern. The highest HQ of 0.009 is associated with the upper bound of the HQ for a canid consuming contaminated fish following an accidental spill. This HQ is below the level of concern (HQ=1) by a factor of over 100.

As with aquatic applications, none of the hazard quotients for terrestrial applications exceed the level of concern. The highest HQs are associated with consumption of contaminated grass by a small mammal—i.e., HQs of 0.2 (0.02 to 0.9). As noted in Table 13, short grass is the standard food item from Fletcher et al. (1997) with the highest residue rates. As discussed in Section 4.2.2.3, this scenario assumes that the small mammal will consume nothing but contaminated grass following a direct spray. While this activity may occur in some instances, most small mammals have a more diverse diet, particularly in a forest environment, and residues on contaminated short grass will often be diminished by foliar interception. Thus, this scenario should be viewed as an extreme worst-case—i.e., the Most Exposed Individual as discussed in Section 3.2.3.1.1.

Notwithstanding the above discussion, the Most Exposed Individual approach is carried over to the ecological risk assessment because of the numerous species that may be exposed to pesticides applied by broadcast application and the enormous range of materials these species might consume. While the consumption of contaminated grass is intended to be a worst-case exposure scenario, it is interpreted as a means by which some small mammals could be exposed to imazapyr doses that approach a level of concern.

As discussed in the dose-response assessment for mammals (Section 4.3.2.1), clear adverse effect levels for mammals exposed to imazapyr have not been defined. A dose of 1000 mg a.e./kg bw/day is associated with salivation in rats over the course of a developmental study (Salamon et al. 1983c). The upper bound HQ of 0.9 for the consumption of contaminated grass is associated with a dose of about 690 mg a.e./kg bw (Attachment 1, Worksheet G01).

All other exposure scenarios for the small (20 g) mammal and all exposure scenarios for all other larger mammals are no greater than 0.2, below the level of concern by a factor of 5.

The largely benign risk characterization for mammals is similar to the risk characterization for mammals in the EPA ecological risk assessments in support of the RED (U.S. EPA/OPP 2005a, p. 5) and the assessment for the California red-legged frog (U.S. EPA/OPP 2007a, p. 17).

4.4.2.2. Birds

The risk characterization for birds is also summarized in the Worksheet G02 of the EXCEL workbooks that accompany this risk assessment. As is the case with mammals, there is no basis for asserting that signs of toxicity will be observed in birds after exposure to imazapyr. For terrestrial exposures, the upper bound of the longer-term HQ for the consumption of contaminated grass is 1.4, which modestly exceeds the level of concern (HQ=1). From a practical perspective, HQs are typically rounded to the nearest digit; hence, an HQ of 1.4 does not reflect a substantial risk. In addition, as discussed in the risk characterization for mammals, the exposure scenarios for the exclusive consumption of contaminated grass by either a small bird or a small mammal should be viewed as extreme worst-case scenarios. Typically, neither small birds nor small mammals will consume only contaminated grass. All other HQs for birds following terrestrial applications of imazapyr are below, and in most cases substantially below, the level of concern.

For aquatic applications, the highest HQ is 0.002, which is below the level of concern by a factor of 500; furthermore, this HQ is associated with the upper bound exposure for a small bird that consumes water contaminated by an accidental spill of imazapyr.

As with the HQs for mammals, the only reservation with the HQs for birds is that they probably overestimate risk. As discussed in the dose-response assessment for birds, toxic exposure levels of imazapyr are not defined for birds.

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 imazapyr to this group of organisms. Based on the risk characterization for birds, as well as all other groups of terrestrial animals for which data are available, there is no basis for assuming that reptiles or terrestrial phase amphibians are likely to be at risk from exposures to imazapyr. This approach has been adopted for amphibians in the recent U.S. EPA/OPP (2007a, pp. 105-106) risk assessment of imazapyr. As discussed in Section 4.1.2.3, however, amphibians may be more sensitive to some pesticides because of the skin of amphibians is more permeable to pesticides than mammalian skin. Thus, it is not clear that the risk characterization for other groups of terrestrial animals is applicable to amphibians and this limitation may also apply to reptiles.

4.4.2.4. Terrestrial Invertebrates

Risks to terrestrial invertebrates are characterized only for terrestrial applications of imazapyr. As summarized in Attachment 1, Worksheet G08b, the upper bounds of the HQs range from 0.04 to 0.6. As with mammals and birds, the upper bound HQ is associated with the consumption of contaminated short grasses. Based the analysis by Fletcher et al. (1997), as detailed in Table 13, pesticide concentrations in short grasses are expected to be substantially higher than pesticide concentrations in the other food sources defined by Fletcher et al. (1997).

For imazapyr, concern with an HQ of 0.6 is essentially negligible. As with all other groups of terrestrial animals, the potential risk of adverse effects in terrestrial invertebrates exposed to imazapyr is not characterized. Furthermore, this risk characterization is limited by the nature of toxicity data on terrestrial invertebrates—i.e., standard acute bioassays in honeybees. This limitation, however, is common in risk assessments of herbicides.

4.4.2.5. Terrestrial Plants

Risks to terrestrial plants are characterized only for terrestrial applications of imazapyr (Attachment 1). All HQs are based on the unit application rate of 1 lb a.e./acre. A quantitative summary of the risk characterization for terrestrial plants is presented in Worksheets G04 for runoff, Worksheets G05 for drift, and Worksheet G06 for off-site contamination due to wind erosion.

4.4.2.5.1. Direct Spray and Spray Drift

In Attachment 1, Worksheet G05 was modified manually to reflect the use of four sets of values for drift: aerial application, ground high-boom broadcast application, ground low-boom broadcast application, and ground backpack 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, all HQs are based on NOAELs from studies on vegetation vigor (foliar applications)—i.e., a NOAEL of 0.000064 lb a.e./acre for sensitive species and a NOAEL of 0.4 lb a.e./acre for tolerant and/or resistant species.

As discussed in Section 4.3.2.5.1, plants may develop resistance to imazapyr; in fact, resistance factors of up to about 500 (corn, Wright and Penner 1998) have been reported. The NOAEL of 0.4 lb a.e./acre is for pumpkins from the open literature study by Bovey and Senseman (1998). This NOAEL is much higher than any NOAEL from registrant-submitted studies (Appendix 3), and is used to reflect either resistance or tolerance in species (target or nontarget) of terrestrial plants, even though it is not clear that the pumpkins in the study by Bovey and Senseman (1998) were resistant to imazapyr.

As summarized in Attachment 1, the highest HQs are associated with direct spray (Worksheet G05). For convenience, the HQs for direct spray and drift based on all four application methods discussed above are summarized in Table 22. Imazapyr is an effective herbicide. If directly sprayed with imazapyr at an application rate of 1 lb a.e./acre, it is possible that even tolerant species of plants may be damaged (HQ=3). As summarized in Table 4, the average application rate used in Forest Service programs is about 0.3 lbs a.e./acre. At this application rate, the HQ would be at the level of concern (HQ=1), and damage to tolerant or very resistant species of terrestrial vegetation would probably not occur. For sensitive species of terrestrial plants, the HQ associated with direct spray is greater than 15,000 at an application rate of 1 lb a.e./acre. Because of the very high HQ for sensitive species of plants, considerations of variations in the application rate are irrelevant. If sensitive species of plants are directly sprayed with imazapyr, they will die.

Based on the estimates of drift using AgDRIFT, potential risks to sensitive and tolerant species of plants differ substantially. Tolerant species of terrestrial plants will probably not display any adverse effects even if they are close to the treatment area. Sensitive species of terrestrial plants, however, may display damage at up to 900 feet downwind of the application site, regardless of the application method. At 900 feet downwind of the application site, HQs for sensitive species of plants are substantial for both aerial application (HQ=194) and high boom ground application (HQ=26). Drift beyond 900 feet is difficult to estimate, particularly using the conservative and generic methods applied in the current risk assessment. Nonetheless, it appears that damage to sensitive species of terrestrial plants could extend well beyond 900 feet, unless effective efforts are made to reduce drift.

The HQs for drift are associated with substantial uncertainty. As noted in Section 4.2.4.2 and explained further in the documentation for WorksheetMaker (SERA 2010a, 2011a), the drift estimates given in Worksheet G05 should be viewed as only crude approximations that do not consider the numerous site-specific variables which can affect pesticide drift. This consideration is particularly important for backpack applications. The drift estimates for backpack applications, which are based on a modified set of assumptions for low-boom ground applications, are likely to overestimate drift associated with carefully conducted backpack applications under conditions that do not favor drift. If risks to nontarget vegetation are a substantial concern in any site-specific application of imazapyr, refinements to the drift estimates used in Worksheet G05 or generated using WorksheetMaker should be considered.

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 tolerant species of plants, the HQs are 0.4 (0.0002 to 15). For sensitive species of plants, the HQs are 33 (0.02 to 1,335). As with the estimates of drift, the estimates of offsite transport in runoff and sediment should be regarded as only crude approximations. The upper bound HQs represent estimates of exposures levels which may not be applicable to many site-specific applications made in Forest Service programs.

For sensitive species of plants, the extreme range of the HQs reflects the nature of the generic (non-site-specific) Gleams-Driver modeling on which the exposure assessment is based. As detailed in Section 3.2.3.4.3 and summarized in Table 8, 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.

Appendix 7, Table A7-1 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 imazapyr 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 imazapyr contaminated surface water for irrigation are summarized in Worksheet G06a of Attachment 1—HQs of 71 (0.008 to 1,841) for sensitive species and 0.01 (0.000001 to 0.3) for tolerant species.

As detailed in Section 4.2.4.4, the EPA requires all product labels for imazapyr to include language restricting the use of water contaminated with imazapyr for irrigation (U.S. EPA/OPP 2006a, p. 27). As also discussed in Section 4.2.4.4, consideration of risks associated with this scenario reflects a misuse rather than an expected event.

As with the HQs for runoff, the HQs associated with irrigation water for tolerant species of plants do not require elaboration. The key variables in this exposure scenario are the Water Contamination Rates 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.

The apparent risks to sensitive plants are substantial. As with the runoff estimates discussed in the previous section, Water Contamination Rates (WCRs) are taken from the Gleams-Driver modeling and adjusted for an application rate of 1 lb a.e./acre. As detailed in Section 3.2.3.4.3, the WCRs are a composite of all sites and soils considered in the Gleams-Driver modeling. As with the risks associated with runoff discussed in the previous subsection, site- or region-specific Gleams-Driver may be used to derive more relevant HQs. Given the label language discussed above, however, the use of imazapyr contaminated surface water for irrigation is not an anticipated event —i.e., the use of contaminated water for irrigation is contrary to the cautionary language on the formulation labels.

4.4.2.5.4. Wind Erosion

As summarized in Worksheet G06b of Attachment 1, the HQs for sensitive species of plants are 1.1 (0.2 to 2) and the corresponding HQs for tolerant species of plants are 0.0002 (0.00003 to 0.0003). 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 imazapyr were to be applied inadvertently to fallow soil.

The HQs for tolerant species of plants are below, and for this scenario, far below the level of concern.

For sensitive species of plants, the central estimate and upper bound of the HQs modestly exceed the level of concern at the unit application rate of 1 lb a.e./acre. Because of the modest exceedances, considerations of application will only modestly alter the risk characterization. As discussed in Section 2.4, the maximum application rate for imazapyr is 1.5 lbs a.e./acre. While potential damage to nontarget vegetation due to the erosion of contaminated soil by wind cannot be totally dismissed, the risks associated with this scenario are far below those of other exposure scenarios for plants considered in this risk assessment (i.e., drift, runoff, and irrigation water).

4.4.2.6. Terrestrial Microorganisms

As summarized in Appendix 7 (Table 2), the peak concentrations of imazapyr expected in the top 12 inches of soil are 0.32 (0.218 to 0.46) mg a.e./kg soil. These concentrations are far below the range of reported LC_{50} values for microorganisms in liquid culture—i.e., 2.61 to 261 mg/L from (Forlani et al. 1995). Ismail and Wong (1994) observed that imazapyr had only a slight effect on the breakdown of cellulose at a soil concentration of 20 mg/kg but had a substantial impact at a

soil concentration of 150 mg/kg. These concentrations, however, are far above any anticipated soil concentrations of imazapyr. Thus, there does not appear to be any basis for asserting that imazapyr is likely to affect soil microorganisms adversely. This conclusion appears to be consistent with the use of imazapyr as an effective herbicide. If imazapyr were extremely toxic to terrestrial microorganisms that are important for the maintenance of soil suitable for plant growth, it seems reasonable to assume that secondary signs of injury to microbial populations would have been reported.

4.4.3. Aquatic Organisms

4.4.3.1. Fish

The quantitative risk characterization for fish as well as other aquatic organisms is given in Worksheet G03 in the EXCEL workbooks for both terrestrial applications (Attachment 1) and aquatic applications (Attachment 2) of imazapyr.

As discussed in the dose-response assessment for fish (Section 4.3.3.1), the acute dose-response assessment for fish is based on toxicity data for the Arsenal formulation (expressed in units of mg a.e./L) rather than toxicity data on imazapyr. Only a single acute NOAEC is available for Arsenal – i.e., the NOAEC of 10.4 mg a.e./L from the trout bioassay conducted by Cohle and McAllister (1984c). The use of a formulation NOAEC is different from the dose-response assessments in U.S. EPA/OPP (2005a, 2007a), which are based on indefinite LC_{50} values of >100 mg a.e./L for technical grade imazapyr. Because the LC_{50} values for technical grade imazapyr are indefinite (i.e., greater than values), U.S. EPA/OPP (2005a, 2007a) does not calculate risk quotients for imazapyr.

In this Forest Service risk assessment, the acute NOAEC of 10.4 mg a.e./L for imazapyr as an Arsenal formulation is used to derive HQs for sensitive species of fish. This approach has little impact on the risk characterization because the HQs are below the level of concern (HQ=1) for all non-accidental exposures. For terrestrial applications of imazapyr, the upper bound HQ for an accidental spill is 1.7. Based on peak acute expected concentrations of imazapyr (i.e., non-accidental exposures) in surface water, the upper bound of the HQ is 0.03, which is below the level of concern by a factor of about 33. For aquatic applications, the upper bound HQ based on non-accidental peak exposures is 0.02, which is below the level of concern by a factor of 50.

As also discussed in dose-response assessment for fish (Section 4.3.3.1), NOAECs for longer-term exposures are based on experimental NOAECs in fathead minnows (tolerant species) and trout (sensitive species). The experimental NOAECs, however, are adjusted downward by a factor of 10 to account for Arsenal's greater toxicity to fish, relative to the toxicity of imazapyr acid. Even with this conservative approach, the upper bounds of the longer-term HQs range from 0.01 to 0.03 for terrestrial applications and from 0.01 to 0.04 for aquatic applications. These HQs are below the level of concern by factors of 25 to 100.

Given the very low acute and chronic HQs in fish and the conservative assumptions used to derive these HQs, there is no basis for asserting that acute or longer-term exposure to imazapyr will cause toxic effects in fish.

4.4.3.2. Amphibians

As with risks to terrestrial phase amphibians (Section 4.4.2.3), risks to aquatic phase amphibians cannot be characterized directly, due to the lack of relevant toxicity data. Based on the risk characterization for fish and all other groups of aquatic and terrestrial animals for which data are available, there is no basis for assuming that aquatic phase amphibians are likely to be at risk from exposures to imazapyr. Nonetheless, a reasonably definitive risk characterization for aquatic phase amphibians (i.e., one based on experimental data on amphibians) cannot be developed.

4.4.3.4. Aquatic Invertebrates

As summarized in Table 21, the acute NOAEC for invertebrates is somewhat higher than that for fish (41 vs. 10.4 mg a.e./L), and the chronic NOAECs for tolerant species are identical. Like the dose-response assessment for fish, the dose-response assessment for aquatic invertebrates differs from and is more conservative than that developed by the U.S. EPA/OPP, in that all NOAECs are based on the Arsenal formulation (which is substantially more toxic than technical grade imazapyr) or NOAELs on imazapyr which are adjusted downward to account for the greater toxicity of the formulation. The EPA did not develop a quantitative risk characterization for aquatic invertebrates, because the LC_{50} values for exposure to imazapyr acid are all indefinite (i.e., greater than values) (U.S. EPA/OPP 2007a, p. 107).

Even with this more conservative approach used in the current risk assessment, there is no apparent basis for asserting that risks to aquatic invertebrates pose a substantial toxicologic concern. The highest HQ is 0.4, the upper bound HQ associated with an accidental spill. For non-accidental exposures (i.e., those associated with the concentrations in water associated with the anticipated uses of imazapyr) the upper bound HQs for terrestrial exposures are 0.006 based on peak concentrations and 0.01 based on longer-term exposures. For aquatic applications, the upper bound HQs are 0.004 for peak exposures and 0.01 for longer-term exposures. These upper bound HQs are below the level of concern by factors of 100 to 250.

The major difference between the risk characterization for aquatic invertebrates and the risk characterization for fish (Section 4.4.3.2) is that sensitive species of aquatic invertebrates are not identified. In other words, differences in species sensitivity for aquatic invertebrates are not substantial, based on the relatively few species on which studies have been conducted. Consequently, the assumption is made that more sensitive species may exist but that risks to the potentially more sensitive species cannot be characterized quantitatively. Notwithstanding this reservation, potentially sensitive species of aquatic invertebrates would need to be 100 to 250 times more sensitive to imazapyr, relative to the presumably tolerant species (i.e., all of the 33 species on which data are available), before the hazard quotients for sensitive species of aquatic invertebrates would be high enough to suggest concern.

4.4.3.4. Aquatic Plants

4.4.3.4.1. Algae

As also summarized in Table 21, the NOAECs for sensitive species of algae are only moderately below the acute NOAECs for sensitive species of fish (i.e., 7.6 mg a.e./L vs 10.4 mg a.e./L) and the NOAECs for tolerant species of algae are only moderately higher than the acute NOAECs for

tolerant species of aquatic invertebrates (i.e., 50.0 mg a.e./L vs 41 mg a.e./L). Consequently, the risk characterization for algae is similar to that for fish and aquatic invertebrates.

None of the central estimates of the HQs for algae exceed the level of concern (HQ=1), even in the case of the accidental spill. For the accidental spill, the upper bound HQ for sensitive species of algae is 2. The concentration of imazapyr in water associated with this upper bound HQ is about 18 mg a.e./L. As summarized in Appendix 6, the EC_{50} values for some of the more sensitive species of algae are lower than 18 mg a.e./L (i.e., 11.5 mg a.e./L for *Selenastrum capricornutum* and 12.2 mg a.e./L for *Anabaena flosaquae*). Thus, in the event of a severe accidental spill, populations of sensitive species of algae would probably be reduced.

Based on expected peak (non-accidental) concentrations of imazapyr in water following terrestrial applications, the upper bound HQs are 0.005 for tolerant species and 0.03 for sensitive species. Based on expected longer-term concentrations of imazapyr in water, the upper bound HQs are 0.002 for tolerant species and 0.02 for sensitive species. These HQs are below the level of concern by factors of about 30 to 500.

Even for aquatic applications, risks to algae are not apparent with upper bound HQs of 0.01 to 0.04 based on peak exposures and 0.003 to 0.02 based on longer-term exposures. These HQs are below the level of concern by factors of 25 to over 300.

The low HQs for algae require no elaboration. Imazapyr is not an effective algaecide, and adverse effects in algae would not be expected following terrestrial and aquatic applications.

4.4.3.4.2. Macrophytes

The risk characterization for aquatic macrophytes is similar to that for terrestrial macrophytes. Imazapyr is relatively nontoxic to aquatic animals and is not an effective algaecide. Imazapyr is, however, labeled for control of aquatic macrophytes and is highly toxic to aquatic macrophytes.

The HQs for macrophytes following an accidental spill range from 0.9 (tolerant species following a small spill) to over 6000 (sensitive species following a large spill). These HQs require little elaboration. In the event of an accidental spill, adverse effects are virtually certain in both sensitive and tolerant species of aquatic macrophytes. In the event of a severe or even a typical spill, extensive mortality would occur. In the event of a small spill, mortality would be expected in sensitive species of macrophytes. Tolerant species could also be adversely affected in areas close to the spill site.

Based on peak expected concentrations of imazapyr in water, the HQs for sensitive species of aquatic macrophytes are 7 (0.003 to 87) following terrestrial applications and 41 (12 to 123) following aquatic applications. The differences in the upper bound HQs (123 vs 87) are insubstantial in terms of interpretation—i.e., macrophytes will be damaged and probably killed.

The central and lower bounds for aquatic applications substantially exceed those for terrestrial applications. Given the reasonably well-controlled nature of aquatic applications, relative to the more variable potential for surface water contamination following terrestrial exposures, this is to be expected. For terrestrial applications in areas where the potential for water contamination is lower (i.e., areas with low rainfall rates), damage to aquatic macrophytes is unlikely. In areas

with moderate rainfall, terrestrial applications of imazapyr could damage sensitive species of aquatic macrophytes. For aquatic applications, there is no ambiguity in the risk characterization. Sensitive species of aquatic macrophytes will be killed. Damage to tolerant species of aquatic macrophytes may or may not occur. If tolerant species of macrophytes are damaged, however, the damage will be less substantial than in sensitive species of aquatic macrophytes.

Based on longer-term expected concentrations of imazapyr in water, the HQs for sensitive species of aquatic macrophytes are 2 (0.001 to 40) following terrestrial applications and 26 (5 to 104) following aquatic applications. As with peak expected concentrations, the HQs for aquatic applications require little interpretation. Imazapyr is an effective aquatic herbicide and damage to aquatic macrophytes following aquatic applications is likely to be evident for a prolonged period of time following aquatic applications. For terrestrial applications of imazapyr, damage to sensitive species of aquatic macrophytes could be evident for a prolonged period of time in locations where conditions favor the transport of imazapyr to surface water. In other locations in which the transport of imazapyr to surface water is less likely, damage to sensitive species of aquatic macrophytes might not be evident.

Following both aquatic and terrestrial applications of imazapyr, longer-term damage to tolerant species of aquatic macrophytes might occur in some case but the damage would be far less substantial than in sensitive species of aquatic macrophytes.

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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.

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E-Docket01	**Selected documents from www.regulations.gov, EPA-HQ-OPP-2005-0495.**
FOIA01	**Freedom of Information Act request to U.S. EPA/OPP HQ-FOI-00010-12.**
FOIA02	**Freedom of Information Act request to U.S. EPA/OPP HQ-FOI-00134-12.**
Imox	**References from 2010 risk assessment on imazamox.**
MCS	**Papers on Multiple Chemical Sensitivity**
MRID04	**Registrant studies from 2004 risk assessment.**
PeerRev	**Information from peer reviewers.**
RA 2004	**Studies from 2004 Forest Service risk assessment**
Sec	**Studies taken from secondary sources in open literature.**
SecEPA	**Studies taken from U.S.EPA reports or summaries.**
Set00	**Preliminary scoping and related risk assessments.**
Set01	**TOXLINE update as well as papers from ECOTOX, U.S.EPA/OPP (2006a, 2007a).**
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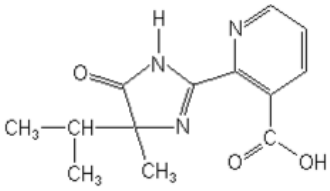
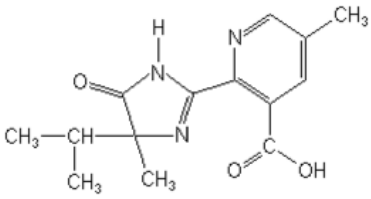


Imazapyr



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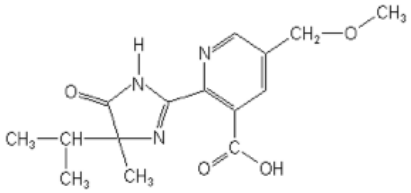

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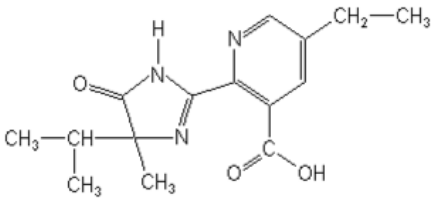

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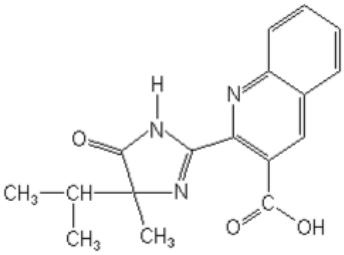
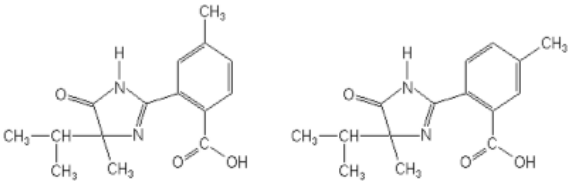


Imazaquin



Imazamethabenz

Figure 1: Imazapyr and Other Imidazolinone Herbicides

Structures reproduced with permission (courtesy of Alan Wood) from the Compendium of Pesticide Common Names (http://www.alanwood.net/pesticides/)
See discussion in Section 2.2.

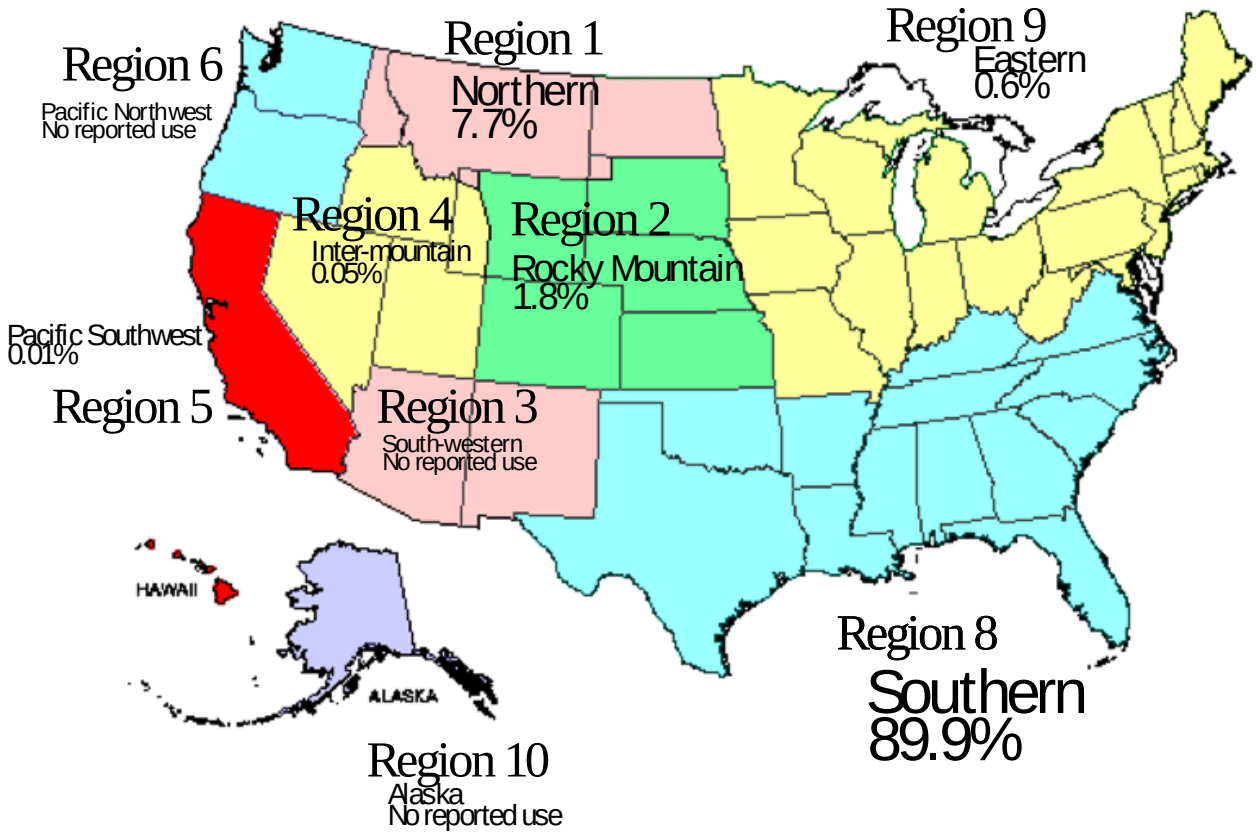
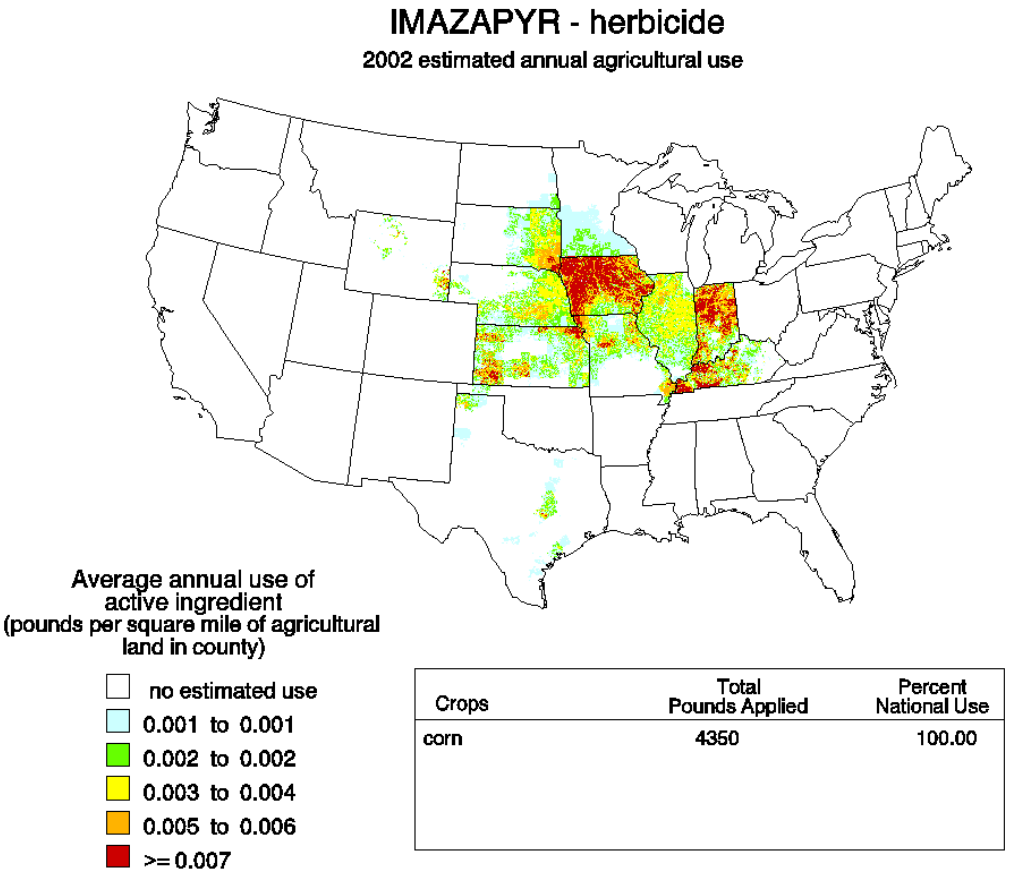


Figure 2: Imazapyr Use by Forest Service Region for 2004

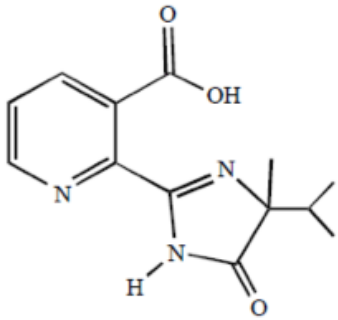
See Table 4 for additional details.
See Section 2.5 for discussion.



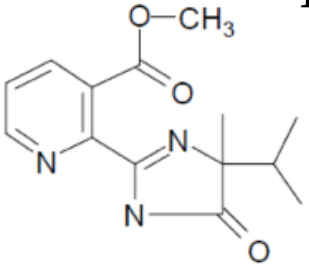
Crops	Total Pounds Applied	Percent National Use
corn	4350	100.00

Figure 3: Estimated Agricultural Use of Imazapyr in the United States for 2002

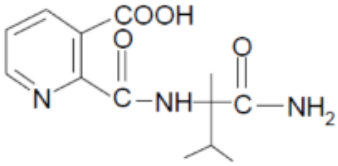
Source: USGS(2003a)
See Section 2.5 for discussion.



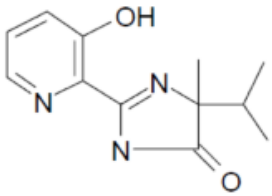
IMAZAPYR



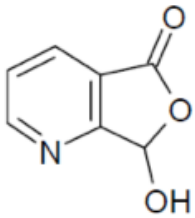
CL 240 000
Grass and water



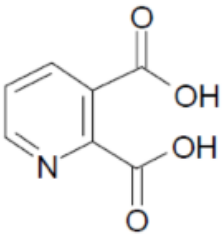
CL 252 974
Mammals, plants, and water



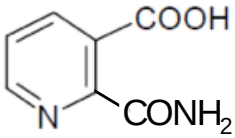
CL 288 247
Water



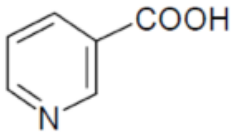
CL 119 060
Crops and water



CL 9140
Crops, grass, and water



CL 60032
Mammals and crops (field corn, fodder, and grain).



Nicotinic acid
Water

Figure 4: Imazapyr and Metabolites

Source: Adapted from U.S. EPA/OPP (2005a).
See Sections 3.1.3.1 and 3.1.15.1 for discussion.

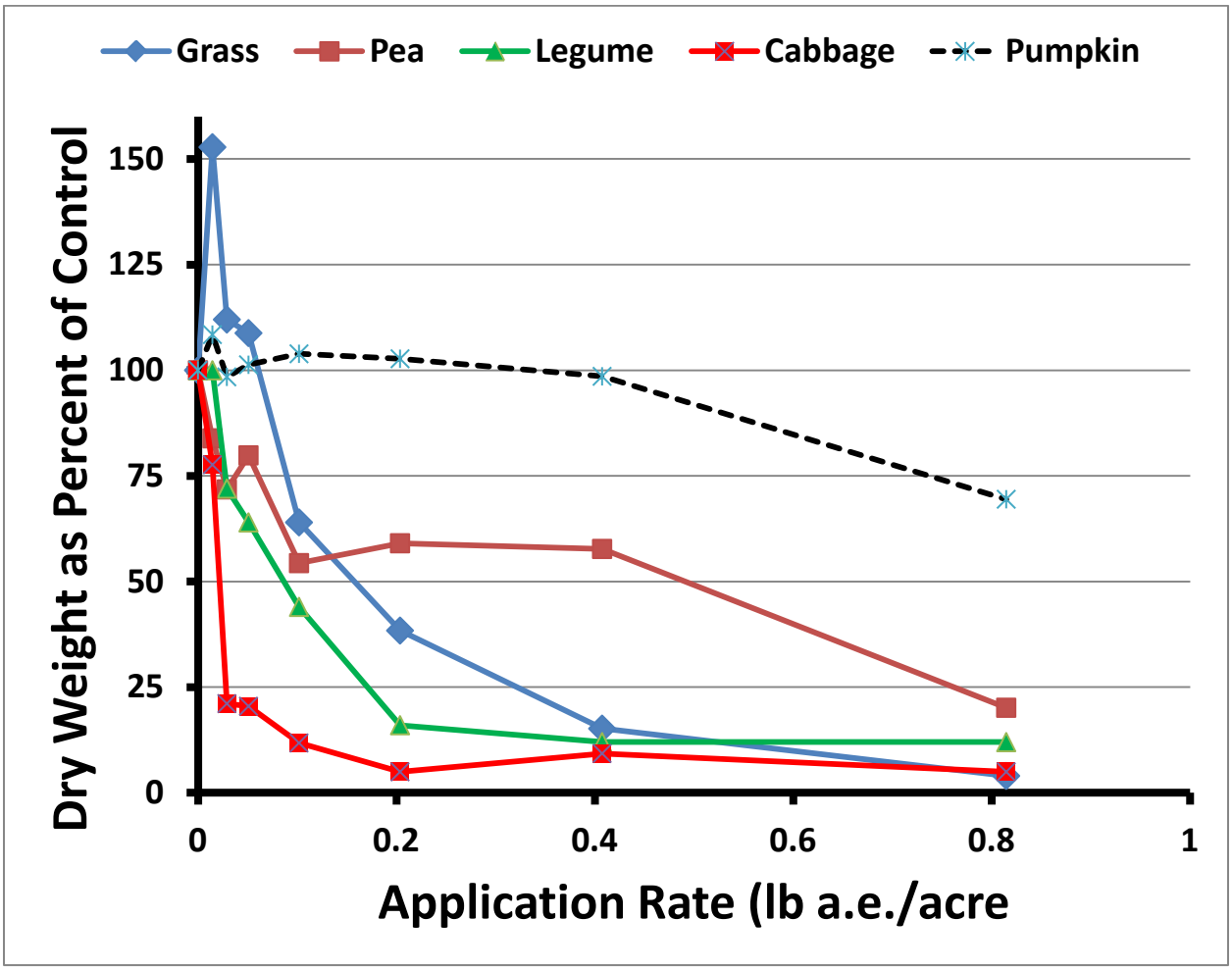


Figure 5: Dose-Response Data from Bovey and Senseman (1998)

Source: Bovey and Senseman 1998, Table 3. See Supplemental table at the end of Appendix 3. See Section 4.1.2.5.2 for discussion.

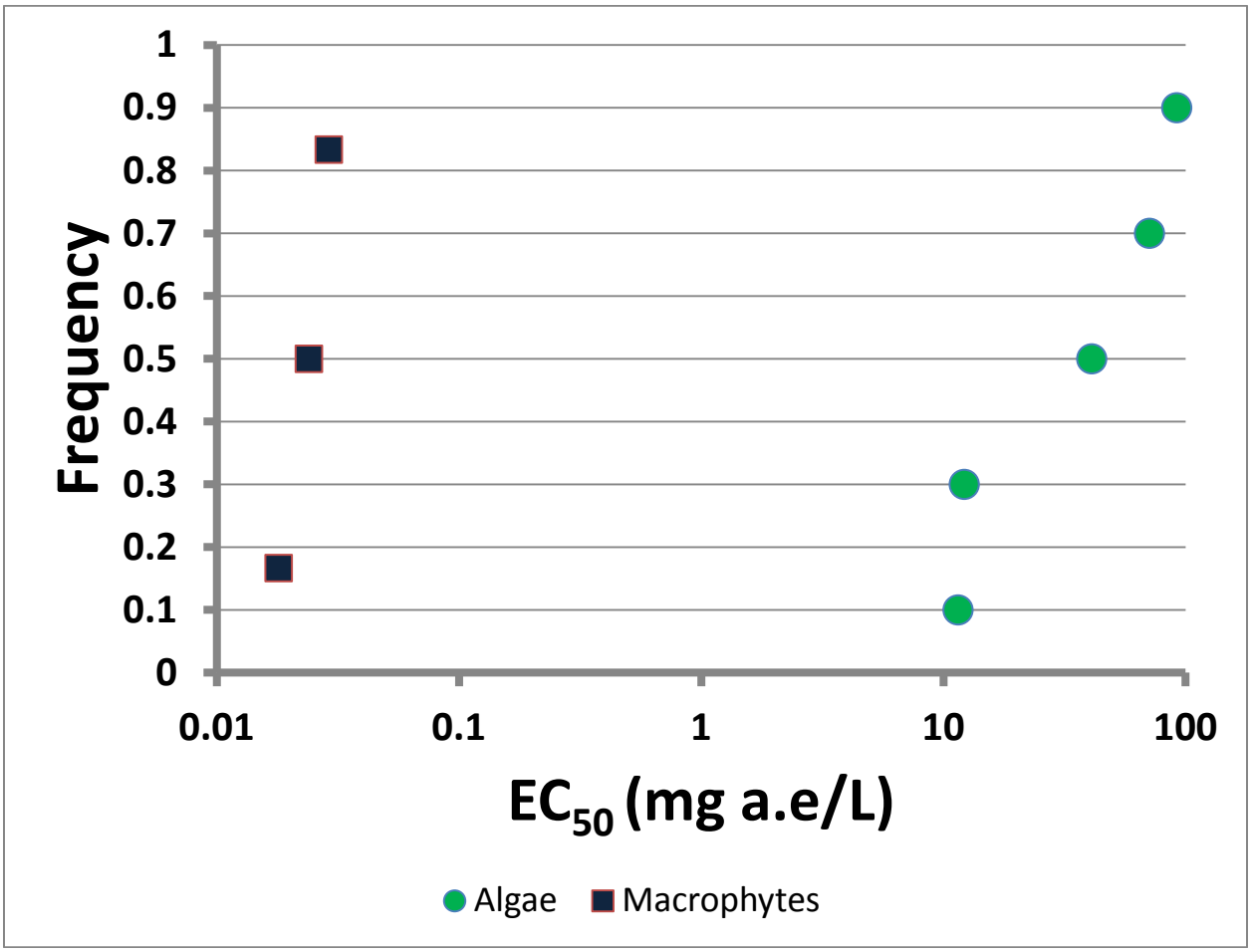


Figure 6: Aquatic Plants, Frequency Distributions of EC_{50} Values

See Table 18 for summary of data.
Source: See Appendix 6 for details.
See Section 4.1.3.4 for discussion.

Table 1: Chemical and Physical Properties of Imazapyr

All values for acid unless otherwise noted.

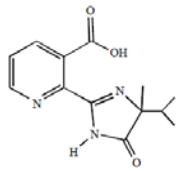
Property	Value	Reference
	Identifiers	
Common name:	Imazapyr	
IUPAC Name	2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid	Tomlin 2004
CAS Name	(±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-3-pyridinecarboxylic acid	Tomlin 2004
CAS No.	81334-34-1 [acid] former CAS numbers for acid: 94795-74-1, 108224-78-8 81510-83-0 [isopropylamine salt]	Tomlin 2004
Development Codes	AC 252 925; CL 252 925 (American Cyanamid); AC 243,997	Tomlin 2004
	AC252 925	Peoples 1984
	CL 243 997, AC 243 997 (BASF)	U.S. EPA/OPP 2005g, p. A-13
Molecular formula	$C_{13}H_{15}N_3O_3$	U.S. EPA/OPP 2006a
Smiles Notation	`CC(C)C1(C)N=C(NC1=O)c2ncccc2C(=O)O`	Tomlin 2004
Structure		U.S. EPA/OPP 2005g
U.S. EPA/OPP Codes	128821 [Acid and salts]	U.S. EPA/OPP 2006a, p. 4
	128829 [Isopropanolamine salt]	http://www.epa.gov/pesticides/foia
	Physical Properties	
K_{ow} [see Section 3.1.3.2 for discussion of discrepancy between Gennari et al. 1998 and other reported values]	≈1.29 [log Kow = 0.11 at 22°C, pH not specified]	Tomlin 2004
	≈1.3 [log Kow = 0.114]	USDA/ARS 1995
	1.3 (value used to estimate dermal absorption)	U.S. EPA/OPP 2005a
	≈1.66 (acid, 22 °C, neutral pH) [Log_{10}=0.22]	Chambarlain et al. 1995
	1.3	Reichert and Stanley-Millner 1983
	1.31 at pH 3 <0.01 at pH 5, 7, and 9	Gennari et al. 1998
Melting Point	169-173 °C	Tomlin 2004
Molecular weight	Form: Acid, MW (g/mole): 261.3 Form: Isopropylamine salt, MW (g/mole): 320.4	Tomlin 2004
a.i. to a.e. conversion	Form (Abbrev): Isopropylamine salt, Factor: 0.8155 a.i. to a.e. calculated as MW of acid ÷ MW of salt.	See entry for Molecular Weight
pKa Values	1.9; 3.6; 11	Tomlin 2004
	1.9 (pyridine) and 3.6 (carboxylate)	American Cyanamid 1983b; ARS 1995; Pusino et al. 1997
	1.81 and 3.64	Chambarlain et al. 1995
Specific gravity		Tomlin 2004
Vapor pressure	<0.013 mPa (60 °C)	Tomlin 2004

Table 1: Chemical and Physical Properties of Imazapyr

All values for acid unless otherwise noted.

Property	Value	Reference
Water solubility	9,740 mg/L (15 °C) 11,300 mg/L (25 °C)	Tomlin 2004
	11,000 mg/L	Knisel and Davis 2000
	13,100 mg/L(acid @ 25C)	Cortes 1990
	10,000 to 15,000 mg/L (acid @ 25C)	Peoples 1984
	11,100 mg/L (25 °C)	U.S. EPA/OPP 2005c, Table B-1
	110,000 to 150,000 mg/L	USDA/ARS 1995
	6,500,000 mg/L (salt)	USDA/ARS 1995
Environmental Properties		
Aerobic aquatic metabolism half-life	4.9 days (CL 119060 metabolism) 3.6 days (CL 9140 metabolism))	Ta 1999b (MRID 45119702) as cited in U.S. EPA/OPP 2005g, Table A-1
Aqueous photolysis half-life	3.7 days at pH 7	American Cyanamid 1986b
	7 days	Curran et al. 1992
	2.5 to 5.3 days	Mangels 1990a ,MRID 00131617, as cited in U.S. EPA/OPP 2005g, Table A-1
	9.1 days	Ramezani et al. 2008
	19.9 days	U.S. EPA/OPP 2007a, Appendix D, MRID 00131617
Bioconcentration Factor	No bioconcentration [BCF≤1] in fish or crayfish.	Borysewicz 1999, MRID 45119707 as cited in U.S. EPA/OPP 2005g
	No bioconcentration [BCF≤1] in oysters or shrimp.	Drottar et al. 1996 as cited in U.S. EPA/OPP 2005g
Field Dissipation half-life	138 days	American Cyanamid 1983b
	25 to 58 days	El Azzouzi et al. 1998
	94 days	Garrett 2000
	90 days	Knisel and Davis 2000
	77 to 155 days	McDowell et al. 1996
	69 to 125	McDowell et al. 1997
	Forestry dissipation: 12-40 days (vegetation) 37-44 (litter)	Michael 1986, MRID 40003714 as cited in U.S. EPA/OPP 2005g, Table A-1
	30 days	Michael et al. 1996
	34-65 days	Michael and Neary 1993
	150 days (Oregon) [cited as 143 days in U.S. EPA/OPP 2005g, Table A1]	York 1992a
	180 days (North Carolina) [cited as 64 days in U.S. EPA/OPP 2005g, Table A1]	York 1992b
Hydrolysis half-life	325 days at pH 7	American Cyanamid 1986b
	Stable	Mangels 1990a; U.S. EPA/OPP 2005c, Table B-1
	Stable at pH 3 and pH 7 ≈288 days (9.6 months) at pH 9	Ramezani et al. 2008
K_{oc}	100	Knisel and Davis 2000
	46	Michael et al. 1996
	30.6 (sand) 98.8 (silt loam)	Holman 2000

Table 1: Chemical and Physical Properties of Imazapyr

All values for acid unless otherwise noted.

Property	Value	Reference
Kd/Koc		U.S. EPA/OPP 2005g, Table A.2

Soil Type	Kd (L/kg)	Koc (g/mL)	MRID
Sand sediment	0.11	31	45119705
Silt loam sediment	0.64	100	45119705
Loamy sand soil	0.04	15	43423703
Silt loam soil	0.86	82	43423703
Sandy loam soil	0.07	8.2	43423703
Loam soil	0.23	17	43423703
Pond sediment	3.4	150	43423703
Sandy loam soil	1.9	110	00131620
Loamy sand soil	0.52	100	00131620
Clay loam soil	0.84	18	00131620
Silt loam soil	2.4	53	00131620
Average	0.998	61.9	
Median	0.64	53	

Kd	0.639 (lowest non-sand)	U.S. EPA/OPP 2005c, Table B-1, MRID 00131617
	Humic Acids 3.7 to 11.1 at pH 4 13.3 to 53.7 at pH 2.8	Negre et al. 2001
	0 to 0.17 (five Alabama soils)	Wehtje et al. 1987
Sediment/water half-life	17 months	American Cyanamid 1986b
	No degradation	American Cyanamid 1988c
	Not metabolized	Sanders 1986
	Stable	U.S. EPA/OPP 2005c, Table B-1, MRID 40003712
Soil half-life, aerobic	210 days	American Cyanamid 1983b
	25 to 58 days (Morocco study)	El Azzouzi et al. 1998
	Biphasic: ≈123 days (k=0.00559 day^{-1} up to day 332) ≈2,972 (k=0.0002332 day^{-1} beyond day 332) Initial rate may be due to dissipation.	Jarvis et al. 2006
	313 days	Ta 1999a. MRID 45119701
	5.9 years (≈2150 days)	Tollackson 1988, MRID 41023201
	Stable	U.S. EPA/OPP 2005c, Table B-1, MRID 00131619
Soil photolysis half-life	149 days, soil surface	Mangels 1986
	30.9 days, soil surface	Ramezani et al. 2008
Vegetation half-life	30 days	Knisel and Davis 2000
	15-37 days (composite of different types of vegetation)	Neary and Michael 1993

Table 2: Representative Imazapyr Formulations

Basic Information							
Formulation Name	**Supplier**	**EPA Reg. No.**	**% a.i.**	**% a.e.[2]**	**lb a.e./gal**	**Uses[1]**	**Surfactant[3]**
Arsenal Herbicide	BASF	241-346	27.8	22.6	2.0	T/F/A	R
Arsenal AC	BASF	241-299	53.1	43.3	4.0	F	N/R
Arsenal Railroad	BASF	241-273	27.6	22.6	2.0	T	Y/R
Chopper	BASF	241-296	27.6	22.6	2.0	F	
Ecomazapyr 2 SL	Alligare	81927-22	27.8	22.6	2.0	A/T	R
Ecomazapyr 2 SL	Vegetation Management	74477-6	27.8	22.6	2.0	A/T	R
Habitat	BASF	241-426	28.7	22.6	2.0	A/T	R
Imazapyr 2 SL	Vegetation Management	74477-4	27.8	22.6	2.0	T/F	R
Imazapyr 4 SL	Alligare	81927-24	52.6	42.9	4.0	F	R
Imazapyr 4 SL	Vegetation Management	74477-5	52.6	42.9	4.0	F	R
Polaris	Nufarm	241-346-228	27.8	22.6	2.0	T/F	R
Polaris AC	Nufarm	241-299-228	53.1	43.3	4.0	F	N/R
Polaris RR	Nufarm	241-273-228	27.6	22.6	2.0	T	Y/R
Polaris SP	Nufarm	241-296-228	27.6	22.6	2.0	F	
Rotary 2 SL	Alligare	81927-6	27.8	22.6	2.0	F	R
Stalker	BASF	241-398	27.6	22.6	2.0	F	

[1] F=Forestry; T=Terrestrial, Other; A=Aquatic (emergent and floating vegetation)
[2] All formulations contain the isopropylamine salt of imazapyr. See Table 1 for conversion of a.i. to a.e.
[3] Y=Yes, N=No; R=Product label recommends nonionic surfactant at 0.25% (v/v) to 1.0% (v/v) depending on the formulation and application method.

Source: Specimen labels from www.greenbook.net.

Other Formulation Information (exactly as specified on the MSDSs)				
Formulation Name	**Color**	**pH**	**Density**	**Other Information**
Arsenal	Blue	6.6 - 7.2	1.04 - 1.09 g/mL	Solvent
Arsenal AC	Green	5.5 - 7.5	1.11 - 1.12 g/cm^3 at 20°C	Solvent
Arsenal Railroad	Blue	6.6 - 7.2	1.04 - 1.07 g/cm^3 at 20°C	Solvent
Chopper	Yellow[1]	6 - 7.5	1.05 - 1.07 g/cm^3 at 20°C	Solvent
Ecomazapyr 2 SL[2]	N.S.	5.5 - 5.7	1.06 g/mL	
Ecomazapyr 2 SL[3]	Blue	6.0 - 7.0	1.06 g/mL at 20°C	
Habitat	Blue	6.6 - 7.2	1.04 - 1.09 g/mL	Solvent
Imazapyr 2 SL	Blue	6.0 - 7.0	1.06 g/mL at 20°C	
Imazapyr 4 SL[2]	Blue	5.0 - 5.5	1.2 g/mL	
Imazapyr 4 SL[3]	Green	5.5 – 7.5 at 25°C	1.12 g/mL at 20°C	
Polaris	Blue	6.6 - 7.2	1.04 - 1.07	Solvent (Arsenal)
Polaris AC	Green	5.5 - 7.5	1.1 - 1.12	Solvent (Arsenal AC)
Polaris RR	Yellow[1]	6 - 7.5	1.06 - 1.09	
Polaris SP	Yellow[1]	6 - 7.5	1.05 - 1.07	
Rotary 2 SL	Blue	6.46	1.06 g/mL	
Stalker	Yellow[1]	6 - 7.5	1.05 - 1.07 g/cm^3 at 20°C	Solvent

N.S.: Not specified.
[1] Color ranges from yellow to dark green.; [2] Alligare; [3] Vegetation Management

Source: MSDSs from www.greenbook.net.

See Section 2.2 for discussion

Table 3: Representative Label Directions

Formulation	Application Methods	Application Rates and Volumes	Recommended Adjuvants
TERRESTRIAL			
Arsenal Polaris [2 lb a.e./gal]	Broadcast, ground or aerial Directed foliar Cut-stump or cut-stem Spot treatment Tree injection	Directed Foliar Low Volume 0.5% to 5% dilution of formulation Ap. Vol.: 5 to 20 gallons/acre High Volume 0.5% to 5% dilution of formulation Ap. Vol.: 100 gallons/acre Broadcast foliar 1 to 6 pints [16 to 96 oz]/acre [0.25 to 1.5 lb a.e./acre] Application Volumes: Up to 100 gallons/acre Injection/Cut-stump/Hack and Squirt Dilute or concentrate applications	Nonionic surfactant, at least 0.25% v/v Antifoaming agents
Arsenal AC Polaris AC [4 lb a.e./gal]	Broadcast, ground or aerial Directed foliar Cut-stump or cut-stem Spot treatment Tree injection	Broadcast foliar 4 to 40 oz/acre [0.125 to 1.25 lb a.e./acre] Application Volumes: Helicopter: 5 to 30 gallons/acre. Ground: 5 to 100 gallons/acre Injection Solution: undiluted or diluted up to 6 oz/gallon [≈0.1875 lb a.e./gal.] 1 mL/site and one site per 3” DBH. Hack-and-squirt 1mL/cut and 1 cut per 3” DBH.	Nonionic surfactant, at least 0.25% v/v
Chopper [2 lb a.e./gal]	Broadcast, ground or aerial Directed foliar Cut-stump or cut-stem Spot treatment Tree injection	Broadcast foliar 12 to 80 oz/acre [≈0.19 to 1.25 lb a.e./acre] Application Volumes: Helicopter: 5 to 20 gallons/acre. Ground: 5 to 40 gallons/acre Injection Solution: diluted in 8 to 12 oz/gallon [≈0.125 to 0.19 lb a.e./gal.] 1 mL/site with no more than 1” intervals.	Surfactant or penetrating agent for cut stump treatments
Stalker [2 lb a.e./gal]	Ground (only) broadcast Cut stump Tree injection Spot treatment	Broadcast foliar Up to 48 oz/acre [0.75 lb a.e./acre] Application Volumes: Ground: 5 or more gallons/acre Injection Identical to label directions for Chopper [see above].	Surfactants or penetrating agents recommended for cut stump treatments.
AQUATIC			
Arsenal Ecomazapyr 2 SL (both Alligare and Vegetation Management formulations) Habitat	Emergent aquatic weeds	No more than 6 pints formulation/acre of water surface [1.5 lb a.e./acre of water surface] Minimum rate [Ecomazapyr 2]: 2 pints/acre or 0.5 lb a.e./acre. Application Volumes: At least 2 gallons/acre. If more than 30 gallons/acre are applied, a methylated seed oil or vegetable oil concentrate at a rate of 1% of the total spray volume is recommended.	Variable surfactants and/or oils with different formulations. See Section 2.4.4. for details.

Source: Specimen labels from www.greenbook.net.
See Sections 2.3 and 2.4 for discussion.

Table 4: Forest Service Use by Region for 2004

Year	Region	Forest	Management Objective	Pesticide Amount (lbs)	Treated Acres	Lb/acre	Percent Total Use
2004	1	2	Noxious Weed Control	0.36	41	0.009	
2004	1	11	Noxious Weed Control	0.38	2.05	0.185	
2004	1	16	Noxious Weed Control	113.74	1190	0.096	
Region 1 Summary				114.48	1233.05	0.093	7.7%
2004	2	3	Agricultural Weed Control	10.80	5	2.160	
2004	2	3	Noxious Weed Control	2.88	42	0.069	
2004	2	6	Noxious Weed Control	11.62	39.5	0.294	
2004	2	7	Noxious Weed Control	0.80	30.6	0.026	
Region 2 Summary				26.10	117.1	0.223	1.8%
2004	4	13	Noxious Weed Control	0.72	5.79	0.124	
Region 4 Summary				0.72	5.79	0.124	0.05%
2004	5	11	Housekeeping/Facilities Maintenance	0.20	0.6	0.333	
Region 5 Summary				0.20	0.6	0.333	0.01%
2004	8	1	Conifer Release	344.00	1003	0.343	
2004	8	1	Noxious Weed Control	2.10	2	1.050	
2004	8	1	Right-of-Way Vegetation Management	1.00	3	0.333	
2004	8	4	Site Preparation	1.00	160	0.006	
2004	8	6	Noxious Weed Control	90.00	*N/A*	*N/A*	
2004	8	6	Site preparation	1.00	*N/A*	*N/A*	
2004	8	7	Conifer Release	732.02	622	1.177	
2004	8	7	Noxious Weed Control	122.17	*N/A*	*N/A*	
2004	8	7	Site preparation	28.22	*N/A*	*N/A*	
2004	8	10	Conifer Release	12.00	470	0.026	
2004	8	12	Noxious Weed Control	5.00	150	0.033	
Region 8 Summary				1338.51	2410	0.455	89.9%
2004	9	19	Right-of-Way Vegetation Management	9.33	324.9	0.029	
2004	9	21	Research	0.01	0.1	0.100	
Region 9 Summary				9.34	325	0.029	0.6%
			All Regions Combined	**1489.35**	**4091.5**	**0.305**	

See Figure 2 for illustration of total use by Region.
See Section 2.5 for discussion.

Table 5: Clinical Effects of Oral Exposures to Arsenal Formulation in Humans

Sex/Age in Year (Conditions)	Body Weight (kg) [1]	Approximate Amount Consumed	Estimated Dose (mg a.e./kg bw) [3]	Primary Clinical Signs
Woman/N.S	[60]	0.3 L [≈71,895 mg a.e.]	≈1,200	Vomiting, cyanosis, incontinence, and impaired consciousness.
Male/52	[70]	0.5 L [≈119,827 mg a.e.]	≈1,700	Vomiting, labored respiration, corrosive damage to the pharynx and the larynx. Signs of eye irritation possibly associated with exposure.
Male/56 (Alcoholic)	[70]	0.120 L [≈28,758 mg a.e.]	≈410	Respiratory distress and cyanosis.
Male/56	[70]	0.100 L [23,965 mg a.e]	≈340	Nausea, vomiting, diarrhea, weakness, abdominal pain.
Male/48	[70]	0.075 L [17,974 mg a.e]	≈260	Coughing and vomiting.
Male Child/4	[14]	0.002 L [479 mg a.e.]	≈34	Vomiting. No signs of damage to oral mucosa.

[1] All weights in brackets indicate that the weight is not specified. Defaults body weights of 70 kg for males, 60 kg for females, and 14 kg for a four year old child are used to estimate the dose. Note that these body weights are less than standard body weights for members of the U.S. population – i.e., ≈90 kg for a 50 year old male, 77.5 kg for a 50 year old female, and about 18 kg for a 3 to 6 year old child (U.S. EPA/NCEA 2011, pp. 8-13 to 8-15).

[2] The formulation is specified as Arsenal containing 23.1% w/w imazapyr. This corresponds approximately to current 2 lb a.e./gallon formulations – i.e., ≈239,653 mg a.e./L. The amount consumed in mg is given in brackets as the product of the liters consumed and the concentration of 239,653 mg a.e./L.

[3] The estimated dose in mg a.e. divided by the estimated body weight rounded to 2 significant figures.

Source: Lee et al. 1999
See Section 3.1.4 for discussion.

Table 6: Summary of Repeated Dose Studies in Mammals

Species, Sex	Duration [1] (Days)	Endpoint [2]	Dose (mg a.e./kg bw/d)[3]		Reference
			NOAEL	LOAEL	
Subchronic Toxicity (Dietary)					
Mice					
M/F	540	No effects.	1855	N/A	Auletta 1988
Rats					
M/F	91	No effects.	1695	N/A	Hess 1992
M/F	730	No effects.	503	N/A	Daly 1988; Hess 1992
Cows					
F	29		60	N/A	Khunachak 1999
Dogs					
M/F	365	No effects	263	N/A	Shellenberger 1987
Developmental/Teratology (Gavage)					
Rats	10				Salamon et al. 1993c [Full study]
Dams		Salivation	300	1000	
Fetal		No effects	1000	N/A	
Rats	10				Salamon et al. 1993d [Pilot]
Dams		Salivation	1000[4]	2000	
Fetal		No effects	2000	N/A	
Rabbits	13				Salamon et al. 1993b [Full study]
Does		No effects	400	N/A	
Fetal		No effects	400	N/A	
Rabbits	13				Salamon et al. 1993a [Pilot]
Does		Mortality	250	1000	
Fetal		Fetal mortality	500	1000	
Reproduction (Dietary)					
Rats	150+ 2 generations				Robinson 1987
Parental		No effects	738	N/A	
Off-spring		No effects	738	N/A	

[a] Durations given in months are converted to days using 30 days/month.
[b] *BW* = body weight, *d* = days; *M* = males; *F* = females. Sex included only is relevant differences between males and females were noted.
[c] For dietary exposures in which no differences were noted between males and females in the NOAEL, doses for NOAELs and LOAELS are based on the lowest dose for NOAELs and LOAELs in either males or females. For doses expressed as ranges (e.g., Auletta 1988), the dose is given as the average of the lower and upper bounds of the range.
[4] NOAEL based on Fisher Exact test. Salivation was noted at all doses – i.e., 250 to 2000 mg/kg bw/day – but was statistically significant only at 2000 mg/kg bw/day.

See Sections 3.1.4 and 3.1.9 for discussion.

See Appendix 1 for additional details [A1 Table 10 (Subchronic), A1 Table 11 (Chronic), A1 Table 8 (Developmental, and A1 Table 9 (Reproduction)].

Table 7: Worker Exposure Rates for Standard Terrestrial Application Methods

Worker Group	Central	Lower	Upper
Absorbed Dose Rates	**mg/kg bw/day per lb applied**		
Directed foliar	0.003	0.0003	0.01
Broadcast foliar	0.0002	0.00001	0.0009
Aerial	0.00003	0.000001	0.0001
Treatment Rate	**Acres Treated per Day**		
Directed foliar	4.4	1.5	8.0
Broadcast foliar	112	66	168
Aerial	490	240	800

See Section 3.2.2.1 for discussion.

Table 8: Precipitation, Temperature and Classifications for Standard Test Sites

Location	Precipitation	Temperature	Average Annual Rainfall (inches)	Average Annual Temperature (◦F)
HI, Hilo	Wet	Warm	126.06	73.68
WA, Quillayute [1]	Wet	Temperate	95.01	49.14
NH, Mt. Washington	Wet	Cool	98.49	27.12
FL, Key West	Average	Warm	37.68	77.81
IL, Springfield	Average	Temperate	34.09	52.79
MI, Sault Ste. Marie	Average	Cool	32.94	40.07
AR, Yuma Test Station	Dry	Warm	3.83	73.58
CA, Bishop	Dry	Temperate	5.34	56.02
AK, Barrow	Dry	Cool	4.49	11.81

[1] Based on composite estimation in WEPP using a latitude of 47.94 N and a longitude of -124.54 W. See SERA (2006c) for details.

Table 9: Field and Waterbody Parameters Used in Gleams-Driver Modeling

Field Characteristics	Description	Pond Characteristics	Description
Type of site and surface	Pine-hardwood	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	Sediment Depth	2 centimeters
Type of clay	Mixed		
Surface cover	No surface depressions		

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

GLEAMS Crop Cover Parameters[3]	Description	Value
ICROP	Trees, hardwood + conifer	71
CRPHTX	Maximum height in feet.	20
BEGGRO	Julian day for starting growth	32
ENDGRO	Julian day for ending growth	334

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/):	N/A	20%	45%	90%
Percent Organic Matter:	OM	3.7%	2.9%	1.2%
Bulk density of soil (g/cc):	BD	1.4	1.6	1.6
Soil porosity (cc/cc):	POR	0.47	0.4	0.4
Soil erodibility factor (tons/acre):	KSOIL	0.24	0.3	0.02
SCS Runoff Curve Number [2]:	CN2	83	70	59
Evaporation constant (mm/d):	CONA	3.5	4.5	3.3
Saturated conductivity below root zone (in/hr):	RC	0.087	0.212	0.387
Saturated conductivity in root zone (in/hr)	SATK	0.087	0.212	0.387
Wilting point (cm/cm):	BR15	0.28	0.11	0.03
Field capacity (cm/cm):	FC	0.39	0.26	0.16

[1] 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 10: Chemical parameters used in Gleams-Driver modeling

Parameter	Values	Note/Reference
Halftimes (days)		
Aquatic Sediment	5000	Note 1
Foliar	30 (15 to 37)	Note 2
Soil	2150 (313 to 2972)	Note 3
Water	19.9 to 199	Note 4
Soil $K_{o/c}$, mL/g	53 (8 to 110)	Note 5
Sediment K_d, mL/g	0.64 (0.07 to 3.4)	Note 5
Water Solubility, mg/L	11,100	Note 6
Foliar wash-off fraction	0.9	Knisel and Davis 2000
Fraction applied to foliage	0.5	Note 7
Depth of Soil Incorporation	1 cm	Note 7
Irrigation after application	none	Note 7

Note 1	Based on U.S. EPA/OPP (2007a, Appendix D, MRID 40003712) which classifies imazapyr as stable in soil and sediment.
Note 2	Central estimate from Knisel and Davis (2000). Lower and upper bounds from Neary and Michael (1993)
Note 3	Lower bound based on Ta (1999a). Central estimate based on Tollackson (1988). Upper bound based on terminal half-lives from Jarvis et al. (2006).
Note 4	Lower bound based on photolysis half-life of 19.9 days from U.S. EPA/OPP (2007a, Appendix D, MRID 00131617) for imazapyr and metabolites. Under field conditions, attenuation of hydrolysis is likely. The upper bound assumes an attenuation factor of 10.
Note 6	The reported Koc and Kd values for imazapyr are highly variable. See Table 1. Values used for modeling are based on Table A.2 in U.S. EPA/OPP 2005g using the median as well as the lower and upper bounds.
Note 6	Value used by Based on U.S. U.S. EPA/OPP (2007a, Appendix D, Table D.1.4) in PRZM/EXAMS modeling. The amine salt will have a much higher water solubility but water solubility is not a sensitive parameter for imazapyr and only imazapyr acid is modeled quantitatively.
Note 7	Standard assumptions used in all Forest Service risk assessments for foliar applications.

See Section 3.2.3.4.3 for discussion.

Note: Central estimates with ranges are modeled with triangular distribution. The database for Gleams-Driver includes only central estimates for the above parameters. The uniform and triangular distributions used in the simulations discussed in this risk assessment were implemented using the Full Run feature in Gleams-Driver.

Table 11: Summary of Modeled Concentrations in Surface Water

Scenario	Concentrations (ppb a.e. or µg a.e./L)	
	Peak	**Long-Term Average**
MODELING FOR THIS RISK ASSESSMENT (1 lb a.e./acre)		
Direct Spray and Spray Drift		
Pond, Direct Spray (Section 3.2.3.4.2) [a]	112	N/A
Pond, drift at 25 feet (Section 3.2.3.4.2) [a]	0.9 to 25	N/A
Stream, Direct Spray (Section 3.2.3.4.2) [a]	91	N/A
Stream, drift at 25 feet (Section 3.2.3.4.2) [a]	0.7 to 20	N/A
Gleams-Driver		
Broadcast Foliar, Single Application (see Appendix 7 for details)		
Pond, Section 3.2.3.4.4	17.9 (0 to 255)	7.24 (0 to 120) (annual)
Stream, Section 3.2.3.4.4	11.1 (0 to 123)	0.49 (0 to 6.4) (annual)
Other Modeling		
U.S. EPA 2005c (RED)		
FIRST (Reservoir model) [b]	97.3	52.7 (annual)
SCIGROW (Ground water) [c]	24	N/A
U.S. EPA 2007a (CA Red-legged Frog analysis)		
PRZM/EXAMS, CA Forestry Scenario [d]	12.3	11.5 (60-day)
PRZM/EXAMS, CA Rangeland Scenario [e]	22.0	20.3 (60-day)
Other Modeling		
No monitoring studies on imazapyr in water have been encountered. See Section 3.2.3.4.5.		

[a] Section 3.2.3.4.2 discusses expected concentrations in terms of the nominal application rate of 1 lb a.e./acre. The values for direct spray and drift are taken from Worksheet B04c (direct spray and drift as 25 feet for a pond) and Worksheet B04d (direct spray and drift as 25 feet for a stream). The ranges for drift reflect the different application methods – lowest for backpack and highest for aerial.

[b] U.S. EPA/OPP (2005c, p. 4): Modeled concentrations of 146 ppb (peak) and 79 ppm (annual average) divided by 1.5 lb a.e./acre to estimate WCRs in ppb per lb a.e./acre..

[c] U.S. EPA/OPP (2005c, p. 4): Modeled concentrations of 36 ppb (peak) divided by 1.5 lb a.e./acre to estimate WCR in ppb per lb a.e./acre..

[d] U.S. EPA/OPP (2007a): Model output on p. 4. The peak of 18.5 ppb and 60 day average of 17.2 ppb is divided by the application rate of 1.5 lb a.e./acre to estimate WCR in ppb per lb/acre.

[e] U.S. EPA/OPP (2007a): Model output on p. 8. The peak of 33 ppb and 60 day average of 30.5 ppb is divided by the application rate of 1.5 lb a.e./acre to estimate WCR in ppb per lb/acre.

Table 12: Concentrations of imazapyr in surface water used in this risk assessment

	Water contamination rate in mg/L per lb/acre applied [a]	
Terrestrial Broadcast Applications	**Peak**	**Longer-term**
Central	0.020	0.007
Lower	0.000009	0.000003
Upper	0.26	0.12
Aquatic Applications	**Peak**	**Longer-term**
Central	0.12	0.06
Lower	0.037	0.0011
Upper	0.37	0.35

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

See Section 3.2.3.4.6 for discussion.

Table 13: Estimated residues in food items per lb a.e. applied

Food Item	Concentration in Food Item (ppm per lb a.e./acre)		
	Central [a]	Lower [b]	Upper [a]
Broadcast Foliar Applications			
Short grass	85	30	240
Tall grass	36	12	110
Broadleaf/forage plants and small insects	45	15	135
Fruits, pods, seeds, and large insects	7	3.2	15

[a] From Fletcher et al. (1997).
[b] Central values × (Central Value ÷ Upper Value).

Table 14: Summary of toxicity values used in human health risk assessment

Duration	Derivation of RfD	Reference	Comment
Acute – single exposure			
NOAEL Dose	300 mg/kg bw	Salamon et al. 1983c MRID 00131611	Note: The U.S. EPA/OPP (2005a) did not derive an acute RfD.
LOAEL Dose	1000 mg/kg bw/day		
LOAEL Endpoint(s)	Salivation		
Species, sex	Rats, females		
Uncertainty Factor	N/A	U.S. EPA/OPP 2005a , p. 21.	
RfD	Not derived		
Chronic – lifetime exposure			
NOAEL Dose	250 mg/kg bw/day	Shellenberger 1987 MRID 41039502	
LOAEL Dose	Not identified		
Species, sex	Dogs, male and female		
LOAEL Endpoint(s)	Not identified		
Uncertainty Factor	100	U.S. EPA/OPP 2005a , pp. 21 to 22.	
RfD	2.5 mg/kg bw/day		

See Section 3.3 for discussion.

Table 15: Summary of Risk Characterization for Workers

Scenario	Hazard Quotients		
	Central	Lower	Upper
Accidental/Incidental Exposures			
Contaminated Gloves, 1 min.	3E-05	3E-06	2E-04
Contaminated Gloves, 1 hour	2E-03	2E-04	1E-02
Spill on Hands, 1 hour	3E-04	2E-05	3E-03
Spill on lower legs, 1 hour	6E-04	5E-05	7E-03
General Exposures			
Backpack Applications:	5E-03	2E-04	3E-02
Ground Broadcast Applications:	9E-03	3E-04	6E-02
Aerial Applications:	6E-03	1E-04	3E-02
Aquatic Applications:	4E-03	2E-03	8E-03

[1] HQs for terrestrial applications taken from Attachment 1, Worksheet E02. HQs for aquatic applications taken from Attachment 1, Worksheet E02.

See Section 3.4.2 for discussion.

Table 16: Risk Characterization for the General Public, Terrestrial Applications

Scenario	Receptor	Hazard Quotients [1]		
		Central	Lower	Upper
Accidental Acute Exposures (dose in mg/kg/event)				
Direct Spray of Child, whole body	Child	1E-02	8E-04	0.1
Direct Spray of Woman, feet and lower legs	Adult Female	1E-03	8E-05	1E-02
Water consumption (spill)	Child	7E-02	2E-03	0.8
Fish consumption (spill)	Adult Male	1E-03	4E-05	8E-03
Fish consumption (spill)	Subsistence Populations	5E-03	2E-04	4E-02
Non-Accidental Acute Exposures (dose in mg/kg/event)				
Vegetation Contact, shorts and T-shirt	Adult Female	1E-03	4E-04	3E-03
Contaminated Fruit	Adult Female	5E-03	2E-03	7E-02
Contaminated Vegetation	Adult Female	6E-02	5E-03	0.5
Swimming, one hour	Adult Female	1E-07	3E-10	3E-06
Water consumption	Child	6E-04	2E-06	1E-02
Fish consumption	Adult Male	9E-06	5E-08	1E-04
Fish consumption	Subsistence Populations	4E-05	2E-07	7E-04
Chronic/Longer Term Exposures (dose in mg/kg/day)				
Contaminated Fruit	Adult Female	2E-03	5E-04	4E-02
Contaminated Vegetation	Adult Female	3E-02	1E-03	0.3
Water consumption	Adult Male	1E-04	8E-08	8E-04
Fish consumption	Adult Male	3E-07	3E-10	2E-06
Fish consumption	Subsistence Populations	2E-06	2E-09	1E-05

[1] The HQs are taken from Attachment 1, Worksheet E04.

See Section 3.4.3 for discussion.

Table 17: Risk Characterization for the General Public, Aquatic Applications

Scenario	Receptor	Hazard Quotients		
		Central	Lower	Upper
Accidental Acute Exposures (dose in mg/kg/event)				
Direct Spray of Child, whole body	Child	No exposure assessment.		
Direct Spray of Woman, feet and lower legs	Adult Female	No exposure assessment.		
Water consumption (spill)	Child	7E-02	2E-03	0.8
Fish consumption (spill)	Adult Male	1E-03	4E-05	8E-03
Fish consumption (spill)	Subsistence Populations	5E-03	2E-04	4E-02
Non-Accidental Acute Exposures (dose in mg/kg/event)				
Vegetation Contact, shorts and T-shirt	Adult Female	No exposure assessment.		
Contaminated Fruit	Adult Female	No exposure assessment.		
Contaminated Vegetation	Adult Female	No exposure assessment.		
Swimming, one hour	Adult Female	7E-07	1E-07	4E-06
Water consumption	Child	4E-03	7E-04	2E-02
Fish consumption	Adult Male	6E-05	2E-05	2E-04
Fish consumption	Subsistence Populations	3E-04	8E-05	8E-04
Chronic/Longer Term Exposures (dose in mg/kg/day)				
Contaminated Fruit	Adult Female	No exposure assessment.		
Contaminated Vegetation	Adult Female	No exposure assessment.		
Water consumption	Adult Male	7E-04	9E-06	5E-03
Fish consumption	Adult Male	2E-06	3E-08	1E-05
Fish consumption	Subsistence Populations	1E-05	3E-07	8E-05

[1]The HQs are taken from Attachment 2, Worksheet E04.

See Section 3.4.3 for discussion.

Table 18: Summary of EC_{50} Values for Algae and Macrophytes		
Organism	**EC_{50} (mg a.e)/L)**	**Reference**
Algae		
Green algae [IPA salt]	11.5	Hughes 1987
Blue-green algae	12.2	Hughes 1987
Freshwater diatom	>41	Hughes 1987
Green algae [acid]	71	Hughes 1987
Marine diatom	92	Hughes 1987
Geometric mean:	**37.2**	
Aquatic Macrophytes		
Duckweed [IPA salt]	0.018	Hughes 1995
Duckweed [acid]	0.024	Hughes 1987
Water milfoil	0.029	Roshon et al. 1999
Geometric mean:	**0.023**	

Source: See Appendix 6 for details.
See Figure 6 for illustration.
See Section 4.1.3.4 for discussion.

Table 19: Terrestrial Nontarget Animals Used in Ecological Risk Assessment

Animal	Representative Species	W[4]	Food Consumption[5]	Water Consumption	Other
MAMMALS[1]					
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]		
Canid	Fox	5,000	$0.6167\ W^{0.862}$ [Eq 3-47]		
Large Herbivorous Mammal	Deer	70,000	$1.518\ W^{0.73}$ [Eq 3-46]		
Large Carnivorous Mammal	Bear	70,000	$0.6167\ W^{0.862}$ [Eq 3-47]		
BIRDS[2]					
Small bird	Passerines	10	$2.123\ W^{0.749}$ [Eq 3-36]	$0.059\ W^{0.67}$ [Eq 3-17]	
Predatory bird	Owls	640	$1.146\ W^{0.749}$ [Eq 3-37]		
Piscivorous bird	Herons	2,400	$1.916\ W^{0.704}$ [Eq 3-38]		
Large herbivorous bird	Geese	4,000	$1.146\ W^{0.749}$ [Eq 3-37]		
INVERTEBRATES[3]					
Honey bee	*Apis mellifera*	0.000116	≈2 (1.2 to 4)[6]	Not used	SA[7]: 1.42 cm^2
Herbivorous Insects	Various	Not used	1.3 (0.6 to 2.2)	Not used	

[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] 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 20: Diets: Metabolizable Energy of Various Food Commodities

Food Item	Animal Group	Caloric Value [1] (kcal/g dw)	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	
Insects	Mammals	4.47	0.70	Water contents from Chapman 1998 (, p. 491). Typical ranges of 60-80%.
	Birds	4.30	0.70	
Vegetation (NOS)	Mammals	2.26	0.85	
	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 dw (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 dw (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 dw x 0.51 ≈ 1.1 kcal/g dw]

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

See Sections 4.2.2.3 for discussion.

Table 21: Toxicity Values Used in Ecological Risk Assessment

Group/Duration	Organism	Endpoint	Toxicity Value (a.e.)	Reference
Terrestrial Animals				
Acute				
	Non-canid Mammals	Use longer-term NOAEL	738 mg/kg bw	Section 4.3.2.1.
	Canids	Use longer-term NOAEL	250 mg/kg bw	
	Birds	Acute gavage NOAEL	2510 mg/kg bw	Section 4.3.2.2
	Insect (oral)	Oral NOAEL	860 mg/kg bw	Section 4.3.2.4.1
	Honey Bee (contact)	Contact NOAEL	860 mg/kg bw	Section 4.3.2.4.2
Longer-term				
	Mammals	Longer-term NOAEL	738 mg/kg bw/day	Section 4.3.2.1
	Canids	Longer-term NOAEL	250 mg/kg bw/day	
	Bird	Reproduction NOAEL	610 mg/kg bw/day	Section 4.3.2.2.
Terrestrial Plants				
Soil	Sensitive	NOAEL (sugar beet)	0.00017 lb/acre	Section 4.3.2.5
	Tolerant	NOAEL (oat)	0.0156 lb/acre	
Foliar	Sensitive	NOAEL (cucumber)	0.000064 lb/acre	Section 4.3.2.5
	Tolerant	NOAEL (pumpkin)	0.4 lb/acre	
Aquatic Animals				
Acute				
Amphibians	Sensitive	No data	N/A	Section 4.3.3.2
	Tolerant	No data	N/A	
Fish	Sensitive	NOAEC (formulation)	10.4 mg/L	Section 4.3.3.1
	Tolerant	Species not identified.	N/A	
Invertebrates	Sensitive	Species not identified.	N/A	Section 4.3.3.3
	Tolerant	NOAEC (formulation)	41 mg/L	Section 4.3.3.3
Longer-term				
Amphibians	Sensitive	No data available	N/A	Section 4.3.3.2
	Tolerant	No data available	N/A	
Fish	Sensitive	Est. NOAEC (formulation)	4.0 mg/L	Section 4.3.3.1
	Tolerant	Est. NOAEC (formulation)	12 mg/L	
Invertebrates	Sensitive	Species not identified	N/A	Section 4.3.3.3
	Tolerant	Est. NOAEC (formulation)	12 mg/L	
Aquatic Plants				
Algae	Sensitive	NOAEC (acid)	7.6 mg/L	Section 4.3.3.4
	Tolerant	NOAEC (acid)	50.9 mg/L	
Macrophytes	Sensitive	NOAEC	0.003 mg/L	Section 4.3.3.4
	Tolerant	Est. NOAEC	0.1 mg/L	

See Section 4.3 for discussion.

Table 22: Hazard Quotients for Terrestrial Plants from Direct Spray or Drift

Distance Downwind (feet)	Hazard Quotients Based on Drift for the Specified Application Methods			
	Aerial	**High Boom Ground Broadcast**	**Low Boom Ground Broadcast**	**Backpack**
	Sensitive Species			
0	**15,625**	**15,625**	**15,625**	**15,625**
25	**3,484**	**1,625**	**547**	**130**
50	**2,672**	**781**	**277**	**68**
100	**1,530**	**388**	**148**	**38**
300	**488**	**118**	**55**	**15**
500	**300**	**61**	**33**	**9**
900	**194**	**26**	**17**	**5**
	Tolerant Species			
0	**3**	**3**	**3**	**3**
25	0.6	0.3	9E-02	2E-02
50	0.4	0.1	4E-02	1E-02
100	0.2	6E-02	2E-02	6E-03
300	8E-02	2E-02	9E-03	2E-03
500	5E-02	1E-02	5E-03	1E-03
900	3E-02	4E-03	3E-03	8E-04

Adapted from Attachment 1, Worksheet G05.
See Section 4.4.2.5 for discussion.

Appendix 1: Toxicity to mammals.

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A1 Table 1: MSDS Mammalian Effects Summary of Selected Imazapyr Formulations

Formulation Name	% a.e.	Oral LD_{50} (mg/kg bw)	Dermal LD_{50} (mg/kg bw)	Inhalation LD_{50} (mg/L x 4 h)	Skin Irritation	Eye Irritation	Sensitiza-tion
Arsenal	22.6	>5000	>2000	5.3	Mild	Non-irritant	No
Arsenal AC	43.3	>5000	>5000	4.62	Mild	Non-irritant	No
Arsenal Railroad	27.6	>5000	>2148	>1.3	Mild	Irritating	No
Chopper	22.6	>5000	>5000	1.58	Irritating	Moderate	Slight
Ecomazapyr 2 SL[a]	22.6	>5000	>5000	>3.5 [1]	Non-irritant	Non-irritant	No
Ecomazapyr 2 SL[b]	22.6	N.S.[4]	N.S.	N.S.	N.S.	Moderate	No
Habitat	22.6	>5000	>2000	5.3	Mild	Non-irritant	No
Imazapyr 2 SL	22.6	N.S. [4]	N.S.	N.S.	N.S.	Moderate	No
Imazapyr 4 SL[c]	42.9	>2000	>2000	> 4.72	Non-irritant	Minimal	No
Imazapyr 4 SL[d]	42.9	N.S.[5]	N.S.	N.S.	N.S.	Moderate	No
Polaris	22.6	>5000	>2000	4.62	Mild	Non-irritant	No
Polaris AC	43.3	>5000	>5000	N.S.	Mild	Non-irritant	N.S.
Polaris RR	22.6	>5000	>2148	N.S.	Mild	Irritating	N.S.
Polaris SP	22.6	>5000	>2000	>1.58[2]	Irritating	Irritating[3]	Mild
Rotary 2 SL	22.6	>2000	>2000	>5.22	Non-irritant	Moderate	No
Stalker	22.6	>5000	>5000	1.58	Irritating	Moderate	Slight

[a] Alligare, EPA Reg. No. 81927-22
[b] Vegetation Management, EPA Reg. No. 74477-4
[c] Alligare, EPA Reg. No. 81927-24
[d] Vegetation Management, EPA Reg. No. 74477-5

[1]Duration not specified.
[2]No mortality.
[3]Recovery within 3 days.
[4] Harmful if swallowed. May cause burns/blisters to mouth, throat and digestive tract.
[5] *Have person sip a glass of water if able to swallow. DO NOT induce vomiting un less told to by a poison control center or doctor*.

Source: Material Safety Datasheets (MSDSs) from www.greenbook.net.

A1 Table 2: Acute Oral Toxicity			
Species	**Exposure**	**Response**	**Reference**
Rats, Sprague-Dawley, albino 8-weeks old, 5 males (bw=223–240 g) and 5 females (bw=161–179 g).	**Technical grade imazapyr** Single oral dose of 5000 mg/kg. [Test material specified as AC 243997, purity 98.8% w/w.]	Clinical signs of toxicity (salivation in 4/5, writhing in 1/5) and one death in males. Surviving males returned to normal appearance by 2 hours post-dosing. No signs of toxicity or mortality in females. No gross pathology in either sex. 14-day observation period. Working Note: Observation of salivation confirmed in Agency DER (Backus 1999) LD_{50} = >5000 mg/kg	Lowe 1999 MRID No. 44735301
Rats, Charles River, albino, 6-weeks old, 5 males (bw=151–157 g) and 5 females (bw=120–124 g).	Single oral dose of 5000 mg/kg or 25 mL/kg. 14-day observation period. [Test material specified as AC 3532-149 or 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid; **2 lb a.e./gallon formulation**.] Fiche contains CBI data on ingredients not summarized in this appendix.	**One male rat died** (necropsy revealed congestion of liver, kidney, and intestinal tract, and hemorrhagic lungs). No mortality among females. Surviving test animals showed no visible lesions. LD_{50} = >5000 mg/kg	Fischer 1983 MRID No. 00132031
Rats, Charles River, albino, 7-weeks old, 5 males (bw=251–265 g) and 5 females (bw=171–190 g).	Single oral dose of 5000 mg/kg or 10 mL/kg. [Test material specified as **Arsenal Herbicide 5% granular formulation** or AC 243,977 Technical.] Fiche contains CBI data on ingredients not summarized in this appendix.	No toxic signs or mortality were observed in any of the test animals. No visible lesions were observed in any of the test animals. LD_{50} = >5000 mg/kg	Fischer 1986a MRID No. 00162964
Rats, Charles River, albino, 6–7 weeks old, 5 males (bw=160–182 g) and 5 females (bw=142–164 g).	Single oral dose of 5000 mg/kg or 4.7 mL/kg. [Test material specified as **Chopper C/S Formulation** or AC 243,997 Technical, sample purity 22.6%.] Fiche contains CBI data on ingredients not summarized in this appendix.	Decreased activity (only sign of intoxication) but no mortality. Necropsies showed no visible lesions. 14-day observation period. LD_{50} = >5000 mg/kg	Fischer 1986b MRID No. 00163195

A1 Table 2: Acute Oral Toxicity			
Species	**Exposure**	**Response**	**Reference**
Rats, Crl: CD(SD)BR strain, albino, 5/sex.	Single oral dose of 5000 mg/kg bw administered via gavage. [Test substance specified as AC 243,997 6% RTU formulation.]	No mortality; signs of toxicity were limited to a bluish discoloration of the urine 2–8 hours after dosing. No other signs of toxicity were observed for the remainder of the 14-day observation period. Necropsy results included hydronephrosis of the kidney in 1/5 males and 3/5 females, but no other visible lesions were observed. LD_{50} = >5000 mg/kg	Fischer 1989c MRID No. 41353404

A1 Table 3: Acute and Subchronic Dermal Toxicity			
Species	**Exposure**	**Response**	**Reference**
ACUTE			
Rats, albino, 5 male and 5 female.	Single dermal dose of 5000 mg/kg bw. 4 lb a.e./gallon formulation.	No mortality, signs of toxicity or changes in body weight. Chromodacryorrhea and brown material around nose. LD_{50}: > 5,000 mg/kg bw	Lowe and Bradley 1996 MRID 44177001
Rabbits, New Zealand, white, albino, males (mean bw 3.09) and females (mean bw 2.64), 12–14 weeks old, 5/sex/dose.	Single dermal dose of 2.0 mL/kg or 2148 mg/kg applied to shaved skin using an impervious plastic cuff that provided 24-hour contact. [Test material specified as AC 3532-149 or 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid; **2 a.e. lb/gallon formulation**.] Fiche contains CBI data on ingredients not summarized in this appendix.	No mortality among females. One male died (necropsy revealed pneumonic areas of the lungs). Of survivors, 1/9 had mottled and pale liver; 1/9 had moderate congestion of the lungs; 7/9 had no visible lesions. LD_{50} = >2000 mg/kg or 2 mL/kg	Fischer 1983 MRID No. 00132031
Rabbits, New Zealand white, albino, 12–14 weeks old, 5 males (mean bw=2.7 kg) and 5 females (mean bw=3.4 kg).	Single dermal dose of 2000 mg/kg applied to the shaved intact dorsal skin (area equals approximately 10% of body surface) of non-fasted animals. Test material held under impervious plastic cuff for 24-hour continuous contact. After 24-hour exposure, cuff removed, treated site wiped with moistened gauze pad, and animals fitted with fiber collars to prevent further ingestion of remaining test material. 14-day observation period. [Test material specified as **Arsenal Herbicide 5% granular formulation** or AC 243,977 Technical.] Fiche contains CBI data on ingredients not summarized in this appendix.	No signs of toxicity were observed during the 14-day observation period. No visible gross lesions were observed in any of the test animals. LD_{50} = >2000 mg/kg	Fischer 1986a MRID No. 00162964

A1 Table 3: Acute and Subchronic Dermal Toxicity

Species	Exposure	Response	Reference
Rabbits, New Zealand white, albino, 12–14 weeks old, 5 males (mean bw=2.3 kg) and 5 females (mean bw=3.0 kg).	Single dermal dose of 2000 mg/kg or 1.9 mL/kg applied by application to shaved intact dorsal skin (area equals approximately 10% of body surface) of non-fasted animals. Test material held under impervious plastic cuff for 24-hour continuous contact. After 24-hour exposure, cuff removed, treated site wiped with moistened gauze pad, and animals fitted with fiber collars to prevent further ingestion of remaining test material. 14-day observation period. [Test material specified as **Chopper C/S Formulation or** AC 243,997 Technical, sample purity 22.6%.] Fiche contains CBI data on ingredients not summarized in this appendix.	Decreased activity (only sign of intoxication), but no mortality. Necropsies showed no visible lesions. LD_{50} = >2000 mg/kg	Fischer 1986b MRID No. 00163195
Rabbits, New Zealand, white, albino, males (mean bw 3.4 kg) and females (mean bw 3.3 kg), 5/sex.	Single dermal dose of 2000 mg test formulation/kg applied to clipped intact trunk skin (≈10% of total body surface area) using an impervious plastic wrap that provided 24-hour contact. [Test material specified as AC 243,997 **6% RTU formulation** (6.0% a.i.).]	No signs of toxicity, mortality, changes in body weight gain, or significant gross pathology (1/10 rabbits had liver with granular texture but no visible lesions). 14-day post-exposure observation period. LD_{50} = >2000 mg/kg [mg AC 243,997 6% RTU formulation/kg]	Fischer 1989a MRID No. 41353405c

Subchronic dermal on next page

A1 Table 3: Acute and Subchronic Dermal Toxicity			
Species	**Exposure**	**Response**	**Reference**
Subchronic			
Rabbits, New Zealand, white, albino, young adults, 10/sex/dose.	0, 100, 200, or 400 mg a.e./kg/day to close-clipped, intact or abraded, occluded backs, 6 hours/day, 5 days/week for 3 weeks. Test material: Technical grade imazapyr (93%), AC 243,997	Two rabbits died with gross evidence (confirmed microscopically) of pneumonia. This effect was not associated with treatment. No systemic toxicity (i.e., no adverse effects on body weight, food consumption, hematology, serum chemistry, or organ weights). Microscopic evaluation of all tissues from control and high-dose group rabbits and all remarkable tissues from low- and middle-dose group rabbits did not indicate consistent or distinct treatment-related effects. U.S. EPA/OPP 2005a NOAEL: 400 mg a.e/kg bw/day	Larson and Kelly 1983 MRID No. 00131609

A1 Table 4: Skin Irritation Studies			
Species	**Exposure**	**Response**	**Reference**
Rabbits, New Zealand, white, albino, 6 males.	0.5 mL applied to shaved, abraded or intact skin (intact and abraded sites were on opposite side of the midline of the same animal) for 24 hours. [Test material specified as AC 3532-149 or 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid; **2 a.e. lb/gallon formulation**.] Fiche contains CBI data on ingredients not summarized in this appendix.	Skin irritation was scored according to the Draize scoring system. At 24 hours, mean scores for erythema were 1.00 (intact skin) and 1.67 (abraded skin); mean scores for edema were 0.00 (intact skin) and 1.50 (abraded skin). At 72 hours, mean scores for erythema were 0.33 (intact skin) and 0.67 (abraded skin); mean scores for edema were 0.00 (intact skin) and 0.00 (abraded skin). The total mean score = 5.17; Primary Irritation Score (total score/4) = 1.29. The test material is considered to be mildly irritating to rabbit skin.	Fischer 1983 MRID No. 00132031
Rabbits, New Zealand white, albino, 6 males.	0.5 g applied to shaved, abraded or intact skin (intact and abraded sites were on opposite side of the midline of the same animal) for 24 hours. [Test material specified as **Arsenal Herbicide 5% granular formulation** or AC 243,977 Technical.] Fiche contains CBI data on ingredients not summarized in this appendix.	Skin irritation was scored according to the Draize scoring system. At 24 hours, mean scores for erythema were 0.50 (intact skin) and 0.83 (abraded skin); mean scores for edema were 0.00 for both intact and abraded skin. At 72 hours, mean scores for erythema and edema were 0.00 for both intact and abraded skin. The total mean score = 1.33; Primary Irritation Score (total score/4) = 0.33. The test material is considered to be mildly irritating to rabbit skin.	Fischer 1986a MRID No. 00162964

A1 Table 4: Skin Irritation Studies			
Species	**Exposure**	**Response**	**Reference**
Rabbits, New Zealand white, albino, 6 males (age and bw not reported).	Test material (0.5 mL) was applied to shaved intact dorsal skin (1" square). An untreated site on the opposite side of the midline served as a control. The sites were covered with a gauze pad and occluded with a plastic wrap for a contact time of 4 hours. [Test material specified as **Chopper C/S Formulation** or AC 243,997 Technical, sample purity 22.6%.] Fiche contains CBI data on ingredients not summarized in this appendix.	Skin irritation was scored according to the Draize scoring system. The maximum possible score for a skin reaction is 4. Sites were scored for irritation at 4, 24, 48, and 72 hours. The test material was 'mildly irritating' to the intact skin of rabbits based on observations of erythema (total score of 0.67 and primary irritation score of 0.17); no edema was observed.	Fischer 1986b MRID No. 00163195
Rabbits, New Zealand white, albino, 6 males (young adult, age 12–14 weeks, bw not reported).	Test material (0.5 mL) was applied to 1" square gauze patches and applied to clipped intact dorsal trunk skin. An untreated site on the opposite side of the midline served as a control. The sites were occluded with a plastic wrap for a contact time of 4 hours. [Test material specified as AC 243,997 **6% RTU formulation** (6.0% a.i.).]	Skin irritation was scored according to the Draize scoring system. The maximum possible score for a skin reaction is 4. Sites were scored for irritation at 1, 24, 48, and 72 hours. The test material was 'mildly irritating' to the intact skin based on observations of barely perceptible erythema in 2/6 rabbits at the 1-hour observation. No edema was observed and there were no overt signs of toxicity or mortality.	Fischer 1989d MRID No. 41353407c

A1 Table 5: Skin Sensitization Studies

Species	Exposure	Response	Reference
Guinea Pigs, Hartley Albino, 10 males (bw not reported).	Dermal sensitization was assessed by 9 induction applications (thrice weekly for 3 weeks) followed by a challenge application 14 days after the last induction. Test material was applied beneath an occlusive covering and left in contact with the skin for 6 hours. 0.4 mL of test material was applied as a minimally irritating 75% dilution in saline for inductions and as a non-irritating 25% dilution for the challenge. [Test material specified as **Chopper RTU 6** (purity not reported).]	No dermal sensitization as determined by erythema and edema reactions to the challenge dose as scored by the Draize method (scoring 24 and 48 hours after application). No Draize scores ≥1 (i.e., barely perceptible erythema or edema). No apparent effects on clinical signs, body weight, or survival.	American Cyanamid Co. 1988a MRID No. 41353409
Guinea Pigs, Hartley, 12 males (mean bw 0.419 kg initial, 0.665 kg final).	Dermal sensitization was assessed by thrice weekly induction applications for 3 weeks (9 total applications) followed by a challenge application 14 days after the last induction. The inductive and challenge applications consisted of 0.4 g of test material applied to intact clipped skin for 6 hours via gauze pad moistened with 0.4 mL of saline and covered with an occlusive wrap. [Test material specified as **Arsenal 5-G** (purity not reported).]	No erythema or edema reactions were observed after any application as scored by the Draize method, indicating that the test material was not irritating or sensitizing to the skin of the guinea pigs. There were no clinical signs of toxicity or significant changes in body weight gain. There was similarly no skin irritation in a naive control group (one challenge application), or in a preliminary screening test in which animals received a single application of unspecified amount of test material for 6 hours and evaluated 24 and 48 hours later.	Costello 1986 MRID No. 00162965
Guinea Pigs, American Shorthair (Hartley derived), 10 males (mean bw 0.54 kg initial, 0.59 kg final).	Dermal sensitization was assessed by once weekly induction applications for 3 weeks followed by a challenge application 14 days after the last induction. 0.3 g of test material moistened with 0.9% saline was used for the inductive and challenge applications. Test material was left in uncovered contact with clipped skin for 6 hours. [Test material specified as AC 243,997 (93% pure).]	No erythema or edema reactions were observed after any application, indicating that the test material was not sensitizing or irritating to the skin of the guinea pigs. There were no clinical signs of toxicity or significant changes in body weight. No skin irritation was observed in a naive control group (one challenge application) or in a preliminary dose range-finding study in which guinea pigs received a single application of 0.08–0.30 g of test material and evaluated for erythema and edema 24 and 48 hours later.	Ledoux 1983 MRID No. 00131607

A1 Table 6: Acute Inhalation Toxicity			
Species	**Exposure**	**Response**	**Reference**
Rats, Sprague-Dawley, 10/sex.	Whole body exposure of 4.62 ± 1.41 mg/L (analytical) for 4 hours. MMAD = 1.6 µg ± 0.06 (GSD). [Test material specified as **Arsenal 4-AS** (purity not reported).]	No mortality (LC_{50} >4.62 mg/L). All animals appeared normal during the 14-day observation period. Gross pathology findings included congested lungs (2/10 males, 4/10 females); slight lung congestion (3/10 males, 5/10 females); and hemorrhagic lungs (1/10 males).	Hershman and Moore 1986 MRID No. 00164539
Rats, Sprague-Dawley, 10/sex.	Whole body exposure of 1.3 mg/L aerosol (measured level) for 4 hours. MMAD = 3.3 µm ± 2.5 (GSD). 88% of particles were respirable (≤10 µm). [Test material specified as AC 243,997 (93% pure) – i.e., technical grade imazapyr.]	Slight nasal discharge occurred in all rats subsequent to exposure on day 1, but animals returned to normal appearance on day 2; the finding was indicative of minor reversible irritation of the nares and/or upper respiratory tract. No mortality (LC_{50} >1.3 mg/L) or changes in body weight or absolute or relative organ weights (liver, kidneys, heart, lungs, testes, ovaries), or gross pathology in lungs or other tissues. 14-day post-exposure observation.	Voss et al. 1983 MRID No. 00132032
Rats, Sprague-Dawley, 10/sex.	Whole body exposure of 3.34 ± 0.76 mg/L aerosol (measured level) for 4 hours. MMAD = 5.00 ± 2.94 µm, 6.15 ± 2.67 µm (two determinations). 65.7% of particles were respirable (≤10 µm). [Test material specified as **Chopper RTU 6** (purity not reported).]	No mortality (LC_{50} >3.34 mg/L) and no clinical signs of intoxication including changes in body weight or absolute or relative organ weights (liver, kidneys, heart, lungs, testes, ovaries), and no changes in the gross pathology of the lungs or other tissues. 14-day post-exposure observation.	Werley 1987 MRID No. 41353408

A1 Table 7: Eye Irritation Studies			
Species	**Exposure**	**Response**	**Reference**
Rabbits, New Zealand, white, albino, males, 6 in group without rinsing, 3 in group with rinsing.	0.1 mL instilled into conjunctival sac of right eye (left eye served as control) with or without rinsing after 20 seconds. [Test material specified as AC 3532-149 or 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid; **2 lb a.e./gallon formulation.**] Fiche contains CBI data on ingredients not summarized in this appendix.	Eye irritation was scored according to the Draize scoring system. The maximum possible scores for eye irritation reactions are: cornea (80); iris (10), and conjunctiva (20). Observations of the cornea, iris, and conjunctiva at 24, 48, and 72 hours and 4 and 7 days indicated that the test material was **irritating** to the rabbit eye with complete recovery by 7 days. The group without rinsing had substantially higher mean irritation scores, compared with the group with rinsing.	Fischer 1983 MRID No. 00132031
Rabbits, New Zealand, albino, 6 males.	100 mg instilled into conjunctival sac of the right eye (left eye served as control) without rinsing for 24 hours, after which time, treated eyes were rinsed with tap water. [Test material specified as **Arsenal Herbicide 5% granular** formulation or AC 243,997 Technical.] Fiche contains CBI data on ingredients not summarized in this appendix.	Examinations of the cornea, iris, and conjunctiva were performed at 1, 24, 48, 72 hours, and 4 and 7 days (with the aid of ultraviolet light and fluorescein). Eye irritation was scored according to the Draize scoring system. The maximum possible scores for eye irritation reactions are: cornea (80); iris (10), and conjunctiva (20). The test material was considered to be '**irritating**' to the rabbit eye based on mean scores of 2.7 and 3.7 for conjunctiva at 1 hour and 24 hours, respectively; and 0.3 from 48 hours to 4 days; and mean scours of 5.8 and 2.5 for cornea at 24 and 48 hours, respectively. All animals recovered by 7 days.	Fischer 1986a MRID No. 00162964

A1 Table 7: Eye Irritation Studies			
Species	**Exposure**	**Response**	**Reference**
Rabbits, New Zealand, albino, 6 males.	0.1 mL instilled into conjunctival sac of right eye (left eye served as control) without rinsing for 24 hours, after which time, treated eyes were rinsed with tap water. [Test material specified as **Chopper C/S Formulation** or AC 243,997 Technical, sample purity 22.6%.] Fiche contains CBI data on ingredients not summarized in this appendix.	Examinations of the cornea, iris, and conjunctiva were performed at 1, 24, 48, and 72 hours (with the aid of ultraviolet light and fluorescein). Eye irritation was scored according to the Draize scoring system. The maximum possible scores for eye irritation reactions are: cornea (80); iris (10), and conjunctiva (20). The test material was '**irritating**' to the rabbit eye based on mean scores of 9.3 for conjunctiva (at 1 and 24 hours) and 8.3 for cornea. All animals recovered by 72 hours.	Fischer 1986b MRID No. 00163195
Rabbits, New Zealand, albino, 6 males.	0.1 mL of powdered test material was instilled into the conjunctival sac of the left eye (right eye served as untreated control) without rinsing for 24 hours, after which time, treated eyes were rinsed with tap water. [Test material specified as AC 243,997, **6% RTU formulation** (6.0% a.i.).]	Examinations of the cornea, iris, and conjunctiva were performed pretreatment and after 1, 24, 48, and 72 hours (with the aid of ultraviolet light and fluorescein). Eye irritation was scored according to the Draize scoring system. The maximum possible scores for eye irritation reactions are: cornea (80); iris (10), and conjunctiva (20). The test material was '**minimally irritating**' to the rabbit eye based on slight injection of the conjunctival vessels, slight chemosis, and slight discharge in 6/6, 3/6 and 1/6 animals, respectively, at the 1-hour observation period. All animals recovered by 24 hours.	Fischer 1989b MRID No. 41353406c

A1 Table 8: Developmental (Teratology) Studies			
Species	**Exposure**	**Response**	**Reference**
Rabbits, New Zealand white, albino, females, nominally 5/dose (only data for gravid females are summarized; VC=4; T-1=5; T-2=3; T-3=5; T-4=5).	0, 250, 500, 1000, or 2000 mg/kg bw by gavage on days 6–18 of gestation. [Test material specified as AC 243,997.]	Salivation in does = 1/5 (250 mg/kg bw, p=0.5); 2/5 (500 mg/kg; p=0.22); 4/5 (1000 mg/kg, p=0.023); and 5/5 (2000 mg/kg; p=0.0040). The p-values are based on the Fisher Exact test. Trend text significant at p=0.00032. Incidence of salivation confirmed in Agency DER (Dykstra 1984). At 250 mg/kg, necropsy revealed fluid in the trachea and chronic non-suppurative pneumonia in one animal and pulmonary exudate and discoloration, gastric mucosal depressions and ulcers in the other.	Salamon et al. 1983a MRID No. 00131614 This is a pilot study for Salamon et al. 1983b, MRID No. 00131613.
Additional Notes on Salamon et al. 1983a: At 1000 mg/kg, necropsy revealed stomach lesions (discolorations/depressions) in all four animals. At 2000 mg/kg, necropsy revealed gastric mucosal changes (erosive lesions) in four animals and gastric and pyloric mucosal discolorations in the other animal. In animals that survived to final sacrifice, there were no treatment-related adverse effects on body weight, mean numbers of corpora lutea, implantation sites, resorption sites, viable fetuses, and gross pathology. Exposure levels of 1000 and 2000 mg/kg resulted in maternal death; exposure levels of 250 and 500 mg/kg did not produce exaggerated pharmacological or embryocidal effects. Note: This study is cited but not explicitly reviewed in U.S. EPA/OPP (2005a) or other Agency risk assessments.			
Rabbits, New Zealand white, albino, females, nominally 18/dose (only data for gravid females are summarized; VC=17; T-1=18; T-2=16; T-3=17).	0, 25, 100, or 400 mg/kg bw by gavage on days 6–18 of gestation. [Test material specified as AC 243,997.]	Two rabbits in the control group and two rabbits in the 400 mg/kg died; gross pathology revealed only pulmonary changes. All other does survived to final sacrifice. A slightly increased incidence of common and expected pulmonary and hepatic changes was observed in the treated does but was not considered treatment related. There was no evidence of reproductive effects in the dams; there were no statistically significant differences in fetal body weight and crown-rump length compared with controls.	Salamon et al. 1983b MRID No. 00131613

A1 Table 8: Developmental (Teratology) Studies			
Species	**Exposure**	**Response**	**Reference**
Additional Notes on Salamon et al. 1983b: **External anomalies:** There was one external anomaly observed in the 25 mg/kg group and four in the 400 mg/kg group. In the 25 mg/kg group (152 fetuses; 17 litters), one fetus had a short tail. [Another fetus had a left eye that appeared larger than normal, but appeared to be normal in size during internal examination.] In the 400 mg/kg group (144 fetuses; 16 litters), one fetus had a kink at the tip of the tail; there were two fetuses (from the same litter) with talipes; and one anurous fetus (from a different litter) with talipes and spina bifida. Evaluations of fetal internal, skeletal, and internal head development indicated no consistent, adverse effects resulting from exposure to AC 243,997. U.S. EPA/OPP (2005a) assessment: NOAEL (maternal and fetal): 400 mg/kg bw/day. LOAEL: Not defined.			
Rats, Charles River, female, 25/dose group (only data for gravid females are summarized; VC=22; T-1=24; T-2=23; T-3=22).	0, 100, 300, or 1000 mg/kg bw by gavage on days 6–15 of gestation. [Test material specified as AC 243,997.]	No mortality; no teratogenicity; salivation was observed in 6/22 animals treated with 1000 mg/kg/day bw. Effect on salivation significant with respect to the control group (p=0.01057) using the Fisher Exact test. Effect also significant using the Cochrane-Armitage trend test: p<0.0001. U.S. EPA/OPP 2005a: Maternal: NOAEL: 300 mg/kg bw/day LOAEL: 1000 mg/kg bw/day Fetal: NOAEL: 1000 mg/kg bw/day LOAEL: Not defined.	Salamon et al. 1983c MRID No. 00131611
Rats, Charles River, female, 5/dose group.	0, 250, 500, 1000, or 2000 mg/kg bw by gavage on days 6–15 of gestation. [Test material specified as AC 243,997.]	No mortality; no pharmacological or embryocidal effects; only recurring effect was salivation: 1/5 (250 mg/kg; p=0.5); 2/5 (500 mg/kg; p=0.22); 3/5 (1000 mg/kg; p=0.083); and 5/5 (2000 mg/kg; 0.0040). The p-values are based on the Fisher Exact test. Effect on salivation dose-related based on Cochrane-Armitage trend test: p=0.0003. U.S. EPA/OPP 2005a: This study is cited but not discussed.	Salamon et al. 1983d MRID No. 00131612 This is a pilot study for Salamon et al. 1983c, MRID No. 00131611.

A1 Table 9: Reproduction Studies			
Species	**Exposure**	**Response**	**Reference**
Rats, Sprague-Dawley, 25 males (bw=187–240 g) and 25 females (bw=128–166 g), forming F_0 generation in a 2-generation reproduction study.	0, 1000, 5000, or 10,000 ppm in the diet. Rats were treated for 64 days prior to mating, throughout the two mating periods and for approximately 3 weeks after the end of the second mating period. Ranges of achieved intake of AC 243,997 between weeks 1 to 10 and 18 to 19 were as follows: **males**: 48.3 to 142.8, 252.8 to 720.8, and 483.4 to 1471.8 mg/kg/day, corresponding to 1000, 5000, and 10,000 ppm, respectively; **females:** 80.2 to 149.9, 404.7 to 736.1, and 761.3 to 1537.1 mg/kg/day, corresponding to 1000, 5000, and 10,000 ppm, respectively.	**In the F_0 and F_{1b} adult generations**: There were no treatment-related effects on mortality or pathology, and no clinical signs of toxicity. There were no adverse effects on body weights or food consumption in any of the dose groups. There were no significant differences in fertility indices, day of mating, or other parameters of parental performance. The incidence of dead pups at birth varied markedly among groups and was occasionally statistically significant but did not show a clear dose-response relationship. Other parameters of reproductive toxicity (i.e., gestation index, length of gestation, number of live pups at birth, and sex ratio) were similar to control values. **In the F_{1a}, F_{1b}, F_{2a}, F_{2b} pups**: There were no adverse effects on viability, survival, or lactation indices, or on the clinical condition of the pups. Except for one occasion, the body weights of pups in the treated group were not significantly different from controls. There were no pathology findings related to treatment. U.S. EPA/OPP (2005a, p.20) Assessment: NOAEL: >10,000 ppm, 738 mg a.e./kg bw/day for males and 933.3 mg a.e./kg bw/day for females.	Robinson 1987 MRID No. 41039505 U.S. EPA/OPP 2005a Classification, Acceptable/ Guideline

A1 Table 10: Subchronic Toxicity Studies			
Species	**Exposure**	**Response**	**Reference**
Rats, Charles River CD (Sprague-Dawley derived), 4.5-weeks old, 10 males (bw=100–130 g) and 10 females (bw=102–120g) per dose group.	0, 15,000, or 20,000 ppm in the diet for 13 weeks. The reported average daily test substance intake values, based on mean weekly body weight and food consumption data measured during the 13-week dosing period, correspond to 1248 and 1695 mg/kg/day for males and 1336 and 1740 mg/kg/day for females for 15,000 and 20,000 ppm concentrations, respectively. [Test material specified as AC 243,997, purity 99.3%.]	No exposure-related adverse effects at either dose level as shown by clinical signs, survival, body weight, food consumption, ophthalmologic condition, hematology, clinical chemistry, urinalysis, organ weights, gross pathology and histopathology. Absolute and relative kidney weights were increased in the high-dose females (≈12–15% higher than controls) but not accompanied by any pathological or urinalysis changes. This study identified a subchronic dietary NOAEL of 20,000 ppm for imazapyr in rats (1695 mg/kg/day in males and 1740 mg/kg/day in females).	Hess 1992 MRID No. 42774401
Cows, Holstein, dairy, 3/group.	Dose levels of 0, 1.2 and 3.6 g for 28 days; 12 and 36 g for 29 days. The corresponding mg a.i./kg/day bw are 0, 2, 6, 20, and 60, respectively. [Test substance specified as CL 342997 (100% purity).]	Test substance residues in milk samples in the control group were ≤2.10 ppb. The pre-treatment milk samples from all cows were <10 ppb. The residues in the cows in the 1.2 g treatment group were<10 ppb. The average residue in the 3.6, 12, and 36 g treatment groups were 24.3–34.9, 75.3–108, and 222–313 ppb, respectively.	Khunachak 1999 MRID No. 45119721
Additional Notes on Khunachak 1999: The residues in muscle, fat, kidney, and liver samples from cows in the control group were <4.49, <4.71, <4.64, and <4.58 ppb, respectively. Residues in muscle samples in the 1.2, 3.6, 12, and 36 g treatment groups were <50.0, <50.0, 97.3, and 234 ppb, respectively. Residues in fat samples in the 1.2, 3.6, 12, and 36 g treatment groups were <50.0, <50.0, 66.7, and 92.1 ppb, respectively. Residues in kidney samples in the 1.2, 3.6, 12, and 36 g treatment groups were 246, 519, 4360, and 7510 ppb, respectively. Residues in liver samples in the 1.2, 3.6, 12, and 36 g treatment groups were <50.0, <50.0, 300, and 809 ppb, respectively.			

A1 Table 11: Chronic Toxicity Studies			
Species	**Exposure**	**Response**	**Reference**
Mice, CD-1, approximately 42-days old, 65 males (mean bw=27 g) and 65 females (mean bw=21g) per dose level.	Dietary exposure to 0, 1000, 5000, or 10,000 ppm for 18 months. Test substance intake based on measured food consumption values ranged as follows: 126–254, 674–1194, and 1301–2409 mg/kg/day in males and 151–303, 776–1501, and 1639–3149 mg/kg/day in females.	No dose-related or statistically significant (Chi-square analysis) differences in mortality between controls and treated mice, but survival in treated males was slightly better than in control males and survival in mid- and high-dose females was slightly worse than in control females.	Auletta 1988 MRID No. 41039504; Hess 1992 MRID No. 42774401
***Additional Notes on Auletta 1988*:** Although there were no treatment-related effects on body weight; increased food consumption was statistically significant among treated mice, but was not considered treatment related in the absence of a dose-response relationship. No statistically significant adverse effects on hematology were observed. Organ weight data indicate a "*few statistically significant differences*," which occurred sporadically and were not considered treatment related. Gross pathology revealed a slightly higher incidence of enlarged mesenteric lymph nodes in all treated mice, but no dose-response relationship; a slightly increased incidence of kidney cysts in high dose males [5/33 (15%)] compared with controls [2/28 (7%); and a dose-related, but not statistically significant increase in the number of enlarged seminal vesicles: [0 ppm 3/28 (11%); 1000 ppm 6/35 (17%); 5000 ppm 9/34 (27%); and 10,000 ppm 10/33 (30%)], which the investigators viewed as "*common findings in old mice*." Microscopic evaluation revealed changes that occurred with greater incidence in high-dose mice, compared with controls. These mild inflammatory changes, which were not statistically significant and not considered treatment related, included plasma cell hyperplasia in the mesenteric lymph nodes and erythrocytes in the sinus of the mediastinal lymph nodes in females. There was no difference in the incidence of pathological findings in gonads between treated and control mice and no dose-related differences in incidence or degree of hydronephrosis. Supplemental information on this study was requested by EPA for their carcinogenicity classification and chronic toxicity NOEL determination (Hess 1992). Additional histopathological examination for brain tumors in the male rats and a statistical analysis of adrenal medullary neoplastic lesions in the female rats supported the conclusion that there was no carcinogenic potential for imazapyr. Additional evaluation of the female rats for extramedullary hematopoiesis in the spleen and bilateral squamous cysts in the thyroid supported determination of a 10,000 ppm NOAEL for chronic toxicity.			

A1 Table 11: Chronic Toxicity Studies			
Species	**Exposure**	**Response**	**Reference**
Rats, Sprague-Dawley, 44-days old, 260 males (bw=158–221 g), and 260 females (bw=121–174 g), 65 males and 65 females per dose group, control plus 3-dose groups.	0, 1000, 5000, or 10,000 ppm for 2 years. Partial sacrifice (10 per group) after 12 months of treatment; all remaining survivors sacrificed after 24 months. Mean test substance intake values calculated over the 2-year study duration, based on individual body weight and food consumption, and the purity of the test material were 49.9, 252.6, and 503.0 mg/kg/day for males and 64.2, 317.6, and 638.6 mg/kg/day for females (cf: p. 13 of study).	No differences in the number of deaths among control and treated animals. In males, there was a slight but statistically insignificant relationship between dose level and time to death. Females (in all treatment groups) showed a slight (and in most cases statistically significant) increase in food consumption during the first year; however, the effect, which did not always exhibit a dose response, was not considered toxicologically significant.	Daly 1988 MRID No. 41039503; Hess 1992 MRID No. 42774401
Additional Notes on Daly 1988: In control and all treated groups there was a random distribution of gross lesions considered to be incidental changes unrelated to exposure to the test material. There were no treatment-related effects on hematology, clinical chemistry or urinalysis, mean organ weights, organ/body weight or organ/brain weight ratios; however, there was an increased incidence of C-cell carcinomas of the thyroid gland in high-dose males: 2/62 in the control group; 0/65 in the low-dose group; 1/63 in the mid-dose group; and 5/63 in the high-dose group. None of the incidences in the dosed groups are significantly higher than the control group based on the Fisher Exact test – i.e., a *p*-value of 0.2265 for 2/62 vs. 5/63. Nonetheless, the Cochran-Armitage trend test is significant (p=0.0175). Supplemental information on this study was requested by EPA for their carcinogenicity classification and chronic toxicity NOEL determination (Hess 1992). Additional histopathological examination for brain tumors in the male rats and a statistical analysis of adrenal medullary neoplastic lesions in the female rats supported the conclusion that there was no carcinogenic potential for imazapyr. Additional evaluation of the female rats for extramedullary hematopoiesis in the spleen and bilateral squamous cysts in the thyroid supported determination of a 10,000 ppm NOAEL for chronic toxicity. [See Section 3.1.5 for a detailed discussion of the significance of these findings and the classification of carcinogenicity by U.S. EPA/OPP (2005a).]			
Dogs, Beagles, 5–6 months old, 6/sex/dose group, 4 dose groups.	0, 1000, 5000, or 10,000 ppm in the diet for 1 year. Based on the summary in U.S. EPA/OPP (2005a, p. 21), the treatment levels correspond to doses of 25, 125, and 250 mg/kg bw/day. [Test material specified as AC 243,997, purity = 99.5%.]	No mortality; no clinical signs of toxicity attributed to treatment, 10,000 ppm considered to be 'no-effect' level. **This the basis for the Chronic RfD:** **NOAEL = 250 mg/kg/day** **Uncertainty Factor: 100**	Shellenberger 1987 MRID No. 41039502

Appendix 2: Toxicity to birds

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A2 Table 1: Acute Oral/Gavage Toxicity to Birds

Species	Exposure	Response	Reference[1]
Quail, Northern bobwhite *(Colinus virginianus)*	**Imazapyr TGAI**, 93% a.e.	LD_{50} >2,510 mg a.e./kg bw. EPA/OPP 2007a, Appendix B No mortality or signs of toxicity. The dose of 2510 mg a.e/kg bw is essentially a NOAEL.	MRID 00131633 From U.S. EPA/OPP 2005b and U.S. EPA/OPP 2007a
Quail, Northern bobwhite (*Colinus virginianus*), 19-weeks old, 5/sex/dose.	**Arsenal Herbicide** 0, 1470, or 2150 mg formulation/kg bw administered via gavage. 21-day observation period. Test substance specified as Arsenal Herbicide. Based on the 0.226 ratio of imazapyr a.e. in Arsenal (Table 2), the doses correspond to imazapyr doses of about 332 and 486 mg a.e/kg bw.	LD_{50} = >486 mg a.e./kg bw No mortality and no abnormal behavioral reactions or systemic signs of toxicity were observed. Gross pathological examination (2/sex/dose) revealed no abnormal tissue alterations.	Fletcher et al. 1984a MRID No. 00153773 Not cited in U.S. EPA/OPP (2006a, 2005b). Cited but not summarized or discussed in U.S. EPA/OPP (2007a).
Ducks, Mallard (*Anas platyrhynchos*)	**Imazapyr TGAI**, 93% a.e.	LD_{50} > 2,510 mg a.e./kg bw. EPA/OPP 2007a, Appendix B No mortality or signs of toxicity. The dose of 2510 mg a.e/kg bw is essentially a NOAEL.	MRID 00131634 From U.S. EPA/OPP 2005b and U.S. EPA/OPP 2007a, Appendix B

A2 Table 1: Acute Oral/Gavage Toxicity to Birds			
Species	**Exposure**	**Response**	**Reference[1]**
Ducks, Mallard *(Anas platyrhynchos)*, 27–30 weeks old, 5/sex/dose.	**Arsenal Herbicide** 0, 1470, or 2150 mg/kg bw 21-day observation period. Test substance specified as Arsenal Herbicide. Based on the 0.226 ratio of imazapyr a.e. in Arsenal (Table 2), the doses correspond to imazapyr doses of about 332 and 486 mg a.e./kg.	LD_{50} = >486 mg a.e./kg bw No mortality and no abnormal behavioral reactions or systemic signs of toxicity were observed. Gross pathological examination (2/sex/dose) revealed no abnormal tissue alterations.	Fletcher et al. 1984b MRID No. 00153774; (Cited in U.S. EPA/OPP 2005b and U.S. EPA/OPP 2007a as 00131634, Bio-Life Assoc., 1983)

A2 Table 2: Acute Dietary Toxicity to Birds

Species	Exposure	Response	Reference[1]
Quail, Northern bobwhite *(Colinus virginianus)*, 11–17 days old at start, 10/dose, body weight of 20–35 g.	**Imazapyr acid** 0, 312, 625, 1250, 2500, or 5000 ppm in the diet for 5 days. Test material specified as AC 243,997. 93% a.e. Based on measured food consumptions, the exposures correspond to doses of 0, 38, 72, 148, 322, and 674 mg a.e./kg bw. Test material specified as AC 243,997. 93% a.e.	No mortality. Study included one control group for each test group. $LC_{50:}$ >5000 mg a.e./kg-diet $LD_{50:}$ >674 mg a.e./kg bw based on measured food consumption.	Fletcher 1983a MRID No. 00131635 (Cited in U.S. EPA/OPP 2005b and U.S. EPA/OPP 2007a as Bio-Life Assoc., 1983)
Quail, Northern, bobwhite *(Colinus virginianus)*, 15-days old, 10/dose.	**Arsenal Herbicide** 0, 312, 625, 1250, 2500, or 5000 ppm in the diet for 5 days and then a basal diet for the next 3 days. Based on the 0.226 ratio of imazapyr a.e. in Arsenal (Table 2) and the food consumption data from Fletcher 1983a, the 5000 ppm level correspond to an imazapyr doses of about 152 mg a.e/kg bw.	No mortality and no abnormal behavioral reactions or systemic signs of toxicity were observed. Gross pathological examination (4 each from the 0, 2500, and 5000 ppm dose groups) revealed no abnormal tissue alterations. LC_{50} = >5000 ppm	Fletcher et al. 1984c MRID No. 00153775; Not cited or summarized in U.S. EPA/OPP 2006a, 2005b. Cited but not discussed in U.S. EPA/OPP 2007a.
Ducks, Mallard *(Anas platyrhynchos)*, 4-days old at start, 10/dose.	**Imazapyr acid** 0, 312, 625, 1250, 2500, or 5000 ppm in the diet for 5 days. Based on measured food consumptions, the exposures correspond to doses of 0, 64, 145, 273, 595, or 1149 mg a.e./kg bw/day.	No mortality. Study included one control group for each test group. 8-day LC_{50} >5000 mg a.e./kg-diet. Working Note: The reason for discrepancies in MRID numbers is not apparent. Both MRID numbers reference the same study.	Fletcher 1983b MRID No. 00133553 Cited in U.S. EPA/OPP 2005b and U.S. EPA/OPP 2007a as MRID 00131636. U.S. EPA/OPP 2006a cites MRID 00133553

A2 Table 2: Acute Dietary Toxicity to Birds

Species	Exposure	Response	Reference[1]
Ducks, Mallard *(Anas platyrhynchos)*, 5-days old, 10/dose.	**Arsenal Herbicide** 0, 312, 625, 1250, 2500, or 5000 ppm in the diet for 5 days and then a basal diet for the next 3 days. Based on the 0.226 ratio of imazapyr a.e. in Arsenal (Table 2) and the food consumption data from Fletcher 1983b, the 5000 ppm level correspond to an imazapyr doses of about 260 mg a.e/kg bw.	No mortality and no abnormal behavioral reactions or systemic signs of toxicity were observed. Gross pathological examination (4 each from the 0, 2500, and 5000 ppm dose groups) revealed no abnormal tissue alterations. LC_{50} = >5000 ppm Note: U.S. EPA/OPP (2007a) considers the study to be scientifically sound; however, test concentrations in the diets were not analytically verified and the toxicity values are based on the nominal concentrations.	Fletcher et al. 1984d MRID No. 00133776 U.S. EPA/OPP 2007a: study classified as *Supplemental* for a formulated product. See note in Column 3. Not cited or summarized in U.S. EPA/OPP 2006a, 2005b.

A2 Table 3: Reproduction Studies in Birds

Species	Exposure	Response	Reference[1]
Reproduction			
Quail, Northern bobwhite *(Colinus virginianus)*, young adults, 12 males and 24 females per dose.	Imazapyr acid 0, 500, 1000, or 2000 ppm in the diet for 18 weeks. [50, 100, or 200 mg/kg bw based on measured food consumption (i.e., the birds consumed approximately 10% body weight as specified in Table I of the study)]. [Test material specified as AC 243,997 Technical.]	No significant reductions for any of the reproductive endpoints examined (i.e., egg production, hatchability, survival of hatchlings). NOEC for reproductive effects = 2000 ppm. Mortality among the birds was as follows: 0 ppm = 2M, 5F 500 ppm = 1M, 4F 1000 ppm = 1M, 3F 2000 ppm = 0M, 5F No dose-response relationship. **U.S. EPA/OPP 2005b**: No treatment-related toxicity NOAEC = 2000 mg a.e./kg-diet LOAEC = >2000 mg a.e./kg-diet	Fletcher et al. 1995a MRID No. 43831401; Cited in U.S. EPA/OPP 2005b and U.S. EPA/OPP 2007a as same MRID, but with year as 1987, which appears to be a typo. The correct year is given in reference list to U.S. EPA/OPP 2006a.

A2 Table 3: Reproduction Studies in Birds

Species	Exposure	Response	Reference[1]
Quail, Northern bobwhite *(Colinus virginianus)*, 16 weeks old at start of study, 16 pairs of male and female birds	Imazapyr acid, 100% a.e. Measured dietary concentrations of 0, 327, and 1670 ppm a.e. Total Exposure Period: 147 days. Mean BW: ≈ 0.2 kg Mean food consumption: ≈0.073 kg/d Food consumption factor: ≈0.365.	No treatment-related toxicity in adults or offspring. No effect on reproductive parameters. NOAEC = 1670 mg a.e./kg-diet LOAEC = >1670 mg a.e./kg-diet U.S. EPA/OPP Classification: Core **NOAEC use by U.S. EPA/OPP 2007a for risk characterization.** Based on mean food consumption and mean BW, 1670 ppm a.e. corresponds to a dose of ≈610 mg a.e./kg bw.	Ahmed et al. 1999 MRID 45119714 Reviewed by U.S. EPA/OPP 2005b; U.S. EPA/OPP 2007a
Ducks, Mallard *(Anas platyrhynchos)*, approximately 23-weeks old, 16/sex/dose.	Imazapyr acid 0, 500, 1000, or 2000 ppm in the diet for 18 weeks. [50, 100, or 200 mg/kg bw based on measured food consumption (birds consumed approximately 10% body weight as specified in Table II of fiche.)] [Test material specified as AC 243,997 Technical.]	No significant reductions for any of the reproductive endpoints examined (i.e., egg production, hatchability, survival of hatchlings). NOEC for reproductive effects = 2000 ppm. **U.S. EPA/OPP 2005b**: No treatment-related toxicity based on measured concentrations in diet: NOAEC = 1890 mg a.e./kg-diet LOAEC = >1890 mg a.e./kg-diet	Fletcher et al. 1995b MRID No. 43831402; Cited in U.S. EPA/OPP 2005b and U.S. EPA/OPP 2007a as same MRID, but with year as 1987, which appears to be a typo
Ducks, Mallard *(Anas platyrhynchos)*, approximately 30-weeks old at start of study, 16/sex/dose.	Imazapyr acid, 100% a.e. Measured dietary concentrations of 0, 327, and 1670 ppm a.e. Mean BW: ≈ 1.2 kg Mean food consumption: ≈0.165 kg/d Food consumption factor: ≈0.138.	U.S. EPA/OPP DER 3/29/2003 **Scientifically INVALID due to bacterial contamination and high embryonic mortality in the control group** Working Note: This is cited for completeness but is not used in the Forest Service risk assessment.	Ahmed et al. 1999 MRID 45119714

Appendix 3: Toxicity to Terrestrial Plants

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A3 Table 1: Vegetative Vigor

<table>
<tr><th>Form</th><th>Exposure</th><th>Species/Response</th><th>Reference</th></tr>
<tr><td>Monocots</td><td></td><td></td><td></td></tr>
<tr><td>Acid, 22.6% a.e.</td><td>Post-emergence/foliar applications. Green house at 24 C. Technical grade acid in 1:1 (v/v) solution of acetone and water and sprayed at 400 L/ha with laboratory belt sprayer. Tween 20 surfactant added to spray solution at 0.25% (v/v). Five seedlings per pot, 3-replicate pots per application rate.</td><td>Summary from U.S. EPA/OPP 2005b, p. 56
<table>
<tr><th rowspan="2">Species</th><th rowspan="2">End-point</th><th colspan="2">lb a.e./acre</th></tr>
<tr><th>EC_{25}</th><th>NOAEC</th></tr>
<tr><td>Corn</td><td>Weight</td><td>>0.0156</td><td>0.0078</td></tr>
<tr><td>Oat</td><td>Height</td><td>0.013</td><td>0.0039</td></tr>
<tr><td>Wheat</td><td>Weight</td><td>0.012</td><td>0.0039</td></tr>
</table>
Values in bold used by U.S. EPA/OPP 2005b (Table IVA-11, p. 63) for risk assessment.
Additional discussion in Appendix E of RED (U.S. EPA/OPP 2005h).</td><td>American Cyanamid 1988b, MRID 40811801, Supplemental</td></tr>
<tr><td>IPA salt</td><td>Test substance specified as AC 252.925 in a 2 lb per gallon aqueous salt (2AS). A single application was made using an overhead track sprayer applied to emerged seedlings. 28-day observation period.

Based on EPA review by Carey et al. (2006), no surfactant was used in this study.</td><td>Summary from U.S. EPA/OPP 2005b, p. 56
<table>
<tr><th rowspan="2">Species</th><th rowspan="2">End-point</th><th colspan="2">lb a.e./acre</th></tr>
<tr><th>EC_{25}</th><th>NOAEC</th></tr>
<tr><td>Onion</td><td>Dry weight</td><td>0.012</td><td>0.005*</td></tr>
</table>
* Uses EC_{05} rather than NOAEC.

Working Note: EC05/NOAEC listed as 0.0039 lb a.e./acre in Table IVA-11 of U.S. EPA/OPP 2005b. Appears to be a double a.i. to a.e. correction.
Working Note: Cited as Feutz and Canez 1995 in U.S. EPA/OPP 2005b, p. 56 but is listed as Christensen et al. 1995 in bibliography (p. 92).</td><td>Christensen et al. 1995 MRID No. 43889101</td></tr>
</table>

A3 Table 1: Vegetative Vigor

<table>
<tr><th>Form</th><th>Exposure</th><th>Species/Response</th><th>Reference</th></tr>
<tr><td>Dicots</td><td></td><td></td><td></td></tr>
<tr><td>Acid, 22.6% a.e.</td><td>Post-emergence/foliar applications. Green house at 24 C. Technical grade acid in 1:1 (v/v) solution of acetone and water and sprayed at 400 L/ha with laboratory belt sprayer. Tween 20 surfactant added to spray solution at 0.25% (v/v). Five seedlings per pot, 3-replicate pots per application rate.</td><td>Summary from U.S. EPA/OPP 2005b, p. 56
<table>
<tr><th rowspan="2">Species</th><th rowspan="2">End-point</th><th colspan="2">lb a.e./acre</th></tr>
<tr><th>EC_{25}</th><th>NOAEC</th></tr>
<tr><td>Sugar beet</td><td>Weight</td><td>0.00097</td><td>0.00039*</td></tr>
<tr><td>Sunflower</td><td>Weight</td><td>0.0054</td><td>0.0039</td></tr>
<tr><td>Cucumber</td><td>Height</td><td>0.0009</td><td>0.000064*</td></tr>
<tr><td>Tomato</td><td>Weight</td><td>>0.0156</td><td>0.00097</td></tr>
</table>
Values in bold used by U.S. EPA/OPP 2005b (Table IVA-11, p. 63) for risk assessment.
* Uses EC_{05} rather than NOAEC.
Additional discussion in Appendix E of RED (U.S. EPA/OPP 2005h).</td><td>American Cyanamid 1988b, MRID 40811801, Supplemental</td></tr>
<tr><td>IPA salt</td><td>Test substance specified as AC 252.925 in a 2 lb per gallon aqueous salt (2AS). A single application was made using an overhead track sprayer applied to emerged seedlings. 28-day observation period.</td><td>Summary from U.S. EPA/OPP 2005b, p. 56
<table>
<tr><th rowspan="2">Species</th><th rowspan="2">End-point</th><th colspan="2">lb a.e./acre</th></tr>
<tr><th>EC_{25}</th><th>NOAEC</th></tr>
<tr><td>Soybean</td><td>Shoot length</td><td>0.034</td><td>0.008</td></tr>
<tr><td>Sugar beet</td><td>Dry weight</td><td>0.002</td><td>0.001</td></tr>
</table></td><td>Christensen et al. 1995 MRID No. 43889101

Cited as Feutz and Canez 1995 in U.S. EPA/OPP 2005b but no reference in MRID listing.</td></tr>
</table>

A3 Table 2: Seedling Emergence

<table>
<tr><th>Form</th><th>Exposure</th><th>Species/Response</th><th>Reference</th></tr>
<tr><td colspan="4">Monocots</td></tr>
<tr><td>Acid, 22.6% a.e.</td><td>Each crop planted in 4-inch Dixie cups filled with sand. Ten seeds per cup. Spray applications of 0.00219 to 1.12 kg/ha in acetone water solution.</td><td>Summary from U.S. EPA/OPP 2005b, p. 56
<table>
<tr><th rowspan="2">Species</th><th rowspan="2">End-point</th><th colspan="2">lb a.e./acre</th></tr>
<tr><th>EC_{25}</th><th>NOAEC</th></tr>
<tr><td>Oat</td><td>Height</td><td>0.054</td><td>0.0156</td></tr>
<tr><td>Onion</td><td>Weight</td><td>0.034</td><td>0.01*</td></tr>
<tr><td>Wheat</td><td>Weight</td><td>0.0046</td><td>0.00099*</td></tr>
</table>
Values in bold used by U.S. EPA/OPP 2005b (Table IVA-11, p. 63) for risk assessment. Values with an asterisk designate EC_{05}s rather than NOAELs.
Additional discussion in Appendix E of RED (U.S. EPA/OPP 2005h).</td><td>American Cyanamid 1988b, MRID 40811801, Supplemental</td></tr>
<tr><td>Barley, corn, cotton, sorghum, sugar beets, sunflower, and wheat.</td><td>Sprayed application of 400 L/ha to give rates up to 63 g/ha; 34-day observation period. [Test substance specified as Arsenal Herbicide (technical grade, purity NOS.]</td><td>The test substance at 63 g/ha or less has little to no effect on the seedling emergence of the crop species tested. Higher levels delayed or significantly reduced seedling emergence. The test substance is a potent inhibitor of plant growth, at 63 g/ha, severe growth inhibition and mortality of all species tested. Sugar beets were noted with being the most susceptible and soybeans being the most tolerant.</td><td>Malefyt 1986 MRID No. 40003711, Supplemental</td></tr>
<tr><td colspan="4">Dicots</td></tr>
<tr><td>Acid, 22.6% a.e.</td><td>Each crop planted in 4-inch Dixie cups filled with sand. Ten seeds per cup. Spray applications of 0.00219 to 1.12 kg/ha in acetone water solution.</td><td>Summary from U.S. EPA/OPP 2005b, p. 56
<table>
<tr><th rowspan="2">Species</th><th rowspan="2">End-point</th><th colspan="2">lb a.e./acre</th></tr>
<tr><th>EC_{25}</th><th>NOAEC</th></tr>
<tr><td>Sugar beet</td><td>Weight</td><td>0.0024</td><td>0.00017*</td></tr>
<tr><td>Tomato</td><td>Weight</td><td>0.008</td><td>0.0003</td></tr>
</table>
Values in bold used by U.S. EPA/OPP 2005b (Table IVA-11, p. 63) for risk assessment.
* Uses EC05 rather than NOAEC.
Additional discussion in Appendix E of RED (U.S. EPA/OPP 2005h).</td><td>American Cyanamid 1988b, MRID 40811801, Supplemental</td></tr>
</table>

A3 Table 2: Seedling Emergence

Form	Exposure	Species/Response	Reference
Rejected study			
Barley, corn, cotton, sorghum, sugar beets, sunflower, and wheat.	Sprayed application of 400 L/ha to give rates up to 63 g/ha; 34-day observation period. [Test substance specified as Arsenal Herbicide (technical grade, purity NOS.]	The test substance at 63 g/ha or less has little to no effect on the seedling emergence of the crop species tested. Higher levels delayed or significantly reduced seedling emergence. The test substance is a potent inhibitor of plant growth, at 63 g/ha, severe growth inhibition and mortality of all species tested. Sugar beets were noted with being the most susceptible and soybeans being the most tolerant. U.S. EPA/OPP (2005h, E-8) Commentary: *Only descriptive summary data was presented; consequently effect levels were not determined. Observed effects included chlorosis, stunting, leaf tip burning, necrosis, and plant death.* Working Note: Have DER from Cleared Reviews.	Malefyt 1986 MRID No. 40003711, Supplemental

A3 Table 3: Seed Germination			
Form	**Exposure**	**Species/Response**	**Reference**
Acid, 22.6% a.e.	Seed germination: cucumber, soybean, wheat, onions, peas, tomato, corn, sugar beets, sunflower, and oats. Seeds on filter paper in Petri dish. Chemical dissolved in acetone/water. Each dish sprayed at rates from 0.035 to 1.12 kg/ha.	Tomatoes: EC_{50} = 1.120 kg/ha Sugar beet: EC_{25} = 0.140 kg/ha	American Cyanamid 1988b, MRID 40811801, Supplemental
AC 243,997 (99.1% purity	Test substance sprayed into Petri dishes (10 seeds per dish) at a concentration of 35, 70, 140, 280, 560, and 1120 g/ha. [Test substance specified as AC 243,997 (99.1% purity).]	Corn, cucumber, oats, onion, peas, soybean, sugar beets, sunflowers, tomatoes, and wheat. The test substance has no statistically significant effect on the germination of cucumber, soybean, wheat, onion, and peas. Tomatoes and corn showed a significant reduction in germination at the highest rate of 1.12 kg/ha. No significant reduction was observed at lower rates. Sugar beet, sunflower, and oats showed some reduction in germination.	Malegyt 1990a MRID No. 93048029

A3 Table 4: Other Toxicity Studies

Species	Exposure	Response	Reference
One monocot and four dicots (see Column 3)	Foliar application of the isopropylamine salt of imazapyr (formulation not specified) to potted plants. Application rates of 0, 0.015, 0.029, 0.051, 0.10, 0.20, 0.41, and 0.81 lb a.e./acre. Measures of dry weight made at 12 months after application.	Plant / Approx. NOEC (lb a.e./acre) / Approx. LOEC (lb a.e./acre) Grass: 0.051 / 0.1 Pea: ND / 0.015 Legume: 0.015 / 0.029 Cabbage: ND / 0.015 Pumpkin: 0.81 / ND See supplemental table below.	Bovey and Senseman 1998
Potatoes (*Solanum tuberosum*), dicot	Drift/foliar exposures. 0.02, 0.1, and 0.5 lb/acre . `Working Note: The formulation is not specified. Units given as "a.i." but the salt (if any) is not specified`	0.02 lb/acre : Little damage at when applied at any stage (emergence, tuber initiation, or tuber bulking). 0.1 and 0.5 lb/acre: Substantial and dose related damage (assessed as visual injury). See Figure 1 in publication. No tabular summary of data.	Eberlein and Guttieri 1994
Several species of tree: alder, poplar, Fritzi pauley, Rap, willow, and Bowles hybrid	Imazapyr applied as a soil drench to potted trees at rates equivalent to 0.2, 0.8, and 3.2 kg a.i./ha [≈0.15, 0.58, and 2.3 lb a.e./acre assuming the IPA salt was the a.i.].	Results are not given as means of all application rates combined. Severe damage to all trees. No growth (based on shoot fresh weight) in Rap and willow. This study cannot be used quantitatively.	Lawrie and Clay 1989
Cuscuta campestris (field dodder) [target] and sorghum and *Amaranthus blitoides* (prostrate amaranth)	Petri dish assays in sand, up to 6 days.	Species / EC_{50} µM / EC_{50} mg/L *Cuscuta campestris*: >1000 / >261.3 Sorghum: 1.5 / 0.392 *Amaranthus blitoides* (sulfonylurea tolerant): 140 / 36.6 *Amaranthus blitoides* (sulfonylurea sensitive): 12 / 3.13	Nadler-Hassar and Rubin 2003

Supplemental Table for Bovey and Senseman (1998): Effect of imazapyr on dry weight (% of control) at 12 months after foliar application.

lb a.e./acre	Species [1] (Description)				
	Brachiaria dictyoneura	*Centrosema acutifolium*	*Stylosanthes capitata*	*Brassica oleracea*	*Cucurbita pepo*
	(Grass)	(Pea)	(Legume)	(Cabbage)	(Pumpkin)
0.015	152.8	83.9	100.0	77.6	108.4
0.029	112.0	71.8	72.0	21.1	98.4
0.051	108.8	79.9	64.0	20.5	101.3
0.10	64.0	54.4	44.0	11.8	103.9
0.20	38.4	59.1	16.0	5.0	102.7
0.41	15.2	57.7	12.0	9.3	98.6
0.81	4.0	20.1	12.0	5.0	69.5

Source: Modified from Table 3 in Bovey and Senseman (1998, p. 616).

Appendix 4: Toxicity to fish.

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A4 Table 2: Chronic toxicity 186

A4 Table 1: Acute Toxicity

Species	Exposure	Response	Reference
Sunfish, Bluegill (*Lepomis macrochirus*)	**Imazapyr acid** Nominal concentrations of the test substance were 0, 10, 18, 32, 53, and 100 mg/L (81–93% nominal). [Test substance specified as AC 243,997 (99.5% purity).]	96-hour LC_{50} >100 mg/L Cited but not reviewed in U.S. EPA/OPP 2005a,b. Not cited in U.S. EPA/OPP 2007a.	Kintner and Forbis 1983a MRID No. 00133549
Silversides, Atlantic (*Menidia menidia*)	**Imazapyr acid** Mean measured concentrations of the test substance were 0, 23.2, 39.5, 58.1, 112, and 184 mg/L (81–93% nominal). [Test substance specified as AC 243,997 (99.5% purity).] Working Note: Referenced as imazapyr IPA in U.S. EPA/OPP 2005h but as acid in U.S. EPA/OPP 2005b. The latter is correct.	NOAEC (mortality) >184 mg a.e./L The test substance was not acutely toxic at concentrations up to 184 mg a.e./L. After 96 hours of exposure, mortality did not exceed 5% in any of the test concentrations.	Manning 1989a MRID No. 41315801 Reviewed in U.S. EPA/OPP 2005a, h Not cited in U.S. EPA/OPP 2007a.
Sunfish, Bluegill (*Lepomis macrochirus*)	**Imazapyr acid**	96-hour LC_{50}: >100 mg a.e./L	MRID 131629 from U.S. EPA/OPP 2005b, 2007a Appendix B
Trout, Rainbow (*Oncorhynchus mykiss*)	**Imazapyr acid**	96-hour LC_{50}: >100 mg a.e./L	MRID 131629 from U.S. EPA/OPP 2005b, 2007a Appendix B
Channel catfish (*Ictalurus punctatus*)	**Imazapyr acid**	96-hour LC_{50}: >184 mg a.e./L	MRID 00131631 from U.S. EPA/OPP 2005b, 2007a Appendix B
Sunfish, Bluegill (*Lepomis macrochirus*), 10/concentration.	**Imazapyr IPA** Nominal concentrations of the test substance were 0, 56, 100, 180, 320, 560, and 1000 mg/L. [Test substance specified as AC 252,925 (combination of AC 243,997 with isopropylamine in water).]	No mortality at any level tested. 96-hour LC_{50} >1000 mg a.i./L >≈815.5 mg a.e./L	Cohle and McAllister 1984a MRID No. 00147116

A4 Table 1: Acute Toxicity

Species	Exposure	Response	Reference
Trout, Rainbow (*Salmo gairdneri*), 20/concentration .	**Imazapyr IPA?** Flow-Through: Mean measured concentrations of a.e. were 13, 29, 39, 68, and 110 mg a.e./L. `Working Note: U.S. EPA/OPP 2005h and 2007a refer to the test agent are imazapyr IPA rather than a formulation. The study title indicates that the Arsenal Herbicide formulation was used.`	96-hour LC_{50}: >110 mg a.e./L NOAEC: 110 mg a.e./L No test substance-related mortalities occurred.	Drotter et al. 1995 MRID No. 45119713 Toxicity values from U.S. EPA/OPP 2007a, Appendix B.
Sunfish, Bluegill (*Lepomis macrochirus*), 10/concentration .	**Arsenal Herbicide** Nominal concentrations of the test substance were 0, 56, 100, 180, 320, 560, and 1000 mg formulation /L (81–93% nominal). Test substance specified as Arsenal Herbicide (22.6% a.e.).	96-hour LC_{50} 180 mg formulation/L ≈40.68 mg a.e./L 96-hour Mortality data Conc. Form. / Resp. / No. / % Resp. 0 / 0 / 10 / 0 56 / 1 / 10 / 10 100 / 2 / 10 / 20 180 / 6 / 10 / 60 320 / 7 / 10 / 70 560 / 9 / 10 / 90 1000 / 10 / 10 / 100 Abnormal effects associated with mortality in responding fish included dark and light discoloration and quiescence were observed at all concentrations during the 96-hour exposure period.	Cohle and McAllister 1984b MRID No. 00153777 Not cited in U.S. EPA/OPP 2005b, 2006a, 2007a

A4 Table 1: Acute Toxicity

Species	Exposure	Response	Reference
Trout, Rainbow (*Salmo gairdneri*), 10/concentration .	**Arsenal Herbicide** Nominal concentrations of the test substance were 0, 32, 56, 100, 180, and 320 mg formulation/L. Nominal concentrations as a.e.: 6.0, 10.4, 18.9, 33.4 and 59.3 mg a.e./L (U.S. EPA/OPP 2007a, Appendix B, p. 12) Test substance specified as Arsenal Herbicide (22.6% a.e.).	96-hour LC_{50} 112 mg formulation/L ≈20.8 mg a.e./L NOAEC (sublethal effects) 10.4 mg a.e./L LOAEC (sublethal effects) 18.9 mg a.e./L 96-hour Mortality data Conc. Form. / Resp. / No. / % Resp. 0 / 0 / 10 / 0 32 / 1 / 10 / 10 100 / 5 / 10 / 50 180 / 9 / 10 / 90 320 / 9 / 10 / 90 *Effects included surfacing, loss of equilibrium, dark discoloration, fish on bottom and quiescence in the nominal 100, 180, and 320 mg Arsenal/L treatment groups by 96 hours.* – U.S. EPA/OPP 2007a, Appendix B. Classification: Supplemental	Cohle and McAllister 1984c MRID No. 00153778 Toxicity values from U.S. EPA/OPP 2007a, Appendix B.
Trout, Rainbow (*Salmo gairdneri*)	96-hours	LC_{50} >100 mg/L	Peoples 1984 Gagne et al. 1991
Sunfish, Bluegill (*Lepomis macrochirus*)	96-hours	LC_{50} >100 mg/L	Peoples 1984 Gagne et al. 1991
Catfish, Channel	96-hours	LC_{50} >100 mg/L	Peoples 1984 Gagne et al. 1991
Working Note: The above three entries are clearly secondary reference to the registrant submitted studies summarized elsewhere in the table.			
Nile tilapia (*Tilapia nilotica*).	Static acute toxicity testing in 2−3 cm fingerlings.	24-hour LC_{50} = 4670 µg/L (4442−4919 µg/L); 48-hour LC_{50} = 4630 µg/L (95% CI: not indicated); 72-hour LC_{50} = 4610 µg/L (95% CI: 4307−4878 µg/L); 96-hour LC_{50} = 4360 µg/L (95% CI: 4207−4529 µg/L).	Supamataya et al. 1981
Silver barb (*Barbus gonionotus*).	Static acute toxicity testing in 2−3 cm fingerlings.	24-hour LC_{50} = 2706 µg/L (95% CI: 2664−2746 µg/L); 96-hour LC_{50} = 2706 µg/L (95% CI: 2664−2746 µg/L).	Supamataya et al. 1981
Working Note: The study by Supamataya et al. 1981 (1981) was identified but rejected by U.S. EPA/OPP 2007a, Appendix H. Rejection Code: NO FOREIGN. This study is discussed in Section 4.1.3.1 (Hazard Identification) but is not used quantitatively in the current Forest Service risk assessment. The units (a.i./a.e./formulation) in which the data are reported is not clear from the study abstract.			

A4 Table 2: Chronic toxicity

Species	Exposure	Response	Reference
Fathead minnow (*Pimephales promelas*).	**Imazapyr acid** **Early life-stage (egg-to-fry)** Nominal concentrations of 7.5, 15, 30, 60, and 120 mg a.i./L. Test substance specified as AC 243997.	NOAEC = 120 mg a.e./L There were no apparent treatment-related effects on time to hatch, hatching success, reproduction, or growth. All biological parameters measured in the treatment groups were comparable and not statistically differ (p>0.05) to negative control fish. Working: Cited in U.S. EPA/OPP 2007a both as "a.i." (in text) and "a.e." in table (p. 13). The a.e. designation appears to be correct.	Drotter et al. 1998 MRID No. 45119711 Cited in U.S. EPA/OPP 2007a, Appendix B as well as U.S. EPA/OPP 2005b and 2005h.
Fathead minnow (*Pimephales promelas*), 20 per replicates, 4 replicates.	**Imazapyr acid** **Full Life Cycle** Mean measured concentrations of 7.4, 15, 31, 62, and 118 mg a.e./L. Test substance specified as AC 342997 (99.6% purity). F1 generation maintained for only 4 weeks rather than 8 weeks per guidelines.	NOAEC: 118 mg a.e./L No apparent treatment-related effects on time to hatch, hatching success, survival, or growth of fathead minnow for 28-days post-hatch.	Drotter et al. 1999 MRID No. 45119712 Cited in U.S. EPA/OPP 2007a, Appendix B as well as U.S. EPA/OPP 2005b and 2005h.
Trout, Rainbow, early life-stage (28-day post swim-up), 20 trout per concentration.	**Imazapyr acid** **Early life-stage (egg-to-fry)** Measured concentrations of 0, 6.59, 12.1, 24.0, 43.1, or 92.4 mg/L for 62 days. Test material specified as AC 243,997.	NOAEC: 43.1 mg a.e/L LOAEC: 92.4 mg a.e./L U.S. EPA/OPP (2005h): *significantly reduced percent hatch and an observed reduction on survival at 92.4 mg/L. No abnormalities in embryonic or juvenile development were observed.*	Manning 1989b MRID No. 41315804 Cited in U.S. EPA/OPP 2007a, Appendix B as well as U.S. EPA/OPP 2005b and 2005h.

Appendix 5: Toxicity to aquatic invertebrates

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A5 Table 1: Acute Toxicity

Species	Exposure	Response	Reference
Daphnia magna, <24-hours old, 5 replicates per concentration 10 animals per replicate.	**Imazapyr Acid** 0, 10, 18, 32, 56, or 100 mg/L for 48 hours. Static, no aeration. Test material specified as AC 243,997 Technical	No mortality at 24 or 48 hours of exposure. 24-hour LC_{50} = >100 mg/L 48-hour LC_{50} = >100 mg/L Classification: Core. Working Note: This study appears to be covered as MRID 00131632 in U.S. EPA/OPP (2007a, Appendix B, 2005h)	Kintner and Forbis, 1983b MRID No. 00133550 Cited in U.S. EPA/OPP 2007.
Daphnia magna	**Imazapyr IPA** Static, 48-hours, no solvent 0, 56, 100, 180, 320, 560, and 1000 mg a.i./L	EC_{50}: 614 mg a.e./L (750 mg a.i./L) Mortality only at 1000 mg a.i./L, 85% at 24 hours and 100% at 48 hours. DER does not discuss any signs of sublethal toxicity. Classification: Core.	Forbis et al. 1984a MRID 00147117 Cited in U.S. EPA/OPP 2007a, Appendix B.
Oyster, Eastern (*Crassostrea virginica*), 20/concentration.	**Imazapyr acid** Mean measure concentrations of 16, 27, 46, 80, and 132 mg a.e./L. 96-hour flow-through test. Test substance specified as AC 243,997 (99.6% purity).	NOAEC: 132 mg a.e./L Working Note: NOAEC cited as 132 mg a.i./L in U.S. EPA/OPP 2005h. The agent tested, however, was the acid – i.e., a nomenclature issue only. Mean oyster new shell deposition (growth) in the negative control was 2.46 mm. Mean shell growth in the 16, 27, 46, 80, and 132 mg a.i./L treatment groups was 2.51, 2.72, 2.70, 2.05, and 2.03 mm, respectively. Oyster shell growth was not significantly reduced in any treatment group. When compared to negative control, percentage of shell growth inhibition ranged from -11% in the 27 mg a.i./L to 17% in the 80 and 132 mg a.i./L treatment groups.	Drotter et al. 1997 MRID No. 45119710 Cited in U.S. EPA/OPP 2005h but not 2007a.

A5 Table 1: Acute Toxicity			
Species	**Exposure**	**Response**	**Reference**
Oyster, Eastern (*Crassostrea virginica*).	**Imazapyr acid** Measured concentrations of the test substance were <10.5, 21.5, 42.4, 65.5, 109, and 173 mg a.e./L. Test substance specified as AC 243,997 (99.5%).	NOAEC: 109 mg a.e./L. LOAEC: 173 mg a.e./L (decreased mean shell deposition) `Working Note: NOAEC and LOAEC cited as mg a.i./L in U.S. EPA/OPP 2005h. The agent tested, however, was the acid – i.e., this is a nomenclature issue only.` Mean new shell growth ranged from 1.25 mm in the 21.5 mg/L to 0.69 mm in the 173 mg/L test concentration. No mortality occurred at any test concentrations. There was a concentration-response relationship; the percentage reduction in new shell growth ranged from 8% (21.5 mg/L) to 49% (173 mg/L). There was a statistical difference in new shell growth between the oysters exposed to 173 mg/L and the controls. Authors state that "*there was no correlation with pH and test concentration; the higher the concentration the lower the pH. The effect observed at 173 mg/L may have been a response of the lower pH rather than directly to the test substance*." This is to be expected for a weak acid.	Ward 1989 MRID No. 41315802
Pink shrimp.	**Imazapyr acid** 96-hour flow-through	LC_{50}: > 189 mg a.e./L NOAEC: 189 mg a.e./L (no overt sublethal effects).	MRID 41315803 in U.S. EPA/OPP 2005h. Not cited in U.S. EPA/OPP 2007a Cleared review not available.
Acute data on Arsenal formulation continued on next page.			

A5 Table 1: Acute Toxicity

<table>
<tr><th>Species</th><th>Exposure</th><th>Response</th><th>Reference</th></tr>
<tr>
<td>Daphnia magna</td>
<td>Arsenal Herbicide (22.6% a.e).]
Nominal: 0, 32, 56, 100, 180, 320, 560, and 1000 mg formulation/L.
U.S. EPA/OPP 2007a, Appendix B, p. 14 adjustment: 0, 5.9, 10.4, 18.5, 59.3, 103.8, 185.3 mg a.e./L

Note: The above concentrations appear to assume that the herbicide contained 22.6% a.i. and an additional factor of 0.8155 is applied to calculated the a.e. This appears to be an error.</td>
<td>U.S. EPA/OPP 2007a, Appendix B
48-hour LC_{50}: 64.9 mg a.e./L
NOAEL: 59.3 mg a.e./L
LOAEL: 103.8 mg a.e./L

U.S. EPA/OPP 2006 DER
48-hour LC_{50}: 350 mg formulation/L (79.1 mg a.e./L)
NOAEL: 180 mg formulation./L (40.68 mg a.e./L)
LOAEL: 320 mg a.e./L (81.36 mg a.e./L)
DER notes that the NOAEL is based on sublethal effects.
Classification: Supplemental (Formulation).

Dose/Response Data
<table>
<tr><th>Conc. Form. mg/L</th><th>Conc. Acid (mg a.e./L)[1]</th><th>Mortality</th><th>Number Exposed</th></tr>
<tr><td>0</td><td>0</td><td>0</td><td>20</td></tr>
<tr><td>32</td><td>7.23</td><td>0</td><td>20</td></tr>
<tr><td>56</td><td>12.7</td><td>0</td><td>20</td></tr>
<tr><td>100</td><td>22.6</td><td>0</td><td>20</td></tr>
<tr><td>180</td><td>40.7</td><td>0</td><td>20</td></tr>
<tr><td>320</td><td>72.3</td><td>9</td><td>20</td></tr>
<tr><td>560</td><td>127</td><td>18</td><td>20</td></tr>
<tr><td>1000</td><td>226</td><td>20</td><td>20</td></tr>
</table>
[1] Based on 22.6% a.e. in formulation.
Test solutions not assayed for imazapyr.

Reanalysis in BDMS 2.2 (U.S. EPA/ORD 2011b)
Trend: $p<0.0001$
EC_{10}: 52.4 mg a.e./L
Lower Limit: 42.1 mg a.e./L
EC_{50}: 79.3 mg a.e./L
Lower Limit: 70.3 mg a.e./L

Study Author:
The NOEC was 180 mg formulation/L after 48 hours, based on the lack of mortality and abnormal effects. Mortality data at 48 hours is as follows: 320 (45%), 560 (90%), and 1000 mg/L (100%).</td>
<td>Forbis et al. 1984b MRID No. 00153779

Cited in U.S. EPA/OPP 2007a.

Note to Reviewers: The DER is in the Scans directory on the CD as Forbis et al. 1984b.</td>
</tr>
</table>

A5 Table 2: Chronic toxicity

Species	Exposure	Response	Reference
Daphnia magna, <26-hours old, 4 replicates per concentration, 10 animals per replicate.	**Imazapyr acid** Measured concentrations of <2.63 (control) 5.73, 11.7, 23.8, 45.6, or 97.1 mg/L in a 21-day flow-through test. [Test material specified as AC 243,997 (99.5% a.i.)]	LC_{50}: >97.1 mg a.e./L; NOEC = 97.1 mg a.e./L; No adverse effects on survival, reproduction, or growth of 1st generation. Classification: Acceptable.	Manning 1989c MRID No. 41315805 Reviewed in U.S. EPA/OPP 2005h and 2007a, Appendix B

A5 Table 3: Bioconcentration/Kinetic Studies

Species	Exposure	Response	Reference
Clam, freshwater (*Corbicula fluminea*), 400 clams.	Single application at nominal rates of 0 or 0.091 lb a.e./acre to a model freshwater pool system. 28-day observation period. [Test substance specified as Arsenal Herbicide (purity NOS).]	The concentrations of the test substance in clam tissue was less than the limit of quantification (<50 ppb) during the conduct of the test.	Christensen et al. 1999 MRID No. 45119722
Oyster, Eastern (*Crassosstrea virginica*) and Grass shrimp (*Paleomonetes pugio*).	The bioconcentration test consisted of a 28-day uptake phase followed by a 14-day depuration phase. During the uptake phase, test concentrations consisted of a mixture of radiolabelled or non-radiolabelled test substance at a total nominal concentration of 0.25 mg a.i./L. [Test substance specified as AC 243,997 (purity NOS).]	The test substance was not found to bioconcentrate in the Eastern oyster. Tissue concentrations of the test substance did not exceed the exposure concentration. Steady-state BCF = <1 (not calculable) Uptake rate = not calculable Depuration rate = not calculable	Drotter et al. 1996 MRID No. 45119709

A5 Table 4: Field/Microcosm Studies			
Species	**Exposure**	**Response**	**Reference**
Mixed macroinvertebrate community in logged pond cypress dome with *Carex* spp. as the dominant emergent macrophyte.	Microcosm with 0.184, 1.84, and 18.4 mg a.e./L. Microcosms *in situ* with 2 week acclimation period and 2 week exposure period. Arsenal Applicators Concentrate (479 g a.e./L).	**Abundance** *Caecidotea* and *Procladius*: Significant increase in abundance but no clear concentration-response relationship. No effect on other organisms: *Crangonyx*, dipterans, chironomids, *Polypedilum*, *Chironomus*, *Ablabesmyia*, and *Procladius*. **Taxa Richness** No impacts on total species richness as well as dipteran and chironomid richness. See paper Table 5 for details. U.S. EPA/OPP 2007a, Appendix B *These results are of limited value because potential effects at the species level were not examined. Individual species could have been affected and the results may not have picked it up because the analysis was conducted at higher taxonomic levels. In addition, effects on aquatic plants were not examined.*	Fowlkes et al. 2003

Appendix 6: Toxicity to Aquatic Plants

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A6 Table 2: Toxicity data in Aquatic Macrophytes..... 194
A6 Table 3: Field/Field Simulation Studies..... 195

A6 Table 1: Toxicity data in Algae

Species	Exposure	Response	Reference
Selenastrum capricornutum, a green algae.	**Imazapyr acid** Nominal concentrations of 10–100 mg a.e./L. Mean measured concentrations of 9.4–101.2 mg/L. 7-day exposure.	Study Only the highest concentration caused inhibition (99.9%). Lower concentration (56 mg/L and less) caused stimulation. Based on cell density, EC_{25} of 48 mg/L and EC_{50} of 71 mg/L. Confidence intervals not provided. U.S. EPA/OPP 2007a EC_{50}: 71 mg a.e./L NOAEC: 50.9 mg a.e./L	Hughes 1987 MRID No. 40811802 Reviewed by U.S. EPA/OPP 2005h and 2007a, Appendix B
Selenastrum capricornutum, a green algae.	**Imazapyr IPA** 7 day exposure	U.S. EPA/OPP 2007a EC_{50}: 11.5 mg a.e./L NOAEC: 7.16 mg a.e./L Slight change in cell shape	Hughes 1987 MRID No. 40811802 from U.S. EPA/OPP 2007a, Appendix B
Anabaena flosaquae, a blue-green algae.	Nominal concentrations of 0, 5.6, 10, 18, 32, 52, and 100 mg a.e./L for 7 days. Working Note: Study indicates a.i. but only identifies the material as AC 243,997. The water solubility given in the study is that of the acid.	Study EC_{25} for cell count 7.3 (<0.0001–51.4) mg/L EC_{50} for cell count 11.7 (<0.0001–105.5) mg/L U.S. EPA/OPP 2007a EC_{50}: 12.2 mg a.e./L NOAEC: 9.6 mg a.e./L	Hughes 1987 MRID No. 40811802 Reviewed by U.S. EPA/OPP 2005h and 2007a, Appendix B
Navicula pelliculosa, a freshwater diatom.	Concentrations of 10 to 100 mg a.e./L for 7 days. Static.	Study All concentrations caused stimulation rather than inhibition of cell number. Extent of stimulation was 1.6 to 17% with no apparent dose/response relationship. U.S. EPA/OPP 2007a EC_{50}: >41 mg a.e./L NOAEC: 41 mg a.e./L	Hughes 1987 MRID No. 40811802 Reviewed by U.S. EPA/OPP 2005h and 2007a, Appendix B

A6 Table 1: Toxicity data in Algae

Species	Exposure	Response	Reference
Skeletonema costatum, a marine diatom.	Nominal concentrations of 10–100 mg a.e./L. Mean measured concentrations of 8.9–90.5 mg/L. 7-day exposure.	Study Cell density EC_{25} = 42.2 mg/L EC_{50} = 85.5 mg/L Confidence limits could not be determined. U.S. EPA/OPP 2007a EC_{50}: 92 mg a.e./L NOAEC: 15.6 mg a.e./L	Hughes 1987 MRID No. 40811802 Reviewed by U.S. EPA/OPP 2005h and 2007a, Appendix B
Chara sp. and *Cladophora* sp. (submergent filamentous algae)	[Test substance specified as AC 252,925 (purity NOS).] Exposures in Petri dishes. Exposure period of 10 weeks with observations at 2 and 10 weeks. Concentrations not specified but exposures expressed as application rates of 0.5, 0.75, and 1.0 1b/ai/A. Raw data not available in submission.	Results 10 weeks after treatment showed algae were resistant to the test substance at all rates applied. Cleared review at http://www.epa.gov/pesticides/foia/reviews.htm. Classification: **INVALID**. Classification confirmed in FOIA02 (Lewis and Urban 1987) This study is not use in Forest Service risk assessment.	Herrick 1986 MRID No. 40003710 Not cited in U.S. EPA/OPP 2005b or 2007a.
Chlorella emersonii, a green algae.	**Imazapyr (NOS)** Concentrations ranging from 1 µM [0.261 mg/L] to about 100 µM [26.1 mg/L].	IC_{50} for acetolactate synthase inhibition of about 0.8 µM [≈0.2 mg a.e./L] taken from Figure 1, p. 2. Resistant strains of *Chlorella* had about 10-fold higher IC_{50}s.	Landstein et al. 1993

A6 Table 2: Toxicity data in Aquatic Macrophytes

Species	Exposure	Response	Reference
Lemna gibba, duckweed	**Imazapyr acid** Nominal concentrations of 0, 0.01, 0.018, 0.032, 0.056, and 0.100 mg a.e./L for 14 days. Static. Measured concentrations not reported.	Study Frond counts EC_{25} = 0.013 (0.009–0.019) mg/L EC_{50} = 0.024 (0.016–0.033) mg/L An NOEC is not defined. At lowest concentration tested, 0.01 mg/L, 15.1 % inhibition. U.S. EPA/OPP 2007a EC_{50}: 0.024 mg a.e./L NOAEC: 0.01 mg a.e./L	Hughes 1987 MRID No. 40811802 Reviewed by U.S. EPA/OPP 2005h and 2007a, Appendix B
Lemna gibba, duckweed	**Arsenal** Nominal concentrations of 0, 6.3, 12.6, 25.2, 50.4, and 100 µg a.i./L (ppb). Test substance specified as AC 252,925 2 AS (purity 23.3%). Working Note: CL 252,925 has been used to designate the Arsenal Herbicide formulation.	Study The fronds in the 22.2, 46.3, and 96.5 µg a.i./L treatment concentrations were smaller than the controls at day 7. The fronds in the 46.3 µg a.i./L were also misshapen at test termination (day 14), with daughter fronds growing an atypically long and thin shoots. No visual phytotoxic effects were observed in concentrations >13.0 µg a.i./L. NOEC was 13.0 µg a.i./L. EC_{25} = 14.1 µg a.i./L EC_{50} = 22.8 µg a.i./L U.S. EPA/OPP 2007a, Appendix B EC_{50}: 0.018 mg a.e./L NOAEC: 0.011 mg a.e./L	Hughes et al. 1995 MRID No. 43889102 Reviewed in U.S. EPA/OPP 2005h and 2007a
Myriophyllum sibiricum, water milfoil	**Arsenal** 14-day static exposure to nominal concentrations of imazapyr. Concentration range used NOS. Test substance specified as Arsenal.	Shoot growth EC_{25} = 0.013 mg a.i./L; EC_{50} = 0.032 mg a.i./L. Root number EC_{25} = 0.022 mg a.i./L; EC_{50} = 0.029 mg a.i./L. Root growth (dry mass) EC_{25} = 0.0079 mg a.i./L; EC_{50} = 0.0099 mg a.i./L (≈0.008 mg a.e./L).	Roshon et al. 1999

A6 Table 3: Field/Field Simulation Studies

Species	Exposure	Response	Reference
Duckweed, water hyacinth, and water lettuce.	0.5 lb a.e./acre. Test substance specified as AC 252,925 (Arsenal).	At 0.5 lb a.e./acre provided 98–100% control 10 weeks after application.	Herrick 1986 MRID No. 40003710
Egeria, *Elodea*, hydrilla, southern naiad, fanwort, coontail, and water milfoil.	0.5 lb a.e./acre. Test substance specified as AC 252,925 (Arsenal).	Control achieved 10 weeks after treatment for *Egeria*, *Elodea*, hydrilla, southern naiad Less effective for fanwort, coontail, and water milfoil.	Herrick 1986 MRID No. 40003710
Alligatorweed (*Alternanthera* philoxeroides) and lemon bacopa (*Bacopa caroliniana*).	0.75 lb a.e./acre. Test substance specified as AC 252,925 (Arsenal).	85% control after 8 weeks of treatment for alligator weed but **ineffective against lemon bacopa**.	Herrick 1986 MRID No. 40003710
Giant Salvinia (*Salvinia molesta*)	1.68 kg/ha [≈1.5 lb/acre] imazapyr (NOS) with methylated seed oil (SunWet) surfactant at 2.3 L/ha	No sign of toxicity until DAT 21 (1.7% control) and only modest toxicity by DAT 42 (13.3% control). This exposure appears to correspond to about 0.1 mg a.e./L. See Section 4.3.3.4.2 for calculation.	Nelson et al. 2001

Appendix 7: Gleams-Driver Modeling for Imazapyr

Imazapyr Terrestrial Application

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.00106	0	0
	(0 - 0.0138)	(0 - 0.00074)	(0 - 0)
Dry and Temperate	0.00079	0	0
Location	(0 - 0.0149)	(0 - 0.0008)	(0 - 0)
Dry and Cold Location	0.000121	0	0
	(0 - 0.0059)	(0 - 9.70E-07)	(0 - 0)
Average Rainfall and	0.0072	0.000109	0
Warm Location	(0.00032 - 0.045)	(9.80E-08 - 0.0052)	(0 - 0)
Average Rainfall and	0.0065	0.000021	0
Temperate Location	(0.00042 - 0.037)	(6.20E-09 - 0.00263)	(0 - 0)
Average Rainfall and Cool	0.00196	3.40E-06	0
Location	(3.16E-05 - 0.0146)	(1.78E-09 - 0.00126)	(0 - 0)
Wet and Warm Location	0.00239	6.60E-06	0
	(0.000046 - 0.0169)	(2.31E-08 - 0.00047)	(0 - 0)
Wet and Temperate	0.00199	1.21E-05	0
Location	(0.000037 - 0.0266)	(3.30E-07 - 0.000256)	(0 - 0)
Wet and Cool Location	0.12	0.0093	0
	(0.0293 - 0.227)	(0.00085 - 0.0295)	(0 - 0)
		Average of Central Values:	0.00561
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.227
		Summary of Values:	0.0056 (0 - 0.227)

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.27 (0.209 - 0.35)	0.241 (0.176 - 0.314)	0.209 (0.152 - 0.311)
Dry and Temperate Location	0.273 (0.209 - 0.36)	0.248 (0.168 - 0.33)	0.221 (0.135 - 0.304)
Dry and Cold Location	0.34 (0.251 - 0.4)	0.298 (0.211 - 0.35)	0.264 (0.171 - 0.33)
Average Rainfall and Warm Location	0.292 (0.217 - 0.33)	0.258 (0.198 - 0.304)	0.22 (0.183 - 0.256)
Average Rainfall and Temperate Location	0.291 (0.222 - 0.34)	0.254 (0.204 - 0.301)	0.217 (0.174 - 0.253)
Average Rainfall and Cool Location	0.288 (0.227 - 0.34)	0.247 (0.204 - 0.297)	0.213 (0.164 - 0.236)
Wet and Warm Location	0.229 (0.177 - 0.269)	0.197 (0.149 - 0.226)	0.18 (0.1 - 0.217)
Wet and Temperate Location	0.231 (0.198 - 0.269)	0.208 (0.172 - 0.237)	0.204 (0.151 - 0.221)
Wet and Cool Location	0.211 (0.185 - 0.253)	0.198 (0.17 - 0.22)	0.17 (0.137 - 0.197)
		Average of Central Values:	0.2397
		25th Percentile of Lower Bounds:	0.166
		Maximum Value:	0.4
		Summary of Values:	0.24 (0.166 - 0.4)

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Table 3: Out_Site01_SOIL36

Site	Clay	Loam	Sand
Dry and Warm Location	0.09 (0.07 - 0.118)	0.08 (0.059 - 0.105)	0.07 (0.051 - 0.106)
Dry and Temperate Location	0.091 (0.07 - 0.119)	0.083 (0.056 - 0.111)	0.074 (0.046 - 0.102)
Dry and Cold Location	0.113 (0.084 - 0.134)	0.099 (0.07 - 0.116)	0.089 (0.058 - 0.109)
Average Rainfall and Warm Location	0.098 (0.076 - 0.112)	0.088 (0.07 - 0.102)	0.077 (0.062 - 0.088)
Average Rainfall and Temperate Location	0.099 (0.077 - 0.113)	0.087 (0.072 - 0.102)	0.075 (0.059 - 0.09)
Average Rainfall and Cool Location	0.102 (0.079 - 0.118)	0.091 (0.074 - 0.105)	0.076 (0.059 - 0.092)
Wet and Warm Location	0.082 (0.063 - 0.095)	0.07 (0.052 - 0.083)	0.062 (0.033 - 0.075)
Wet and Temperate Location	0.1 (0.072 - 0.117)	0.08 (0.06 - 0.099)	0.068 (0.05 - 0.079)
Wet and Cool Location	0.1 (0.076 - 0.113)	0.088 (0.061 - 0.109)	0.061 (0.05 - 0.076)
		Average of Central Values:	0.0849
		25th Percentile of Lower Bounds:	0.057
		Maximum Value:	0.134
		Summary of Values:	0.085 (0.057 - 0.134)

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Table 4: Maximum Penetration into Soil Column (inches)

Site	Clay	Loam	Sand
Dry and Warm Location	12 (4 - 24)	12 (4 - 24)	12 (4 - 30)
Dry and Temperate Location	18 (8 - 36)	18 (8 - 36)	18 (8 - 36)
Dry and Cold Location	18 (12 - 30)	18 (12 - 24)	18 (12 - 30)
Average Rainfall and Warm Location	30 (18 - 36)	30 (18 - 36)	36 (24 - 36)
Average Rainfall and Temperate Location	36 (18 - 36)	30 (18 - 36)	36 (24 - 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:	28.7
		25th Percentile of Lower Bounds:	12
		Maximum Value:	36
		Summary of Values:	28.7 (12 - 36)

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

Site	Clay	Loam	Sand
Dry and Warm Location	3.8	0	0
	(0 - 33)	(0 - 2.3)	(0 - 0)
Dry and Temperate	2.14	0	0
Location	(0 - 28.8)	(0 - 1.74)	(0 - 2.39)
Dry and Cold Location	0.6	0	0
	(0 - 22.3)	(0 - 0.004)	(0 - 0)
Average Rainfall and	17.4	0.24	0
Warm Location	(0.5 - 69)	(0.00029 - 8.3)	(0 - 38)
Average Rainfall and	13.8	0.15	0.023
Temperate Location	(1 - 54)	(0.000013 - 5.4)	(0 - 13.3)
Average Rainfall and Cool	5.2	0.31	5.3
Location	(0.23 - 42)	(0.012 - 4.2)	(0.6 - 23.1)
Wet and Warm Location	5.4	3.6	12.2
	(0.5 - 47)	(0.13 - 15.3)	(3.9 - 24.6)
Wet and Temperate	12.4	15.1	24.6
Location	(3.7 - 51)	(7.5 - 24.7)	(15.4 - 43)
Wet and Cool Location	84	30.3	62
	(41 - 123)	(17.9 - 52)	(39 - 94)
		Average of Central Values:	11.1
		25th Percentile of Lower Bounds:	0
		Maximum Value:	123
		Summary of Values:	11.1 (0 - 123)

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.013	0	0
	(0 - 0.11)	(0 - 0.007)	(0 - 0)
Dry and Temperate	0.007	0	0
Location	(0 - 0.09)	(0 - 0.005)	(0 - 0.008)
Dry and Cold Location	0.0016	0	0
	(0 - 0.06)	(0 - 0.00001)	(0 - 0)
Average Rainfall and	0.07	0.001	0
Warm Location	(0.004 - 0.3)	(2.6E-06 - 0.028)	(0 - 0.3)
Average Rainfall and	0.06	0.0005	0.00007
Temperate Location	(0.006 - 0.23)	(4.0E-08 - 0.021)	(0 - 0.11)
Average Rainfall and Cool	0.023	0.0023	0.07
Location	(0.0018 - 0.15)	(0.00008 - 0.05)	(0.004 - 0.4)
Wet and Warm Location	0.03	0.05	0.24
	(0.0027 - 0.15)	(0.0013 - 0.5)	(0.05 - 0.7)
Wet and Temperate	0.7	1.35	1.47
Location	(0.11 - 2.24)	(0.4 - 2.65)	(0.7 - 2.58)
Wet and Cool Location	1.48	2.92	4.7
	(0.7 - 3.6)	(0.9 - 5.7)	(2.6 - 6.4)
		Average of Central Values:	0.488
		25th Percentile of Lower Bounds:	0
		Maximum Value:	6.4
		Summary of Values:	0.49 (0 - 6.4)

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

Site	Clay	Loam	Sand
Dry and Warm Location	1.11	0	0
	(0 - 17.6)	(0 - 0.9)	(0 - 0)
Dry and Temperate	0.8	0	0
Location	(0 - 15.8)	(0 - 0.8)	(0 - 1.12)
Dry and Cold Location	0.13	0	0
	(0 - 6.5)	(0 - 0.0011)	(0 - 0)
Average Rainfall and	7	0.13	0
Warm Location	(0.28 - 47)	(0.00018 - 5.7)	(0 - 78)
Average Rainfall and	6.5	0.06	0.007
Temperate Location	(0.5 - 38)	(0.000007 - 3.1)	(0 - 16.8)
Average Rainfall and Cool	2.12	0.29	9.4
Location	(0.14 - 16.9)	(0.009 - 7)	(0.7 - 50)
Wet and Warm Location	3.2	4.2	27.8
	(0.31 - 19.4)	(0.16 - 31.1)	(7 - 73)
Wet and Temperate	20.3	49	40
Location	(4.7 - 68)	(10.4 - 88)	(21.4 - 80)
Wet and Cool Location	50	102	159
	(24.3 - 111)	(38 - 198)	(77 - 255)
		Average of Central Values:	17.9
		25th Percentile of Lower Bounds:	0
		Maximum Value:	255
		Summary of Values:	17.9 (0 - 255)

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.29	0	0
	(0 - 4.6)	(0 - 0.28)	(0 - 0)
Dry and Temperate	0.15	0	0
Location	(0 - 3.6)	(0 - 0.14)	(0 - 0.025)
Dry and Cold Location	0.04	0	0
	(0 - 1.71)	(0 - 0.00029)	(0 - 0)
Average Rainfall and	2.21	0.04	0
Warm Location	(0.12 - 13.5)	(0.00009 - 1.73)	(0 - 16.6)
Average Rainfall and	2.04	0.019	0.0006
Temperate Location	(0.14 - 10.9)	(1.8E-06 - 0.9)	(0 - 5.7)
Average Rainfall and Cool	0.6	0.1	2.97
Location	(0.06 - 5.6)	(0.0025 - 2.47)	(0.21 - 15.3)
Wet and Warm Location	0.9	1.16	10.4
	(0.14 - 5.4)	(0.02 - 10.8)	(1.36 - 39)
Wet and Temperate	9.3	21.9	19.2
Location	(1.61 - 28.9)	(3.9 - 39)	(4.9 - 38)
Wet and Cool Location	17.1	34	73
	(8.2 - 39)	(13.5 - 90)	(33 - 120)
		Average of Central Values:	7.24
		25th Percentile of Lower Bounds:	0
		Maximum Value:	120
		Summary of Values:	7.24 (0 - 120)