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Imazapic - Human Health and Ecological Risk Assessment – Final Report

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TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

LIST OF APPENDICES

LIST OF TABLES

LIST OF FIGURES

NOTE: Tables followed by figures are places after Section 5, References.

LIST OF WORKSHEETS

Supplement 1: Imazapic – WordPerfect Worksheets for Human Health and Ecological Risk Assessments, SERA WPWS 04-43-17-04b, Version 2.04d, dated December 22, 2004.

Supplement 2: Imazapic -EXCEL Worksheets for Human Health and Ecological Risk Assessments, SERA EXWS 04-43-17-04b, Version 2.04d, dated December 22, 2004.

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

a.e.	acid equivalents
AEL	adverse-effect level
a.i.	active ingredient
ALS	acetolactate synthase
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
CBI	confidential business information
CI	confidence interval
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
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
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
g	gram
ha	hectare
HQ	hazard quotient
IARC	International Agency for Research on Cancer
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

MMAD	mass median aerodynamic diameter
MCS	multiple chemical sensitivity mg milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
MOS	margin of safety
MRID	Master Record Identification Number
MSDS	material safety data sheet
MW	molecular weight
NCI	National Cancer Institute
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
ppm	parts per million
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SRC	Syracuse Research Corporation
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
µ	micron
>	greater than
<	less than

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

OVERVIEW

The USDA Forest Service uses two commercial formulations of the herbicide imazapic, Plateau and Plateau DG, in its vegetation management programs. This document is an update to a risk assessment of imazapic formulations that was prepared for the USDA Forest Service in 2001.

Adverse effects in human or other animal species do not appear to be plausible. There is no route of exposure or scenario suggesting that workers or members of the general public will be at any substantial risk from exposure to imazapic. For workers, no exposure scenarios, acute or chronic, exceed the RfD even at the upper ranges of estimated dose. For members of the general public, the upper limits for hazard quotients are below a level of concern except for the accidental spill of a large amount of imazapic into a very small pond. While imazapic has been tested in only a limited number of animals species and under conditions that may not well-represent populations of free-ranging nontarget animals, the available data are sufficient to assert that no adverse effects on animals are anticipated.

Imazapic is an effective herbicide and even tolerant plants that are directly sprayed with imazapic at normal application rates are likely to be damaged. Some sensitive plant species could be affected by the off-site drift of imazapic depending on local site-specific conditions in areas relatively close to the application site. Damage to terrestrial plants from runoff is possible in some areas but is not likely to be substantial. Under conditions in which runoff is favored – i.e., clay soils and relatively high rainfall rates – some aquatic macrophytes could also be affected by peak but not longer term concentrations of imazapic. No effects in unicellular algae are anticipated.

PROGRAM DESCRIPTION

Imazapic is used in the control of grasses, broadleaves, and vines, and for turf height suppression in non-cropland areas. The Forest Service will typically use imazapic in noxious weed control and rights-of-way management. The Forest Service may use two commercial formulations of imazapic, Plateau and Plateau DG. Both of these formulation contain the ammonium salt of imazapic as the active ingredient. Plateau is a liquid formulation that contains imazapic (22.2%) at a concentration of 2 lbs per gallon and Plateau DG is a dispersible granule formulation that contains the ammonium salt of imazapic (70%).

Imazapic may be applied by directed foliar, broadcast foliar, or aerial (Plateau only) methods. The most common method of application in Forest Service programs will involve broadcast foliar applications. For Plateau, the labeled application rates range from 2 to12 ounces of Plateau per acre, corresponding to 0.03125 to 0.1875 lbs a.e. imazapic/acre. For Plateau DG, the labeled application rates range from 1 to 2 water soluble pouches of Plateau DG per acre, corresponding to about 0.0625 to 0.1875 lbs imazapic per acre. For this risk assessment, the typical application rate will be taken as 0.1 lb a.e./acre with a range of 0.03125 to 0.1875 lbs a.e. imazapic/acre.

HUMAN HEALTH RISK ASSESSMENT

Hazard Identification **–** In experimental mammals, the acute oral LD_{50} for imazapic is greater than 5000 mg/kg, which indicates a low order of acute toxicity. Nevertheless, oral doses as low as 175 mg/kg bw/day were associated with increases in maternal mortality in a multiple dose study designed to assess the potential of imazapic to cause birth defects. While it is not clear if the maternal mortality at 175 mg/kg bw/day was attributable to the chemical or experimental dosing errors, a somewhat higher dose of 700 mg/kg bw/day was clearly associated with increased mortality attributed to the toxicity of imazapic.

Imazapic does not appear to be toxic to experimental rodents at relatively high concentrations in the diet but is toxic to dogs, causing adverse effects on muscle, blood, and liver. The NOAEL in rats is about 1625 mg/kg bw in the 13-week study or 1133 mg/kg bw in the 2-year study. Dogs, however, appear to be more sensitive than rodents, and the major signs of toxicity include adverse effects on the muscle, blood, and liver. Chronic exposure to imazapic at doses as low as 150 mg/kg bw have been associated with treatment-related effects on skeletal muscle.

In several standard tests required for pesticide registration, imazapic has failed to show any indication of adverse effects on development or reproduction and no carcinogenic or mutagenic activity.

Data regarding the dermal absorption kinetics of imazapic are not available in the published or unpublished literature. For this risk assessment, estimates of dermal absorption rates—both zero order and first order—are based on quantitative structure-activity relationships. The lack of experimental data regarding dermal absorption of imazapic adds uncertainty to this risk assessment. Uncertainties in the rates of dermal absorption, however, can be expressed quantitatively and this uncertainty is incorporated in the exposure assessment.

Based on standard studies required for pesticide registration, imazapic appears to be essentially non-irritating and non-sensitizing to the skin and minimally irritating to the eyes. Concentrations of imazapic in the air that would be much higher than any plausible concentrations in human exposure scenarios have been associated with lung congestion in rats. The potential inhalation toxicity of imazapic is not of substantial concern to this risk assessment, however, because of the implausibility of inhalation exposure involving high concentrations of this compound.

Exposure Assessment **–** Exposure assessments are conducted for both workers and members of the general public for the typical application rate of 0.1 lb/acre. The consequences of using the maximum application rate that might be used by the Forest Service, 0.1875 lb/acre, are discussed in the risk characterization.

For workers, three types of application methods are modeled: directed ground, broadcast ground, and aerial. Central estimates of exposure for workers are approximately 0.001 mg/kg/day, with somewhat higher amount for backpack and aerial workers (about 0.0015 mg/kg/day) and a somewhat lower rate for ground broadcast workers (about 0.0006 mg/kg/day). Upper range of

exposures are approximately 0.008 mg/kg/day for directed ground spray and aerial applications and 0.004 mg/kg/day for broadcast ground spray. All of the accidental exposure scenarios for workers involve dermal exposures and all of these accidental exposures lead to estimates of dose that are either in the range of or substantially below the general exposure estimates for workers.

For the general public, the range of acute exposures is from approximately 0.0000007 mg/kg associated with the lower range for the consumption of contaminated water from a stream by a child to 0.5 mg/kg associated with the upper range for consumption of contaminated water by a child following an accidental spill of imazapic into a small pond. High dose estimates are also associated with the direct spray of a child (0.145 mg/kg/day). Other acute exposures are lower by about an order of magnitude. For chronic or longer term exposures, the modeled exposures are much lower than for acute exposures, ranging from approximately 0.00000000002 mg/kg/day associated with the lower range for the normal consumption of fish to approximately 0.004 mg/kg/day associated with the upper range for consumption of contaminated fruit.

Dose-Response Assessment – The Office of Pesticide Programs of the U.S. EPA has derived a chronic RfD of 0.5 mg/kg/day for imazapic. This chronic RfD is based on a chronic LOAEL in dogs of 5000 ppm in the diet corresponding to an estimated daily dose of 137 mg/kg/day and an uncertainty factor of 300 (i.e., 0.456 mg/kg/day which rounds to 1 significant digit as 0.5 mg/kg/day). The dog LOAEL is based on adverse effects on skeletal muscle. In the current risk assessment, this chronic RfD is used to characterize risks to both acute and chronic exposures.

Risk Characterization – Typical exposures to imazapic do not lead to estimated doses that exceed a level of concern. For workers, no exposure scenarios, acute or chronic, exceed the RfD even at the upper ranges of estimated dose. For members of the general public, the upper limits for hazard quotients are below a level of concern except for the accidental spill of a large amount of imazapic into a very small pond.

Although there are several uncertainties in the exposure assessments for workers and the general public, the upper limits for hazard quotients associated with the longer-term exposures are sufficiently below a level of concern that the risk characterization is relatively unambiguous: based on the available information and under the foreseeable conditions of application, there is no route of exposure or scenario suggesting that the workers or members of the general public will be at any substantial risk from exposure to imazapic even at the upper range of the application rate considered in this risk assessment.

Mild irritation to the eyes can result from exposure to relatively high levels of imazapic. From a practical perspective, eye irritation is likely to be the only overt effect as a consequence of mishandling imazapic. These effects can be minimized or avoided by prudent handling of the compound.

ECOLOGICAL RISK ASSESSMENT

Hazard Identification **–** Larger mammals, such as dogs and rabbits, may be more sensitive to imazapic than smaller mammals such as mice and rats. Essentially no toxic effects have been observed in rats and mice even at very high dietary concentrations of imazapic over prolonged periods of time. The chronic NOAEL in rats is about 1133 mg/kg bw/day. In dogs, however, imazapic has been associated with effects on muscle, blood, and liver at a dietary LOAEL of 5000 ppm, corresponding to an average daily dose of about 150 mg/kg bw over a period of two years. In rabbits, increased mortality has been noted after repeated oral (gavage) exposure to doses from 175 mg/kg bw/day to 700 mg/kg bw/day. The chronic toxicity of imazapic to birds is comparable to that in dogs with a NOAEL of 113 mg/kg bw/day and a LOAEL of 170 mg/kg bw/day. Only one bioassay is available on terrestrial invertebrates (i.e., the honey bee with an acute LD_{50} of greater than 1075 mg/kg bw).

The toxicity of imazapic to terrestrial plants has been assayed in both pre-emergence and post-emergence studies. In the pre-emergence study, no effects on emergence were noted for any plants (NOEC = 0.064 lb/acre) except ryegrass (NOEC = 0.032 lb/acre and EC_{25} of 0.055 lb/acre). NOEC values for survival were also 0.064 lb/acre except for ryegrass, which evidenced an NOEC of 0.016 lb/acre. Imazapic was much more toxic in the post-emergence assay, with 21-day NOEC values for visual injury of 0.001 lb/acre for cabbage, cucumber, and tomato; 0.002 lb ai/acre for onion, oat, and radish; 0.004 lb/acre for ryegrass, 0.008 for soybean, 0.016 for corn, and 0.032 for lettuce.

Aquatic animals appear to be relatively insensitive to imazapic exposures, with LC_{50} values of >100 mg/L for both acute toxicity and reproductive effects. Aquatic macrophytes may be much more sensitive, with an acute EC_{50} of 6.1 µg/L in duck weed (*Lemna gibba*). Aquatic algae appear to be much less sensitive, with EC_{50} values of greater than 45 µg/L. No toxicity studies have been located on the effects of imazapic on amphibians or microorganisms.

Exposure Assessment **–** Terrestrial animals might be exposed to any applied herbicide from direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect dermal contact with contaminated vegetation. In acute exposure scenarios, the highest exposures for small terrestrial vertebrates will occur after a direct spray and could reach up to about 2.4 mg/kg at an application rate of 0.1 lb a.e./acre. There is a wide range of exposures anticipated from the consumption of contaminated vegetation by terrestrial animals: central estimates range from 0.125 mg/kg for a small mammal to 2.69 mg/kg for a large bird with upper ranges of about 0.27 mg/kg for a small mammal and 7.6 mg/kg for a large bird. The consumption of contaminated water leads to much lower levels of exposure. A similar pattern is seen for chronic exposures. Estimated daily doses for the a small mammal from the consumption of contaminated vegetation at the application site are in the range of about 0.0001 mg/kg to 0.01 mg/kg. The upper ranges of exposure from contaminated vegetation far exceed doses that are anticipated from the consumption of contaminated water, which range from 0.0000001 mg/kg/day to 0.00000044 mg/kg/day for a small mammal. Based on general relationships of body size to body volume, larger vertebrates will be exposed to lower doses and smaller animals,

such as insects, to much higher doses than small vertebrates under comparable exposure conditions. Because of the apparently low toxicity of imazapic to animals, the rather substantial variations in the different exposure assessments have little impact on the assessment of risk to terrestrial animals.

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 considered in this risk assessment, 0.1 lb a.e./acre and should be regarded as an extreme/accidental form of exposure that is not likely to occur in most Forest Service applications. Estimates for the other routes of exposure are much less. All of these exposure scenarios are dominated by situational variability because the levels of exposure are highly dependent on site-specific conditions. Thus, the exposure estimates are intended to represent conservative but plausible ranges that could occur but these ranges may over-estimate or under-estimate actual exposures in some cases. Spray drift is estimated using AgDRIFT. The proportion of the applied amount transported off-site from runoff is based on GLEAMS modeling of clay, loam, and sand. The amount of imazapic that might be transported off-site from wind erosion is based on estimates of annual soil loss associated with wind erosion and the assumption that the herbicide is incorporated into the top 1 cm of soil. Exposure from the use of contaminated irrigation water is based on the same data used to estimate human exposure from the consumption of contaminated ambient water and involves both monitoring studies as well as GLEAMS modeling.

Exposures to aquatic plants and animals is based on essentially the same information used to assess the exposure to terrestrial species from contaminated water. The peak concentrations of imazapic in contamination water is estimated at 0.0005 mg/L (0.00005 to 0.01) mg a.e./L per 1 lb a.e./acre. For longer-term exposures, average estimated rate of contamination of ambient water associated with the normal application of imazapic is 0.00002 (0.00001 to 0.00003) mg a.e./L at an application rate of 1 lb a.e./acre. For the assessment of potential hazards, these contamination rates are adjusted based on the application rates considered in this risk assessment.

Dose-Response Assessment – For terrestrial mammals, the dose-response assessment is based on the same data as the human health risk assessment (i.e., an acute NOAEL of 350 mg/kg/day and a chronic NOAEL of 45 mg/kg/day). None of the exposure scenarios, acute or longer term, result in exposure estimates that exceed the applicable NOAEL. Birds appear to be somewhat less sensitive to imazapic than mammals. The 5-day dietary NOEL of 1100 mg/kg/day in bobwhite quail is used to characterize risks to birds associated with acute exposures. For chronic toxicity, NOAEL for birds is taken as 113 mg/kg bw/day from a dietary reproduction study. The only data available on terrestrial invertebrates is the standard bioassay in honey bees in which the NOAEL based on mortality was 387 mg/kg bw, very close to the NOAEL of 350 mg/kg bw in mammals.

The toxicity data for terrestrial plants involves standard bioassays for pre-emergent and post-emergent applications. For exposures involving the off-site drift of imazapic, the range of NOAEL values for post-emergence applications is 0.001 lb/acre for sensitive species and 0.032

for tolerant species. For exposures involving off-site runoff, the range of NOAEL values for pre-emergence applications is 0.032 lb/acre for sensitive species and 0.064 lb/acre for tolerant species.

Imazapic does not appear to be very toxic to aquatic fish or invertebrates. The available data are not sufficient to identify sensitive and tolerant species because the screening tests conducted at nominal concentrations 100 mg/L failed to demonstrated adverse effects in either acute or longer-term exposures. *Lemna gibba*, an aquatic macrophyte, is much more sensitive to imazapic than aquatic animals. An NOEC of 0.00127 mg/L in *Lemna minor* is used for quantifying effects in aquatic macrophytes. By comparison to *Lemna gibba*, unicellular aquatic algae appear to be relatively insensitive to imazapic and a concentration of 50 µg/L is taken as an LOEC for moderate growth inhibition and is used for the risk characterization.

Risk Characterization – There is very little indication that the use of imazapic in Forest Service programs will lead to substantial unintended adverse effects. Imazapic is an effective herbicide and even tolerant plants that are directly sprayed with imazapic at normal application rates are likely to be damaged. Some sensitive plant species could be affected by the off-site drift of imazapic depending on local site-specific conditions within a relatively small distance from the application site – i.e., up to about 50 feet in ground applications and somewhat over 100 feet in aerial applications. Damage to terrestrial plants from runoff is possible in some areas but is not likely to be substantial. Under conditions in which runoff is favored – i.e., clay soils and relatively high rainfall rates – some aquatic macrophytes could also be affected by peak concentrations of imazapic. No effect in unicellular algae are anticipated.

Adverse effects in terrestrial or aquatic animals do not appear to be likely. The weight of evidence suggests that no adverse effects in mammals, birds, fish, and terrestrial or aquatic invertebrates are plausible using typical or worst-case exposure assumptions at the typical application rate of 0.1 lb/acre or the maximum application rate of 0.1875 lb/acre.

As in any ecological risk assessment, this risk characterization must be qualified. Imazapic has been tested in only a limited number of species and under conditions that may not well-represent populations of free-ranging nontarget animals. Notwithstanding this limitation, the available data are sufficient to assert that no adverse effects on animals are anticipated based on the information that is available.

1. INTRODUCTION

The USDA Forest Service uses the herbicide, imazapic, in its vegetation management programs. Two commercial formulations, Plateau and Plateau DG, may be used by the Forest Service. The present document provides risk assessments for human health effects and ecological effects to support an assessment of the environmental consequences of using imazapic in Forest Service programs. This is an update to the risk assessment conducted for the USDA Forest Service in 2001 (SERA 2001a).

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 associated with imazapic, 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. These are the basic steps recommended by the National Research Council of the National Academy of Sciences (NRC 1983) for conducting and organizing risk assessments.

This is a technical support document and it 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 2001b). Some of the more complicated terms and concepts are defined, as necessary, in the text.

The Forest Service has not conducted previous risk assessments on imazapic and no risk assessments on this compound have been published in the open literature. Moreover, almost all of the mammalian toxicology studies as well as ecotoxicology and environmental fate studies are unpublished reports submitted to the U.S. EPA as part of the registration process for this compound. The only studies on imazapic encountered in the published literature that relate to toxicologic effects involved field trials assessing the efficacy of imazapic for the control of various weed species (e.g., Grichar and Sestak 1998; Noldin et al. 1998; Taylor and Oliver 1997).

As part of the registration process, the U.S. EPA has conducted risk assessments on and other evaluations of the potential effects of this compound on humans and ecological species (U.S. EPA 1995, 1996b, 1999a,b, 2001). These assessments have been consulted as part of this current risk assessment for the Forest Service.

Because of the lack of a detailed, recent review concerning imazapic and the preponderance of unpublished relevant data in U.S. EPA files, a complete search of the U.S. EPA files was conducted in the preparation of this risk assessment. Full text copies of the most relevant studies were kindly provided by the U.S. EPA Office of Pesticide Programs. The studies were reviewed, and synopses of the most relevant studies are included in the appendices to this document.

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; however, they are not intended to be as detailed as the information generally presented in Chemical Background documents or other comprehensive reviews.

For the most part, the risk assessment methods used in this document are similar to those used in risk assessments previously conducted for the Forest Service as well as risk assessments conducted by other government agencies. Details regarding the specific methods used to prepare the human health risk assessment are provided in SERA (2001a).

Risk assessments are usually expressed with numbers; however, the numbers are far from exact. *Variability* and *uncertainty* may be dominant factors in any risk assessment, and these factors should be expressed. Within the context of a risk assessment, the terms *variability* and *uncertainty* signify different conditions.

Variability reflects the knowledge of how things may change. Variability may take several forms. For this risk assessment, three types of variability are distinguished: *statistical*, *situational*, and *arbitrary*. *Statistical variability* reflects, at least, apparently random patterns in data. For example, various types of estimates used in this risk assessment involve relationships of certain physical properties to certain biological properties. In such cases, best or maximum likelihood estimates can be calculated as well as upper and lower confidence intervals that reflect the statistical variability in the relationships. *Situational variability* describes variations depending on known circumstances. For example, the application rate or the applied concentration of a herbicide will vary according to local conditions and goals. As discussed in the following section, the limits on this variability are known and there is some information to indicate what the variations are. In other words, *situational variability* is not random. *Arbitrary variability*, as the name implies, represents an attempt to describe changes that cannot be characterized statistically or by a given set of conditions that cannot be well defined. This type of variability dominates some spill scenarios involving either a spill of a chemical on to the surface of the skin or a spill of a chemical into water. In either case, exposure depends on the amount of chemical spilled and the area of skin or volume of water that is contaminated.

Variability reflects a knowledge or at least an explicit assumption about how things may change, while *uncertainty* reflects a lack of knowledge. For example, the focus of the human health dose-response assessment is an estimation of an 'acceptable' or 'no adverse effect' dose that will not be associated with adverse human health effects. For imazapic and for most other chemicals, however, this estimation regarding human health must be based on data from experimental animal studies, which cover only a limited number of effects. Generally, judgment is the basis for the methods used to make the assessment. Although the judgments may reflect a consensus (i.e., be used by many groups in a reasonably consistent manner), the resulting estimations of risk cannot be proven analytically. In other words, the estimates regarding risk involve uncertainty.

The primary functional distinction between variability and uncertainty is that variability is expressed quantitatively, while uncertainty is generally expressed qualitatively.

In considering different forms of variability, almost no risk estimate presented in this document is given as a single number. Usually, risk is expressed as a central estimate and a range, which is sometimes very 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. Some of the calculations are relatively simple are included in the body of the document. Some sets of the calculations, however, are cumbersome. For those calculations, worksheets are included with this risk assessment. The worksheets provide the detail for the estimates cited in the body of the document. As detailed in SERA (2003a), two versions of the worksheets are available: one in a word processing format (Supplement 1) and one in a spreadsheet format (Supplement 2). The worksheets that are in the spreadsheet format are used only as a check of the worksheets that are in the word processing format. Both sets of worksheets are provided with the hard-text copy of this risk assessment as well as with the electronic version of the risk assessment.

2. PROGRAM DESCRIPTION

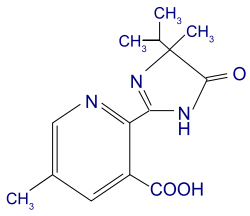
2.1. OVERVIEW

Imazapic is a herbicide that is used in the control of grasses, broadleaves, and vines, and for turf height suppression in non-cropland areas. The Forest Service will typically use imazapic in noxious weed control and rights-of-way management. The Forest Service may use two commercial formulations of imazapic, Plateau and Plateau DG. Both of these formulation contain the ammonium salt of imazapic as the active ingredient. Plateau is a liquid formulation that contains imazapic (22.2%) at a concentration of 2 lbs per gallon and Plateau DG is a dispersible granule formulation that contains the ammonium salt of imazapic (70%).

Imazapic may be applied by directed foliar, broadcast foliar, or aerial (Plateau only) methods. The most common method of application in Forest Service programs will involve broadcast foliar applications. For Plateau, the labeled application rates range from 2 to12 ounces of Plateau per acre, corresponding to 0.03125 to 0.1875 lbs a.e. imazapic/acre. For Plateau DG, the labeled application rates range from 1 to 2 water soluble pouches of Plateau DG per acre, corresponding to about 0.0625 to 0.1875 lbs imazapic per acre. For this risk assessment, the typical application rate will be taken as 0.13 lb a.e./acre with a range of 0.03125 to 0.1875 lbs a.e. imazapic/acre.

2.2. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS

Imazapic is the common name for (±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1 *H*-imidazol-2-yl]-5-methyl-3-pyridinecarboxylic acid and is identical to imazapyr with the addition of a methyl group on the pyridine ring:



Selected chemical and physical properties of imazapic are summarized in Table 2-1. Additional information is presented in worksheet B03.

Two commercial formulations of imazapic may be used in Forest Service programs, Plateau and Plateau DG. These formulations were originally developed and distributed by American Cyanamid (1998c, 2000) but the registration has been transferred to BASF (C&P Press 2003; BASF 2000, 2001).

Both Plateau and Plateau DG contain the ammonium salt of imazapic. Plateau is a liquid formulation that contains imazapic (22.2%) at a concentration of 2 lbs a.e. per gallon and inerts (77.8%). Plateau DG is a dispersible granule formulation that contains the ammonium salt of imazapic (70%) and inerts (30%). Plateau and Plateau DG are recommended for the control of

weeds, specifically grasses, broadleaves, and vines, and for turf height suppression in noncropland areas such as rights-of-way, fence rows, non-irrigation ditch banks, and pipelines. Plateau and Plateau DG are not labeled for food or feed crops (C&P Press 2003; BASF 2000, 2001).

The identity of the inerts in the imazapic formulations are considered proprietary information; therefore, the manufacturer does not identify the inerts on the general or supplemental product labels or material safety data sheets (American Cyanamid 1997, 1998c, 2000; BASF 2000, 2001; C&P Press 2003). This lack of disclosure indicates that none of the inerts present at a concentration of 0.1% or greater is classified as hazardous. Nonetheless, as discussed by Levine (1996), the testing requirements for inerts are less rigorous than the testing requirements for active ingredients (i.e., imazapic). The identity of the inerts has been disclosed to the U.S. EPA by both American Cyanamid (American Cyanamid 1998a,b; Birk 1999) and BASF (Overholt 2001) and this information has been obtained and reviewed in the preparation of this risk assessment. Specific information on the inerts, however, are considered proprietary and are not disclosed in this risk assessment. Nonetheless, the potential significance of these inerts can be inferred based on differences in the toxicity of the formulations and technical grade imazapic, as discussed further in Section 3.1.14.

Information about the impurities in technical grade imazapic was submitted to the U.S. EPA (Birk 1999; Steller 1998a,b) and reviewed during the preparation of this risk assessment. Since the identities of the impurities are considered proprietary by American Cyanamid, this information cannot be disclosed in this document. The potential impact of impurities in technical grade imazapic is discussed further in Section 3.1.15.

2.3. APPLICATION METHODS

Plateau may be applied by directed foliar, broadcast foliar, or aerial methods and Plateau DG may be used in directed foliar or broadcast foliar applications. The most common method of application for imazapic in Forest Service programs will involve broadcast foliar applications. Broadcast foliar ground applications will most often involve the use of a two to six nozzle boom mounted on a tractor or other heavy duty vehicle. With this equipment, workers will typically treat 2 to 6 acres per hour, with the low end of this range representative of a four-wheel drive vehicle in tall grass and the upper end of the range representative of a large bulldozer. This rate of treatment is substantially lower than the typical rates used in herbicide applications - i.e., 11 to 21 acres/hour (USDA 1989b, p 2-9 to 2-10). For this risk assessment, the treatment rates of 2 to 6 acres per hour are used in worker exposure assessments to define the upper and lower limits of exposure and 4 acres per hour is used as a central value (Worksheet A03b).

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 plausible. To reduce the likelihood of significant exposure, application crews are directed not to walk through

treated vegetation. Usually, a worker treats approximately 0.5 acre/hour with a plausible range of 0.25-1.0 acre/hour (Worksheet A03a).

Plateau, but not Plateau DG, is registered for aerial applications by fixed-wing aircraft or helicopter (American Cyanamid 1998c, 2000; C&P Press 2003). In Forest Service programs, aerial applications for imazapic would be restricted to helicopter only. Plateau 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 (Worksheet A03c).

2.4. MIXING AND APPLICATION RATES

For Plateau, the labeled application rates range from 2 to12 ounces of Plateau/acre. This corresponds to about 0.015625 to 0.09375 gallons [128 ounces per gallon] of Plateau per acre which in turn corresponds to about 0.03125 to 0.1875 lbs imazapic a.e. per acre [2 lbs a.e. per gallon × 0.015625 to 0.09375 gallons/acre]. For Plateau DG, the labeled application rates range from 1 to 2 water soluble pouches of Plateau DG/acre. Since each water soluble pouch contains 0.0625 lbs imazapic a.e., this corresponds to about 0.0625 to 0.1875 lbs imazapic a.e. per acre.

The use of imazapic in Forest Service Programs for fiscal year 2001, the most recent year for which data are available, is summarized in Table 2-2. Imazapic is used currently in Forest Service Programs in both noxious weed control (about 72% of total pounds in Regions 1 and 2) and rights-of-way maintenance (about 28% of total pounds in Region 9). Based on the total amount used and total number of acres treated, the average application rate is about 0.13 lb/acre, relatively near the maximum labeled rate of 0.1875 lb/acre.

For this risk assessment, the typical application rate will be taken as 0.1 lb a.e./acre. This is about the average of the range of labeled rates [(0.03125 lb/acre + 0.1875 lb/acre)÷2 = 0.109375 lb/acre]. The range of application rates will be taken as 0.03125 lb/acre to 0.1875 lb/acre, the range of application rates recommended for Plateau on the product label. As indicated in Table 2-2, the lower range of application rates has not been used by the Forest Service. Given the very narrow range of application rates used by the Forest Service, the selection of the lowest recommended rate is intended to provide the Forest Service with an assessment of the consequences of using lower application rates in the future. The worksheets that accompany this risk assessment are based on the typical application rate of 0.1 lb/acre rather than the full range of application rates. The consequences of varying application rates within the range of 0.03125 lbs a.e./acre to 0.1875 lbs a.e./acre is considered in the risk characterization for human health (Section 3.4) and ecological effects (Section 4.4).

Mixing volumes for imazapic vary only modestly depending on the type of vegetation to be treated as well as the application method. For ground applications of Plateau and Plateau DG, 2 to 10 gallons of water per acre are recommended (American Cyanamid 1998c; American

Cyanamid 2000; BASF 2000; C&P Press 2003). For aerial applications of Plateau, five or more gallons of water per acre are recommended (American Cyanamid 2000; C&P Press 2003).

For this risk assessment, the extent to which a formulation of imazapic is diluted prior to application primarily influences dermal and direct spray scenarios, both of which are dependent on 'field dilution'(i.e., the concentration of imazapic in the applied spray). In all cases, the higher the concentration of imazapic - equivalent to the lower dilution of imazapic - the greater the risk. For this risk assessment, the lowest dilution is taken as 2 gallons/acre, the minimum recommended for ground applications. The highest dilution is based on 10 gallons of water per acre, the highest application volume specifically recommended for ground applications. This range encompasses the range of concentrations that might be used in aerial applications. A typical dilution rate is taken as 6 gallons/acre, the arithmetic mean of the range. Details regarding the calculation of field dilution rates are given in worksheet B01, and the calculations following this worksheet are summarized in worksheet B02.

It should be noted that the selection of application rates and dilution volumes in this risk assessment is intended to simply reflect typical or central estimates as well as plausible lower and upper ranges. In the assessment of specific program activities, the Forest Service will use program specific application rates in the worksheets that are included with this report to assess any potential risks for a proposed application.

2.5. USE STATISTICS

Imazapic is a relatively new herbicide. Production and use data on this compound have not been encountered in the open literature. Thus, at this time, it is not possible to estimate reliably the amount of imazapic that the Forest Service uses relative to other groups that may also use this product.

Nonetheless, the USDA Forest Service (USDA/FS 2002) tracks and reports use by geographical areas referred to as "*Regions*". The Forest Service classification divides the U.S. into nine regions designated from Region 1 (Northern) to Region 10 (Alaska). [Note: There is no *Region 7* in the Forest Service system.] As illustrated in Figure 2-1 and detailed further in Table 2-2, the greatest proportion of imazapic used by the Forest Service occurs in Region 1 (Northern, 57.6%) with lesser amounts used in Region 9 (Eastern, 28.2%) and Region 2 (Rocky Mountain, 15%).

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview. In experimental mammals, the acute oral LD_{50} for imazapic is greater than 5000 mg/kg, which indicates a low order of acute toxicity. Nevertheless, oral doses as low as 175 mg/kg bw/day were associated with increases in maternal mortality in a multiple dose study designed to assess the potential of imazapic to cause birth defects. While it is not clear if the maternal mortality at 175 mg/kg bw/day was attributable to the chemical or experimental dosing errors, a somewhat higher dose of 700 mg/kg bw/day was clearly associated with increased mortality attributed to the toxicity of imazapic.

Imazapic does not appear to be toxic to experimental rodents at relatively high concentrations in the diet but is toxic to dogs, causing adverse effects on muscle, blood, and liver. The NOAEL in rats is about 1625 mg/kg bw in the 13-week study or 1133 mg/kg bw in the 2-year study. Dogs, however, appear to be more sensitive than rodents, and the major signs of toxicity include adverse effects on the muscle, blood, and liver. Chronic exposure to imazapic at doses as low as 150 mg/kg bw have been associated with treatment-related effects on skeletal muscle.

In several standard tests required for pesticide registration, imazapic has failed to show any indication of adverse effects on development or reproduction and no carcinogenic or mutagenic activity.

As discussed in the exposure assessment, skin absorption is the primary route of exposure for workers. Data regarding the dermal absorption kinetics of imazapic are not available in the published or unpublished literature. For this risk assessment, estimates of dermal absorption rates—both zero order and first order—are based on quantitative structure-activity relationships. These estimates of dermal absorption rates are used in turn to estimate the amounts of imazapic that might be absorbed by workers, which then are used with the available dose-response data to characterize risk. The lack of experimental data regarding dermal absorption of imazapic adds uncertainty to this risk assessment. Uncertainties in the rates of dermal absorption, however, can be expressed quantitatively in the regression equation used to estimate dermal absorption rates and this uncertainty is incorporated in the human health exposure assessment.

Based on standard studies required for pesticide registration, imazapic appears to be essentially non-irritating and non-sensitizing to the skin and minimally irritating to the eyes. Concentrations of imazapic in the air that would be much higher than any plausible concentrations in human exposure scenarios have been associated with lung congestion in rats. The potential inhalation toxicity of imazapic is not of substantial concern to this risk assessment because of the implausibility of inhalation exposure involving high concentrations of this compound.

3.1.2. Mechanism of Action. The mechanism of action for imazapic is well characterized in plants but not in mammals. Imazapic affects plants by inhibiting the function of an enzyme required for the synthesis of branched chain amino acids (Section 4.1.2.4). The specific enzyme

is not present in animals and thus this mechanism is not relevant to the assessment of potential effects in experimental mammals. As summarized in Appendix 1 and discussed below, the signs of toxicity associated with longer term exposures to imazapic include effects on the blood and bone marrow, muscular degeneration, as well as biochemical markers of liver toxicity. The specific mechanisms by which these effects are induced, however, is not known.

3.1.3. Kinetics and Metabolism. The metabolism of imazapic was studied in rats (Cheng 1993), hens (Afzal 1994; Gatterdam 1993a,b), and goats (Kao 1993a,b; Sharp and Thalacker 1999). All of these studies were submitted to the U.S. EPA during registration of imazapic, but have not been published in the open literature. The studies on hens are discussed in Section 4.1.2.2, toxicity to birds. In rats, oral and intravenous studies were conducted using ^{14}C-labeled imazapic. The compound is readily absorbed after oral exposure (95%) and virtually completely excreted, mostly as parent compound, in the urine with greater than 50% elimination within 6 hours of dosing. Less than 3.5% of the administered dose is excreted in the feces (Cheng 1993).

In the goat metabolism study by Kao (1993a,b), three goats were exposed to ^{14}C-imazapic at doses of 0, 3.76, and 15.1 mg in gelatin capsules for seven consecutive days. These levels were considered to be 0, 33X, and 197X of maximum residue that foraging animals would likely receive in the diet. The limits of detection for imazapic were 0.02 ppm in fat and 0.01 ppm for milk, blood, tissues, and feces. Daily blood and milk residues were below the limits of detection as were all tissue concentrations with the exception of the kidney: 0.01 ppm at the low dose and 0.05 ppm at the high dose. Urine accounted for 67.2% and 94% of the excretion and feces for 7% and 9.6% of the excretion at the low and high doses, respectively. The urine contained essentially all unchanged parent compound. In the feces, 58% of the residues consisted of the parent compound. Residues from the kidney consisted of 30% parent compound. The major metabolite in feces was characterized as a hydroxymethyl analog that accounted for 10% of residue. In a separate study the hydroxymethyl metabolite was found to be excreted mainly in the feces and not detectable in milk samples (Kao 1994).

Sharp and Thalacker (1999) studied the metabolism of imazapic in one lactating goat. Imazapic was eliminated primarily in the urine (81.7%) with less in the feces (6.57%) and very little (0.03%) in milk. The total recovered in edible tissues and blood was 0.01%. As in the rats, elimination was rapid with 75% excreted within 24 hours following each dose.

3.1.4. Acute Oral Toxicity. Other than standard bioassays for acute toxicity that were conducted as part of the registration process, little information is available on the acute toxicity of imazapic. No case reports of human poisoning have been encountered in the open literature or EPA files.

The most common measure of acute oral toxicity is the LD_{50}, the estimate of a dose that is most likely to cause 50% mortality in the test species after a single oral dose. As summarized in Appendix 1, three acute oral studies on imazapic were submitted to U.S. EPA in support of

registration of imazapic: Lowe (1992), Fischer (1993), and Bradley (1995b). In these studies, a single oral dose of 5000 mg/kg caused no mortality or other signs of toxicity in groups of five male and female rats. Because the acute oral LD_{50} for this compound is thus over 5000 mg/kg, the U.S. EPA (1996b) classified imazapic as Risk Category IV: no hazard from acute oral exposure.

As discussed in Section 3.1.9, rabbits may be more sensitive to imazapic than rats. In a teratology study, mortality rates of 15% to 55% were noted in dams given imazapic by gavage at doses of 175 mg/kg bw/day to 700 mg/kg bw/day on days 7 to 19 of gestation (MacKenzie 1992).

3.1.5. Subchronic or Chronic Systemic Toxic Effects. No studies have been published on the subchronic or chronic toxicity of imazapic to humans or mammals. Four unpublished studies have been submitted to the U.S. EPA to support the registration of imazapic. As summarized in Appendix 1, there is one subchronic (13-week) study in rats (Fischer 1992), a chronic (1-year) study in dogs (Wolford 1993), and chronic (2-year) studies in rats (Fischer 1994a) and mice (Fischer 1994b). Imazapic does not appear to be toxic to experimental rodents at relatively high concentrations in the diet (except in pregnant rabbits) but is toxic to dogs, causing adverse effects on muscle, blood, and liver.

No signs of toxicity were observed in studies on rats or mice at the highest doses tested (i.e., 20,000 ppm or approximately 1625 mg/kg bw in the 13-week study or 1133 mg/kg bw in the 2-year study in rats and 7000 ppm or about 1288 mg/kg bw in the 2-year study in mice).

Dogs, however, appear to be more sensitive than rodents. At the highest dose tested — 40,000 ppm in the diet over a period of one year, corresponding to about 1000 mg/kg bw/day — signs of toxicity in dogs that could be attributed to imazapic included adverse effects on the blood and bone marrow, muscular degeneration, as well as biochemical markers of liver toxicity. Similar but less severe effects were observed at 20,000 ppm corresponding to about 500 mg/kg bw. Even at the lowest dose tested, 5000 ppm in the diet corresponding to about 150 mg/kg bw, treatment-related effects were observed on skeletal muscle. While these effects were not considered adverse by Wolford (1993), the U.S. EPA (1996b) classified the 5000 ppm exposure as a LOAEL based on these effects in skeletal muscle. As discussed in Section 3.3., the U.S. EPA (1996b) derived an RfD for imazapic based on this study in dogs.

3.1.6. Effects on Nervous System. As discussed in Durkin and Diamond (2002), a neurotoxicant is a chemical that disrupts the function of nerves, either by interacting with nerves directly or by interacting with supporting cells in the nervous system. This definition of neurotoxicant distinguishes agents that act directly on the nervous system (direct neurotoxicants) from those agents that might produce neurologic effects that are secondary to other forms of toxicity (indirect neurotoxicants). Virtually any chemical will cause signs of neurotoxicity in severely poisoned animals and, thus, can be classified as an indirect neurotoxicant.

No studies designed specifically to detect impairments in motor, sensory, or cognitive functions in animals or humans exposed to imazapic have been reported in the open literature or in the studies submitted to the U.S. EPA to support the registration of imazapic. Specifically, the U.S. EPA (2003a,b) has standard protocols for neurotoxicity studies including a neurotoxicity screening battery (Guideline 870.6200), and an acute and 28-day delayed neurotoxicity assay of organophosphorus substances (Guideline 870.6100). Neither of these types of studies have been conducted on imazapic. This is not surprising, since the undertaking of such studies on a substance such as imazapic, for which the clinical and experimental toxicology experience provides no reason to suspect a direct neurotoxic potential, would be highly unusual.

3.1.7. Effects on Immune System. There is very little direct information on which to assess the immunotoxic potential of imazapic. The only studies specifically related to the effects of imazapic on immune function are skin sensitization studies (Section 3.1.11). While these studies provide information about the potential for imazapic to act as a skin sensitizer, they provide no information useful for directly assessing the potential for imazapic to disrupt immune function.

The toxicity of imazapic has been examined in numerous acute, subchronic, and chronic bioassays. Although many of these studies did not focus on the immune system, changes in the immune system (which could potentially be manifest as increased susceptibility to infection compared to controls) were not reported in any of the available long-term animal studies (Appendix 1).

3.1.8. Effects on Endocrine System. 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). Mechanistic assays are generally used to assess the potential for direct action on the endocrine system (Durkin and Diamond 2002). Imazapic has not been tested for activity as an agonist or antagonist of the major hormone systems (e.g., estrogen, androgen, thyroid hormone), nor have the levels of these circulating hormones been measured following imazapic exposures. Thus, any judgments concerning the potential effect of imazapic on endocrine function must be based on inferences from standard toxicity studies. The available toxicity studies have not reported any histopathologic changes in endocrine tissues that have been examined as part of the standard battery of tests. As indicated in the following section (Section 3.1.9), extensive data are available on the reproductive performance and development of experimental animals exposed to imazapic.

3.1.9. Reproductive and Teratogenic Effects. Imazapic has been tested for its ability to cause birth defects (i.e., teratogenicity) as well as its ability to cause reproductive and developmental impairment. Teratogenicity studies typically entail gavage administration to pregnant rats or rabbits on specific days of gestation. Two such studies (each of which is detailed in Appendix 1) were conducted on imazapic: one in rats (Schardein 1992) and one in rabbits (MacKenzie 1992). No signs of maternal toxicity, teratogenicity or fetal toxicity were noted in the rat study at the highest dose tested (i.e., 1000 mg/kg/day).

In the rabbit study, maternal mortality was noted at all tested dose levels: 20% mortality at 175 mg/kg bw, 25% mortality at 350 mg/kg bw, 25% mortality at 500 mg/kg bw, and 60% mortality at 700 mg/kg bw compared to a control group mortality of 5% (MacKenzie 1992). The U.S. EPA (1996b, p. 7) asserts that the mortalities in the control group and all dose groups below 700 mg/kg bw were due to gavage error rather than toxicity. The basis for this assertion is unclear but it is a common experience in gavage studies that pulmonary intubation, leading to death, can occur. The study reports that: *All treated animals that died during the study had one or a combination of the following effects: oral discharge, nasal discharge, fluid-filled trachea and or lungs, reddened trachea, and stomach lesions.* The study does not specify whether or not the animal that died in the control group evidenced these signs of toxicity. In any event, no dose-related developmental abnormalities were observed in any dose groups. Because of the high mortality at 700 mg/kg bw, the U.S. EPA (1996b) set the fetal NOAEL at 500 mg/kg bw, identical to their assessment of the NOAEL for maternal toxicity.

Another type of reproduction study involves exposing more than one generation of the test animal to the compound. One such study (Schroeder 1994) was conducted on imazapic. In this study, 56 day old Sprague-Dawley rats were given imazapic in the diet at concentrations of 0, 5000, 10,000, or 20,000 ppm and were allowed to mate. The F_1 generation was similarly exposed to imazapic in the diet for 14 weeks and allowed to mate. No signs of toxicity in either the parental or F_1 generation were observed and there was no indication of any effect on reproductive performance (Schroeder 1994). Based on measured food consumption, the NOAEL of 20,000 ppm corresponded to daily doses of approximately 1200 to 1700 mg/kg bw/day. This is consistent with the NOAEL values noted for rats in subchronic and chronic toxicity studies (i.e., 1133 mg/kg bw in the 2-year study and 1625 mg/kg bw in the 13-week study) Section 3.1.5. The available data does not suggest that imazapic is a selective developmental toxin.

3.1.10. Carcinogenicity and Mutagenicity. The two-year feeding studies in rats (Fischer 1994a) and mice (Fischer 1994b), discussed in Section 3.1.5 and summarized in detail in Appendix 1, involved complete histopathology in order to assess the potential carcinogenicity of imazapic. No statistically significant increase in any tumor type was found in either study. As reviewed by U.S. EPA (1996b), imazapic was also negative in four assays for mutagenicity: reverse mutation assays with *Salmonella typhimurium*, the rat bone marrow *in vivo* cytogenetic assay, the *in vitro* Chinese hamster ovary assay, and the induction of forward mutations in Chinese hamster ovary cells. Thus, there is no basis for asserting that exposures to imazapic are likely to be associated with a carcinogenic risk. Based on the available information from rodent bioassays and mutagenicity studies, the U.S. EPA (1996b) concluded that:

> *...the chemical (imazapic) should be classified as 'Group E', evidence of non-carcinogenicity for humans; i.e., the chemical is **not likely** to be carcinogenic to humans via relevant routes of exposures. ... It should be noted, however, that the designating of an agent as being in Group E is based on the available evidence and should not be interpreted as a definitive*

conclusion that the agent will not be a carcinogen under any circumstances.

3.1.11. Irritation and Sensitization (Effects on the Skin and Eyes). When applied directly and repeatedly to the skin of guinea pigs, technical grade imazapic did not cause skin irritation or sensitization (Costello 1992; Reilly 1992). When applied to the skin of rabbits for four hours, erythema was barely perceptible after one hour in 2/6 animals. No effect was apparent after 24 hours in any treated animal (Lowe 1993c). Similarly, when instilled directly into the eyes of rabbits and allowed to remain for 24 hours, 4/6 animals had slight redness of the conjunctivae after 1 hour and this effect was reversed at 24 hours (Fischer 1987b). In a second similarly designed study (Lowe 1993b), somewhat greater irritation was observed including corneal opacity, slight conjunctival irritation, and slight chemosis in some animals after 48 hours. No effects were apparent after 72 hours.

Based on these studies (Appendix 1), the U.S. EPA (1996b, p. 4) has classified imazapic as non-irritating (Category IV) to the skin of rabbits, non-sensitizing to the skin of guinea pigs, and minimally irritating to the eyes of rabbits (Category III).

3.1.12. Systemic Toxic Effects from Dermal Exposure. 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. Thus, it is necessary to assess the consequences of dermal exposure relative to oral exposure and the extent to which imazapic is likely to be absorbed from the surface of the skin.

Several studies, summarized in Appendix 1, on the effects of dermal exposure to imazapic in experimental animals have been conducted and submitted to the U.S. EPA in support of the registration of imazapic. These studies indicate that dermal exposures to single acute doses of up to 5000 mg/kg imazapic were below the LD_{50} for rabbits (Bradley 1995a; Fischer 1987a; Lowe 1993a,b; Moore 1992). No signs of systemic toxicity were reported in any of the test animals.

The kinetics of dermal absorption of imazapic are not documented in the open literature and no studies on the kinetics of dermal absorption have been submitted to U.S. EPA. Such studies are not required for pesticide registration.

As detailed in SERA (2001b), dermal exposure scenarios involving immersion or prolonged contact with chemical solutions use Fick's first law and require an estimate of the permeability coefficient, K_p, expressed in cm/hour. Using the method recommended by U.S. EPA (1992), the estimated dermal permeability coefficient for imazapic is 0.0021 cm/hour with a 95% confidence interval of 0.0014 to 0.0030 cm/hour. The details of the U.S. EPA (1992) method for estimating K_p based on the molecular weight and octanol-water partition coefficient are given in Worksheet A07b. The application of this method to imazapic is summarized in Worksheet B05.

The estimated K_p is used in all exposure assessments in this document that are based on Fick's first law.

For exposure scenarios like direct sprays or accidental spills, which involve deposition of the compound on the skin's surface, dermal absorption rates (proportion of the deposited dose per unit time) rather than dermal permeability rates are used in the exposure assessment. Using the methods detailed in SERA (2001b), the estimated first-order dermal absorption coefficient is 0.0033 $hour^{-1}$ with 95% confidence intervals of 0.0016 to 0.0067 $hour^{-1}$. The details of the method specified in SERA (2001a) for estimating the first-order dermal absorption coefficient based on the molecular weight and octanol-water partition coefficient are given in Worksheet A07a. The application of this method to imazapic is summarized in Worksheet B05.

The lack of experimental data regarding the dermal absorption of imazapic adds uncertainty to this risk assessment. Nonetheless, the available data, albeit relatively sparse, do not suggest that imazapic is likely to be absorbed through the skin in amounts that may cause systemic toxic effects. This is detailed further in the risk characterization. Uncertainties in the rates of dermal absorption, although they are substantial, can be estimated quantitatively and are incorporated in the human health exposure assessment (Section 3.2).

3.1.13. Inhalation Exposure. As summarized in Appendix 1, there are three inhalation toxicity studies on imazapic that were submitted in support of the registration requirements: Hershman (1993a,b) and Hoffman (1995). These studies follow a relatively standard protocol involving acute (4-hour) exposure of rats to relatively high concentrations ranging from 2.3 mg/L (2300 mg/m^3) to 4.83 mg/L (4830 mg/m^3). The latter study (Hershman 1993b) was apparently conducted in response to initial concerns from U.S. EPA (1996b) that the particle size in the study by Hershman 1993a (i.e., median aerodynamic diameter of 6.47 to 8.28 μm) was too large. The study by Hershman (1993b) involved a particle size of 1.97 μm. In any event, no mortality was observed in any of the studies.

These extremely limited data on the effects of exposures to relatively high air concentrations of imazapic suggest only that imazapic can induce irritant effects and perhaps effects at the portal of entry (congested lungs in 2/10 males and 1/10 females and slight discolored foci on the lungs of 2/5 males and 1/5 females) at very high exposure levels. As discussed in Section 3.3, these findings are not directly relevant to this risk assessment because of the implausibility of exposure to such high concentrations of the compound.

3.1.14. Inerts and Adjuvants. Plateau and Plateau DG, the commercial formulations of imazapic used by the Forest Service, contain materials other than imazapic that are included as adjuvants to improve either efficacy or ease of handling and storage. The identity of these materials is confidential. The additives were disclosed to the U.S. EPA (American Cyanamid Company 1998b,c) and were reviewed in the preparation of this risk assessment. All that can be disclosed explicitly is that none of the additives is classified by the U.S. EPA as toxic. This is consistent with the MSDS for Plateau (American Cyanamid Company 1997) that does not

disclose the occurrence of toxic inerts in the formulation. Because none of the studies in experimental animals specifically tested Plateau or Plateau DG as the subject compound, a comparison of relative toxicity of technical imazapic and Plateau formulations cannot be used to assess the potential for inerts to affect the toxicity. Note that the identity of the inert ingredients in several herbicides has been obtained by the Northwest Coalition for Alternatives to Pesticides (NCAP) under the Freedom of Information Act and this information is publicly available at http://www.pesticide.org/FOIA/inertslinks.html. Imazapic, however, is not among the herbicides whose inert ingredients are listed by NCAP.

As reviewed by Levine (1996), testing requirements for pesticide inerts that have been used as additives or adjuvants for many years are minimal, and the scarcity of information on the toxicity of inert ingredients in pesticide formulations is a general problem in many pesticide risk assessments. For new inerts, the U.S. EPA does require more extensive testing (Levine 1996).

3.1.15. Impurities and Metabolites.

3.1.15.1. Impurities **–** There is no published information regarding the impurities in technical grade imazapic or any of its commercial formulations. Information on all of the impurities in technical grade imazapic were disclosed to the U.S. EPA (Birk 1999), and the information was obtained and reviewed as part of this risk assessment. Because this information is classified as confidential business information, details about the impurities cannot be disclosed. Nonetheless, all of the toxicology studies on imazapic involve technical imazapic, which is presumed to be the same as or comparable to the active ingredient in the formulation used by the Forest Service. Thus, if toxic impurities are present in technical imazapic, they are likely to be encompassed by the available toxicity studies using technical grade imazapic.

3.1.15.2. Metabolites **–** As discussed in Section 3.2, the metabolism and kinetics of imazapic has been studied in rats (Cheng 1993), hens (Afzal 1994; Gatterdam 1993a,b), and goats (Kao 1993a,b; Sharp and Thalacker 1999). These studies suggest that imazapic is rapidly excreted in the urine, principally as the parent compound (i.e., imazapic). Although these studies do not rule-out the formation of minor metabolites, all toxicity studies used quantitatively in this risk assessment (Section 3.3) involved *in vivo* exposures the potential toxicity of the metabolites is encompassed by these studies. Thus, there is no basis for asserting that metabolites may be formed *in vivo* that would have any substantial impact on this risk assessment.

3.1.16. Toxicological Interactions. American Cyanamid Company (1996) has suggested combinations of imazapic with glyphosate for the control of tall fescue and this combination may be considered by the Forest Service. No information on the potential interactions of imazapic and glyphosate have been encountered in the published literature or U.S. EPA files.

Acute studies have been submitted to the U.S. EPA involving mixtures of imazapic with 2,4-D by oral (Lowe 1999, 2001b); ocular (Boczon 1999c, 2001c), dermal (Boczon 1999a,b, 2001a,b; Lowe 2001a), and inhalation (Hoffman 1999) exposures. A detailed review of these studies is beyond the scope of the current assessment. These studies have been reviewed but are not

detailed in Appendix 1. It is apparent, however, that the acute toxicity of mixtures of imazapic and 2,4-D may be more toxic and irritating than imazapic alone. This is not to suggest, however, that these two compounds display a toxicologic interaction. For example, the acute oral LD_{50} of an approximately 1:3:1 mixture of imazapic:2,4-D:inerts is about 3066 mg/kg bw for male rats. Given that 2,4-D was about 60% of the mixture, the LD_{50} expressed as 2,4-D is about 1840 mg/kg (3066 mg/kg × 0.6). As summarized in the SERA risk assessment on 2,4-D (SERA 1998), the acute oral LD_{50} of 2,4-D in rats is about 1800 mg/kg. Thus, while the imazapic:2,4-D mixture is more toxic than imazapic alone, the data on the mixture are consistent with the assumption that the toxicity of the mixture is attributable entirely to 2,4-D with no indication of any toxic interaction. This is consistent with the very low oral toxicity of imazapic as summarized in Section 3.1.4.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview. Exposure assessments are conducted for both workers and members of the general public for the typical application rate of 0.1 lb/acre. The consequences of using the maximum application rate that might be used by the Forest Service, 0.1875 lb/acre, are discussed in the risk characterization.

For workers, three types of application methods are modeled: directed ground, broadcast ground, and aerial. Central estimates of exposure for workers are approximately 0.001 mg/kg/day, with somewhat higher amount for backpack and aerial workers (about 0.0015 mg/kg/day) and a somewhat lower rate for ground broadcast workers (about 0.0006 mg/kg/day). Upper range of exposures are approximately 0.008 mg/kg/day for directed ground spray and aerial applications and 0.004 mg/kg/day for broadcast ground spray. All of the accidental exposure scenarios for workers involve dermal exposures and all of these accidental exposures lead to estimates of dose that are either in the range of or substantially below the general exposure estimates for workers.

For the general public, the range of acute exposures is from approximately 0.0000007 mg/kg associated with the lower range for the consumption of contaminated water from a stream by a child to 0.5 mg/kg associated with the upper range for consumption of contaminated water by a child following an accidental spill of imazapic into a small pond. High dose estimates are also associated with the direct spray of a child (0.145 mg/kg/day). Other acute exposures are lower by about an order of magnitude. For chronic or longer term exposures, the modeled exposures are much lower than for acute exposures, ranging from approximately 0.00000000002 mg/kg/day associated with the lower range for the normal consumption of fish to approximately 0.004 mg/kg/day associated with the upper range for consumption of contaminated fruit.

3.2.2. Workers.

The Forest Service uses a standard set of exposure assessments in all risk assessment documents. While these exposure assessments vary depending on the characteristics of the specific chemical as well as the relevant data on the specific chemical, the organization and assumptions used in the exposure assessments are standard and consistent. All of the exposure assessments for workers as well as members of the general public are detailed in the worksheets on imazapic that accompany this risk assessment (Supplement 1). This section on workers and the following section on the general public provide a plain verbal description of the worksheets and discuss imazapic specific data that are used in the worksheets.

A summary of the exposure assessments for workers is presented in Worksheet E02 of the worksheets for imazapic that accompany this risk assessment. Two types of exposure assessments are considered: general and accidental/incidental. The term *general* exposure assessment is used to designate those exposures that involve estimates of absorbed dose based on the handling of a specified amount of a chemical during specific types of applications. The accidental/incidental exposure scenarios involve specific types of events that could occur during any type of application. The exposure assessments developed in this section as well as other similar assessments for the general public (Section 3.2.3) are based on the typical application rate

of 0.1 lbs a.i./acre (Section 2). The consequences of using different application rates in the range considered by the Forest Service are discussed further in the risk characterization (Section 3.4).

3.2.2.1. General Exposures – As described in SERA (2001b), 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.

The specific assumptions used for each application method are detailed in worksheets C01a (directed foliar), C01b (broadcast foliar), and C01c (aerial). In the worksheets, the central estimate of the amount handled per day is calculated as the product of the central estimates of the acres treated per day and the application rate.

No worker exposure studies with imazapic were found in the literature. The estimated exposure rates used in this risk assessment are based on worker exposure studies on nine different pesticides with molecular weights ranging from 221 to 416 and log K_{ow} values at pH 7 ranging from -0.75 to 6.50. The estimated exposure rates are based on estimated absorbed doses in workers as well as the amounts of the chemical handled by the workers. As summarized in Table 2-1 of this risk assessment, the molecular weight of imazapic is 275.31 and the log K_{ow} is 2.47. These values are within the range of the herbicides used in SERA (2001b). As described in SERA (2001b), 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 sprayers). It seems that much of the variability can be attributed to the hygienic measures taken by individual workers (i.e., how careful the workers are to avoid unnecessary exposure); however, pharmacokinetic differences among individuals (i.e., how individuals absorb and excrete the compound) also may be important.

An estimate of the number of acres treated per hour is needed to apply these worker exposure rates. As discussed in Section 2, the values used for the number of acres treated per hour in ground broadcast applications is different from those used in most Forest Service risk assessments. For these applications, values of 2 to 6 acres per hour with a central estimate is used in Worksheet C01b. The low end of this range is considered representative of a four-wheel drive vehicle in tall grass and the upper end of the range is considered to be representative of applications made using a large bulldozer. These rates are substantially lower than the typical rates used for ground broadcast herbicide applications - i.e., 11 to 21 acres/hour (USDA 1989b, p 2-9 to 2-10) with a central estimate of 16 acres per hour. The typical application rate is taken directly from the program description (see section 2.4). The number of hours worked per day is expressed as a range, the lower end of which is based on an 8-hour work day with 1 hour at each end of the work day spent in activities that do not involve herbicide exposure. The upper end of the range, 8 hours per day, is based on an extended (10-hour) work day, allowing for 1 hour at each end of the work day to be spent in activities that do not involve herbicide exposure.

It is recognized that the use of 6 hours as the lower range of time spent per day applying herbicides is not a true lower limit. It is conceivable and perhaps common for workers to spend much less time in the actual application of a herbicide if they are engaged in other activities. Thus, using 6 hours may overestimate exposure. In the absence of any published or otherwise documented work practice statistics to support the use of a lower limit, this approach is used as a protective assumption.

The range of acres treated per hour and hours worked per day is used to calculate a range for the number of acres treated per day. For this calculation as well as others in this section involving the multiplication of ranges, the lower end of the resulting range is the product of the lower end of one range and the lower end of the other range. Similarly, the upper end of the resulting range is the product of the upper end of one range and the upper end of the other range. This approach is taken to encompass as broadly as possible the range of potential exposures.

The central estimate of the acres treated per day is taken as the arithmetic average of the range. Because of the relatively narrow limits of the ranges for backpack and boom spray workers, the use of the arithmetic mean rather than some other measure of central tendency, like the geometric mean, has no marked effect on the risk assessment.

3.2.2.2. Accidental Exposures – Typical occupational exposures may involve multiple routes of exposure (i.e., oral, dermal, and inhalation); nonetheless, dermal exposure is generally the predominant route for herbicide applicators (Ecobichon 1998; van Hemmen 1992). Typical multi-route exposures are encompassed by the methods used in Section 3.2.2.1 on general exposures. Accidental exposures, on the other hand, are most likely to involve splashing a solution of herbicides into the eyes or to involve various dermal exposure scenarios.

Imazapic can cause mild irritant effects to eyes and is classified as minimally irritating to the eyes but as non-irritant to the skin (see Section 3.1.11). The available literature does not include quantitative methods for characterizing exposure or responses associated with splashing a solution of a chemical into the eyes; furthermore, there appear to be no reasonable approaches to modeling this type of exposure scenario quantitatively. Consequently, accidental exposure scenarios of this type are considered qualitatively in the risk characterization (section 3.4).

There are various methods for estimating absorbed doses associated with accidental dermal exposure (U.S. EPA 1992, SERA 2001b). Two general types of exposure are modeled: those involving direct contact with a solution of the herbicide and those associated with accidental spills of the herbicide onto the surface of the skin. Any number of specific 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 surface of the skin and by varying the surface area of the skin that is contaminated.

For this risk assessment, 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 summarize in Worksheet E01, which references other worksheets in which the specific calculations are detailed.

Exposure scenarios involving direct contact with solutions of the chemical are characterized by immersion of the hands for 1 minute or wearing contaminated gloves for 1 hour. Generally, it is not reasonable to assume or postulate that the hands or any other part of a worker will be immersed in a solution of a herbicide for any period of time. On the other hand, contamination of gloves or other clothing is quite plausible. For these exposure scenarios, the key element is the assumption that wearing gloves grossly contaminated with a chemical solution is equivalent to immersing the hands in a solution. In either case, the concentration of the chemical in solution that is in contact with the surface of the skin and the resulting dermal absorption rate are essentially constant.

For both scenarios (the hand immersion and the contaminated glove), the assumption of zero-order absorption kinetics is appropriate. Following the general recommendations of U.S. EPA (1992), Fick's first law is used to estimate dermal exposure. As discussed in Section 3.1.3, an experimental dermal permeability coefficient (Kp) for imazapic is not available. Thus, the Kp for imazapic is estimated using the algorithm from U.S. EPA (1992), which is detailed in Worksheet A07b. The application of this algorithm to imazapic, based on molecular weight and the $k_{o/w}$, is given in Worksheet B04.

Exposure scenarios involving chemical spills onto the skin are characterized by a spill on to the lower legs as well as a spill on to the hands. In these scenarios, it is assumed that a solution of the chemical is spilled onto a given surface area of skin and that a certain amount of the chemical adheres to the skin. The absorbed dose is then calculated as the product of the amount of the chemical on the surface of the skin (i.e., the amount of liquid per unit surface area multiplied by the surface area of the skin over which the spill occurs and the concentration of the chemical in the liquid) the first-order absorption rate, and the duration of exposure.

For both scenarios, it is assumed that the contaminated skin is effectively cleaned after 1 hour. As with the exposure assessments based on Fick's first law, this product (mg of absorbed dose) is divided by body weight (kg) to yield an estimated dose in units of mg chemical/kg body weight. The specific equation used in these exposure assessments is specified in Worksheet B03.

Confidence in these exposure assessments is diminished by the lack of experimental data on the dermal absorption of imazapic. Nonetheless, as summarized in Worksheet E01, there is a noteworthy similarity between the exposure scenario in which contaminated gloves are worn for 1 hour (Worksheet C02b) and the exposure scenario in which a chemical solution is spilled onto the skin surface of the hands and cleaned after 1 hour (Worksheet C03a). Confidence in these assessments is enhanced somewhat by the fact that two similar scenarios based on different empirical relationships yield similar estimates of exposure.

3.2.3. General Public.

3.2.3.1. General Considerations – Under normal conditions, members of the general public should not be exposed to substantial levels of imazapic. Nonetheless, any number of exposure scenarios can be constructed for the general public, depending on various assumptions regarding application rates, dispersion, canopy interception, and human activity. Several scenarios are developed for this risk assessment which should tend to over-estimate exposures in general.

The two types of exposure scenarios developed for the general public include acute exposure and longer-term or chronic exposure. All of the acute exposure scenarios are primarily accidental. They assume that an individual is exposed to the compound either during or shortly after its application. Specific scenarios are developed for direct spray, dermal contact with contaminated vegetation, as well as the consumption of contaminated fruit, water, and fish. Most of these scenarios should be regarded as extreme, some to the point of limited plausibility. The longer-term or chronic exposure scenarios parallel the acute exposure scenarios for the consumption of contaminated fruit, water, and fish but are based on estimated levels of exposure for longer periods after application.

The exposure scenarios developed for the general public are summarized in Worksheet E03. As with the worker exposure scenarios, details of the assumptions and calculations involved in these exposure assessments are given in the worksheets that accompany this risk assessment (Worksheets D01a to D09b). The remainder of this section focuses on a qualitative description of the rationale for and quality of the data supporting each of the assessments.

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. For these exposure scenarios, it is assumed that during a ground application, a naked child is sprayed directly with imazapic. These scenarios also assume that the child is completely covered (that is, 100% of the surface area of the body is exposed). These exposure scenarios are likely to represent upper limits of plausible exposure. An additional set of scenarios are included involving a young woman who is accidentally sprayed over the feet and legs. For each of these scenarios, some assumptions are made regarding the surface area of the skin and body weight, as detailed in Worksheet A03.

3.2.3.3. Dermal Exposure from Contaminated Vegetation – In this exposure scenario, it is assumed that the herbicide is sprayed at a given application rate and that an individual comes in contact with sprayed vegetation or other contaminated surfaces at some period after the spray operation. For these exposure scenarios, some estimates of dislodgeable residue and the rate of transfer from the contaminated vegetation to the surface of the skin must be available. No such data are available on dermal transfer rates for imazapic and the estimation methods of Durkin et al. (1995) are used as defined in Worksheet D02. The exposure scenario assumes a contact period of one hour and assumes that the chemical is not effectively removed by washing for 24

hours. Other estimates used in this exposure scenario involve estimates of body weight, skin surface area, and first-order dermal absorption rates, as discussed in the previous section.

3.2.3.4. Contaminated Water – Water can be contaminated from runoff, as a result of leaching from contaminated soil, from a direct spill, or from unintentional contamination from aerial applications. For this risk assessment, the two types of estimates made for the concentration of imazapic in ambient water are acute/accidental exposure from an accidental spill and longer-term exposure to imazapic in ambient water that could be associated with the application of this compound to a 10 acre block that is adjacent to and drains into a small stream or pond.

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

The accidental spill scenario assumes that a young child consumes contaminated water shortly after an accidental spill into a small pond. The specifics of this scenarios are given in Worksheet D05. Because this scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation or degradation of imazapic is considered. This scenario is dominated by arbitrary variability and the specific assumptions used will generally overestimate exposure. The actual concentrations in the water would depend heavily on the amount of compound spilled, the size of the water body into which it is spilled, the time at which water consumption occurs relative to the time of the spill, and the amount of contaminated water that is consumed. Based on the spill scenario used in this risk assessment, the concentration of picloram in a small pond is estimated to range from about 0.9 mg/L to 4.5 mg/L with a central estimate of about 1.5 mg/L (Worksheet D05).

The other acute exposure scenario for the consumption of contaminated water involves runoff into a small stream. No monitoring studies have been encountered on concentrations of imazapic in streams after applications similar to those used in Forest Service programs or any other defined applications – i.e., defined in terms of the amount applied, terrain conditions, stream flow, and meteorologic conditions. Consequently, for this component of the exposure assessment, estimated concentrations in stream water are based solely on GLEAMS (Groundwater Loading Effects of Agricultural Management Systems) modeling. GLEAMS is a root zone model that can be used to examine the fate of chemicals in various types of soils under different meteorological and hydrogeological conditions (Knisel and Davis 2000). As with many environmental fate and transport models, the input and output files for GLEAMS can be complex. The general application of the GLEAMS model and the use of the output from this model to estimate concentrations in ambient water are detailed in SERA (2003b).

For the current risk assessment, the application site was assumed to consist of a 10 acre square area that drained directly into a small pond or stream. The chemical specific values as well as the details of the pond and stream scenarios used in the GLEAMS modeling are summarized in Table 3-1. The GLEAMS modeling yielded estimates runoff, sediment and percolation that

were used to estimate concentrations in the stream adjacent to a treated plot, as detailed in Section 6.4 of SERA (2003b). The results of the GLEAMS modeling for the small stream are summarized in Table 3-2 and the corresponding values for the small pond are summarized in Table 3-3. These estimates are expressed as both average and maximum water contamination rates (WCR) - i.e., the concentration of the compound in water in units of mg/L normalized for an application rate of 1 lb a.e./acre.

As indicated in Table 3-2, no stream contamination is estimated in very arid regions – i.e., annual rainfall of 10 inches of less. The modeled maximum concentrations in the stream range from about less than 0.05 µg/L to about 2 µg/L at annual rainfall rates from 15 to 250 inches per year, with the highest concentrations associated with clay. While not detailed in Table 3-2, the losses from clay are associated primarily with runoff (about 80%), with the remaining amount due to sediment loss. For clay, the maximum losses occur with the first rainfall after application. Losses from loam are less than those from clay but follow a similar pattern with most of the pesticide loss is associated with runoff (about 90%) are the remaining loss associated with sediment. As with clay, most of the herbicide loss from loam occurs after the first rainfall event. For sand, the pesticide loss is associated exclusively with percolation. For sand, the maximum contamination occurs after subsequent rainfall events.

The GLEAMS scenarios do not specifically consider the effects of accidental direct spray. For example, the steam modeled using GLEAMS is about 6 feet wide and it is assumed that the herbicide is applied along a 660 foot length of the stream with a flow rate of 4,420,000 L/day. At an application rate of 1 lb/acre, accidental direct spray onto the surface of the stream would deposit about 41,252,800 µg [1 lb/acre = 112,100 µg/m^2 , 6'x660' = 3960 ft^2 = 368 m^2, 112,100 µg/m^2 × 368 m^2 = 41,252,800 µg]. This would result in a downstream concentration of about 10 µg/L [41,252,800 µg/day ÷ 4,420,000 L/day].

For the current risk assessment, the upper range for the short-term water contamination rate will be taken as 10 µg/L per lb/acre based on the direct spray scenario discussed above. This approach is taken because the expected peak concentrations based on GLEAMS are substantially below 10 µg/L at rainfall rates of up to 250 inches per year. This value, converted to 0.01 mg/L per lb/acre, is entered into Worksheet B06. The central estimate of the peak concentration will be taken as 0.5 µg/L (0.0005 mg/L), about the maximum concentration for clay at an annual rainfall rate of 50 inches. The lower range will be taken as 0.05 µg/L (0.00005 mg/L), concentrations that might be expected in relatively arid regions with clay soil – i.e., annual rainfall of 15 inches. As discussed further in the risk characterization (Section 3.4), the selection of the higher concentration rates associated with clay have no qualitative impact on the assessment of risk.

3.2.3.4.2. LONGER-TERM EXPOSURE – The scenario for chronic exposure to imazapic from contaminated water is detailed in worksheet D07. This scenario assumes that an adult (70 kg male) consumes contaminated ambient water from a contaminated pond for a lifetime. The estimated concentrations in pond water are based both the modeled estimates from GLEAMS, summarized in Table 3-3.

For this risk assessment, the typical WCR is taken as 0.02 µg/L or 0.00002 mg/L per lb/acre. This is about the average concentration that modeled in a pond using GLEAMS at a rainfall rates of 50 inches per year in clay or 50 to 250 inches per year in sand. The upper range of the WCR is taken as 0.03 µg/L or 0.00003 mg/L per lb/acre. This is the highest average concentration modeled from clay soil – i.e., at rainfall rates of 100 to 250 inches per year – rounded to one significant digit. The lower range is taken as 0.01 µg/L or 0.00001 mg/L per lb/acre. This selection is somewhat arbitrary but would tend to encompass concentrations that might be found in relatively arid areas.

The WCR values discussed in this section summarized in Worksheet B06 and used for all longer term exposure assessments involving contaminated water. As with the corresponding values for a small stream, these estimates are expressed as the water contamination rates (WCR) in units of mg/L per lb/acre.

3.2.3.5. Oral Exposure from Contaminated Fish -- Many chemicals may be concentrated or partitioned from water into the tissues of animals or plants in the water. 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 bioconcentration factor to standard pharmacokinetic principles are provided in Calabrese and Baldwin (1993).

The only available study regarding the bioconcentration of imazapic is a standardized test that is required as part of the registration process (Robinson 1994). In this study, bluegill sunfish were placed in water containing ^{14}C-labeled imazapic at a concentration of 0.5 mg/L for 28 days. Over this period, the BCF in whole fish was measured at BCF 0.11 ± 0.02 L/kg with 3 days as the time to 90% steady state. Because of the very low bioconcentration factor in whole fish and the rapid time to steady state, the distinctions between acute and chronic BCFs and edible and inedible fractions is not necessary and are not used in this risk assessment..

For both the acute and longer-term exposure scenarios involving the consumption of contaminated fish, the water concentrations of imazapic used are identical to the concentrations used in the contaminated water scenarios (see Section 3.2.3.4). The acute exposure scenario is based on the assumption that an adult angler consumes fish taken from contaminated water shortly after an accidental spill of 200 gallons of a field solution into a pond that has an average depth of 1 m and a surface area of 1000 m^2 or about one-quarter acre. No dissipation or degradation is considered. Because of the available and well-documented information and substantial differences in the amount of caught fish consumed by the general public and native American subsistence populations, separate exposure estimates are made for these two groups, as illustrated in worksheet D08. The chronic exposure scenario is constructed in a similar way, as

detailed in worksheet D09, except that estimates of imazapic concentrations in ambient water are based on GLEAMS modeling as discussed in Section 3.2.3.4.

3.2.3.6. Oral Exposure from Contaminated Vegetation – None of the Forest Service applications of imazapic will involve the treatment of crops. Thus, under normal circumstances and in most types of applications conducted as part of Forest Service programs, the consumption by humans of vegetation contaminated with imazapic is unlikely. Nonetheless, any number of scenarios could be developed involving either accidental spraying of crops or the spraying of edible wild vegetation, like berries. In most instances, and particularly for longer-term scenarios, treated vegetation would probably show signs of damage from exposure to imazapic (Section 4.3.2.4), thereby reducing the likelihood of consumption that would lead to significant levels of human exposure. Notwithstanding that assertion, it is conceivable that individuals could consume contaminated vegetation. One of the more plausible scenarios involves the consumption of contaminated berries after treatment of a right-of-way or some other area in which wild berries grow.

The two accidental exposure scenarios developed for this exposure assessment include one scenario for acute exposure, as defined in Worksheet D03 and one scenario for longer-term exposure, as defined in Worksheet D04. In both scenarios, the concentration of imazapic on contaminated vegetation is estimated using the empirical relationships between application rate and concentration on vegetation developed by Fletcher et al. (1994) which is in turn based on a re-analysis of data from Hoerger and Kenaga (1972). These relationships are defined in worksheet A04. For the acute exposure scenario, the estimated residue level is taken as the product of the application rate and the residue rate (Worksheet D03).

For the longer-term exposure scenario (D04), a duration of 90 days is used. The rate of decrease in the residues over time is taken from the vegetation half-times reported by Hallman and Leonard (1999). The range of 1.2 to 12 days is taken directly from Hallman and Leonard (1999) and the central estimate of 4 days is the approximate geometric mean of this range [i.e., $(1.2\times12)^{0.5} = 3.79$]. Although the duration of exposure of 90 days is somewhat arbitrarily chosen, this duration is intended to represent the consumption of contaminated fruit that might be available over one season. Longer durations could be used for certain kinds of vegetation but would lower the estimated dose (i.e., would reduce the estimate of risk).

For the longer-term exposure scenarios, the time-weighted average concentration on fruit is calculated from the equation for first-order dissipation. Assuming a first-order decrease in concentrations in contaminated vegetation, the concentration in the vegetation at time t after spray, C_t, can be calculated based on the initial concentration, C_0, as:

$$C_t = C_0 \times e^{-kt}$$

where k is the first-order decay coefficient [$k=\ln(2)\div t_{50}$]. Time-weighted average concentration (C_{TWA}) over time t can be calculated as the integral of C_t (De Sapio 1976, p. p. 97 ff) divided by the duration (t):

$$C_{TWA} = C_0 (1 - e^{-k\ t}) \div (k\ t).$$

A separate scenario involving the consumption of contaminated vegetation by drift rather than direct spray is not developed in this risk assessment. As detailed further in Section 3.4, this elaboration is not necessary because the direct spray scenario leads to estimates of risk that are below a level of concern. Thus, considering spray drift and a buffer zone quantitatively would have no impact on the characterization of risk.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview. The Office of Pesticide Programs of the U.S. EPA has derived a chronic RfD of 0.5 mg/kg/day for imazapic. This chronic RfD is based on a chronic LOAEL in dogs of 5000 ppm in the diet corresponding to an estimated daily dose of 137 mg/kg/day and an uncertainty factor of 300 (i.e., 0.456 mg/kg/day which rounds to 1 significant digit as 0.5 mg/kg/day). The dog LOAEL is based on adverse effects on skeletal muscle. In the current risk assessment, this chronic RfD is used to characterize risks to both acute and chronic exposures.

3.3.2. Chronic RfD. U.S. EPA's Office of Pesticide Programs (U.S. EPA 1996b) has derived an RfD of 0.5 mg/kg/day for imazapic. This RfD is also cited in the most recent pesticide tolerance listing for imazapic (U.S. EPA 2001). The RfD is based on a 52-week dietary exposure study using dogs. The dogs were given imazapic in the diet at concentrations of 0 (control), 5000, 20,000, or 40,000 ppm for 52 weeks (Wolford 1993). Based on measured food consumption, these dietary concentrations corresponded to average daily doses of 0, 137, 501, and 1141 mg/kg/day in males and 0, 180, 534, and 1092 mg/kg/day in females. Signs of toxicity in dogs included effects on the blood and bone marrow, muscular degeneration, as well as biochemical markers of liver toxicity. Similar but less severe effects were observed at 20,000 ppm. Even at the lowest dose tested, 5000 ppm in the diet, treatment related effects were observed on skeletal muscle.

In deriving the RfD, the U.S. EPA classified the 5000 ppm exposure group as a LOAEL, used the daily intake at 137 mg/kg/day for male dogs, and used an uncertainty factor of 300. The uncertainty factor consists of three components: a factor of 10 for extrapolating from animals to humans, a factor of 10 for extrapolating to sensitive individuals within the human population, and a factor of 3 for extrapolating from a LOAEL to a NOAEL. Thus, the functional NOAEL for imazapic is taken as about 45 mg/kg/day (i.e., 137 mg/kg/day ÷ 3 = 45.7 mg/kg/day).

FQPA requires the U.S. EPA to use an additional uncertainty factor of 10 to encompasses concerns for exposures involving children unless the available toxicologic demonstrate that such an uncertainty factor is unnecessary. In the review of this RfD by U.S. EPA in the most recent pesticide tolerances (U.S. EPA 2001), the Food Quality Protection Act (FQPA) uncertainty factor was set to one – i.e., no additional uncertainty factor was used. The rationale for waiving this uncertainty factor is given by U.S. EPA (2001) as: *"Based on the available data, no evidence of increased susceptibility was seen in the rat and rabbit prenatal toxicity studies or following prenatal/postnatal exposure in the 2-generation reproduction study."* (U.S. EPA 2001, p. 66329). The U.S. EPA (2001) does not specifically identify the supporting studies. The rabbit pre-natal study appears to refer to MacKenzie (1992) in which the NOEL for embryo/fetotoxicity and teratogenicity was 700 mg/kg and the maternal NOAEL was 500 mg/kg – i.e., effects on the offspring occurred at higher doses than effects on the dams. The pre-natal toxicity study in rats appears to refer to Shardein (1992) in which no effects in dams or offspring were noted at the highest dose tested – i.e., 1000 mg/kg/day. The two-generation reproduction study in rats appears to refer to Schroeder (1994) with a dietary NOAEL of 20,000 ppm (the highest

concentration tested) for effects on both the parents and offspring. Consistent with the assessment given by U.S. EPA (2001), these studies provide no indication that young mammals are more sensitive to imazapic than adults and the decision to waive the FQPA uncertainty factor appears to be appropriate.

3.3.3. Acute RfD. As summarized in Section 3.2 (Exposure Assessment) and discussed further in Section 3.4 (Risk Characterization), all but one of the estimated acute exposures to imazapic are substantially less than the chronic RfD and most estimated levels of chronic exposure are below the RfD by factors of over 10 to 10 billion. Consequently, there is no need to develop elaborate dose-severity relationships to characterize risk or to develop an acute RfD for this compound. The U.S. EPA (1996b, p. 14) uses a short-term NOAEL of 350 mg/kg/day from the study by (MacKenzie 1992, summarized in Appendix 1) for assessing the consequences of short-term (1 to 7 days) exposures to imazapic. This acute NOAEL is also used by U.S. EPA (2001) for incidental short-term oral exposures with a recommended level of concern (LOC) of 100. This is essentially equivalent to using an uncertainty factor of 100 on the NOAEL and would correspond to a short-term RfD of 0.35 mg/kg/day. This is less than the chronic RfD and the use of this value would not assist in the risk characterization. Thus, the RfD of 0.5 mg/kg/day is used for both acute and chronic exposures.

3.4. RISK CHARACTERIZATION

3.4.1. Overview. Typical exposures to imazapic do not lead to estimated doses that exceed a level of concern. For workers, no exposure scenarios, acute or chronic, exceed the RfD even at the upper ranges of estimated dose. For members of the general public, the upper limits for hazard quotients are below a level of concern except for the accidental spill of a large amount of imazapic into a very small pond. Based on the available information and under the foreseeable conditions of application, there is no route of exposure or scenario suggesting that workers or members of the general public will be at any substantial risk from longer-term exposure to imazapic.

Mild irritation to the eyes can result from exposure to relatively high levels of imazapic. From a practical perspective, eye irritation is likely to be the only overt effect as a consequence of mishandling imazapic. These effects can be minimized or avoided by prudent industrial hygiene practices during the handling of the compound.

3.4.2. Workers. A quantitative summary of the risk characterization for workers associated with exposure to imazapic is presented in Worksheet E02 (Supplement 1). The quantitative risk characterization is expressed as the hazard quotient, the ratio of the estimated doses from Worksheet E01 to the RfD. For both acute exposures (i.e., accidental or incidental exposures) and general exposures (i.e., daily exposures that might occur over the course of an application season), the chronic RfD of 0.5 mg/kg/day is used to characterize risk (Section 3.3.2).

As indicated in Section 2, the exposures in Worksheet E01 and the subsequent hazard quotients in Worksheet E02 are based on the typical application rate of 0.1 lb a.e./acre and the "level of concern" is one – i.e., if the hazard quotient is below 1.0, the exposure is less than the RfD. For all exposure scenarios, the estimated dose scales linearly with application rate. Thus, at an application rate of 0.1875 lb a.e./acre, the highest labeled application rate, the level of concern would be 0.5 – i.e., 0.1 lb/acre ÷ 0.1875 lb/acre = 0.533, which rounds to 0.5 using one significant digit.

The highest hazard quotient for workers based on general exposures is 0.02 – the upper range for directed ground spray and aerial applications. Thus, even at the highest application rate that might be used in Forest Service programs, the upper range of hazard quotients is below the level of concern by a factor of 25 [0.5 ÷ 0.02]. Confidence in these assessments is diminished by the lack of a worker exposure study.

While the accidental exposure scenarios are not the most severe one might imagine (e.g., complete immersion of the worker or contamination of the entire body surface for a prolonged period of time) they are representative of reasonable accidental exposures. The highest hazard quotient for accidental worker exposures given in Worksheet E02 is 0.4 – i.e., the upper range for a worker wearing contaminated gloves for 1 hour. Because the estimate of the absorbed dose is linearly related to the hazard quotient, a scenario in which the worker wore contaminated gloves for 2.5 hours would be required to reach a level of concern (a hazard quotient of one) at the

typical application rate. The hazard quotient of 0.4 is only modestly below the level of concern of 0.5 that is associated with the maximum application rate. At the maximum application rate, a worker would need to wear contaminated gloves for 1 hour and 15 minutes to reach the level of concern.

The simple verbal interpretation of this quantitative characterization of risk is that under a protective set of exposure assumptions, workers would not be exposed to levels of imazapic that are regarded as unacceptable so long as reasonable and prudent handling practices are followed. The scenario of greatest concern appears to be contaminated gloves and this concern can be addressed by reasonable worker hygiene practices. Confidence in this risk characterization for acute worker exposures is diminished by the lack of experimental data on the dermal absorption kinetics of imazapic (Section 3.1). Nonetheless, the statistical uncertainties in the estimated dermal absorption rates, both zero-order and first-order, are incorporated into the exposure assessment and risk characterization.

As discussed in Section 3.1.11, imazapic is minimally irritating to the eyes. Quantitative risk assessments for eye irritation are not derived; however, from a practical perspective, effects on the eyes are likely to be the only overt effects as a consequence of mishandling imazapic. These effects can be minimized or avoided by prudent industrial hygiene practices during the handling of imazapic.

3.4.3. General Public. The quantitative hazard characterization for the general public associated with exposure to imazapic is summarized in Worksheet E04 (Supplement 1). Like 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 0.5 mg/kg/day both acute and longer term exposures.

Although there are several uncertainties in the longer-term exposure assessments for the general public, as discussed in Section 3.2.3, the upper limits for hazard quotients associated with the longer-term exposures are sufficiently below a level of concern that the risk characterization is relatively unambiguous: based on the available information and under the foreseeable conditions of application, there is no route of exposure or scenario suggesting that the general public will be at any substantial risk from longer-term exposure to imazapic even if the level of concern is set to 0.5 – i.e., that associated with the maximum application rate considered in this risk assessment. The upper range of the hazard quotient for the consumption of contaminated vegetation is 0.007, a factor of about 140 below the level of concern at the typical application rate [1÷0.007=142.9] and about 70 below the level of concern at the maximum application rate [0.5÷0.007=71.4].

For the acute/accidental scenarios, the none of the central estimates of the hazard quotients in Worksheet E04 exceed 0.5. Thus, even at the highest application rate that might be used, none of the exposure scenarios reach a level of concern. At the upper range of the hazard quotients, the scenario for drinking contaminated water after an accidental spill into a small pond reaches a level of concern at the typical application rate. At the maximum application rate, this scenario

would exceed the level of concern by a factor of 2. As noted in Section 3.2.3.4.1., the exposure scenario for the consumption of contaminated water is an arbitrary scenario: scenarios that are more or less severe, all of which may be equally probable or improbable, easily could be constructed. All of the specific assumptions used to develop this scenario have a simple linear relationship to the resulting hazard quotient. Thus, if the accidental spill were to involve 20 rather than 200 gallons of a field solution of imazapic, all of the hazard quotients would be a factor of 10 less and all would be below the level of concern. 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 imazapic 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.

The direct spray of a small child yields a hazard quotient of 0.3, below the level of concern both at the typical application rate as well as the highest application rate. Similar to the accidental spill scenario, this is an extreme accidental scenario that is intended to serve as a general guide for comparing risks among different herbicides. While the level of concern is not exceeded for imazapic, it would be prudent to take reasonable protective measures in the case of any accidental spray of a child or adult – i.e., cleaning the contaminated skin surface as quickly as possible.

All of the other acute exposure scenarios summarized in Worksheet E04 lead to hazard quotients of 0.03 or less, well below the level of concern at either the typical application rate (LOC=1) or the maximum application rate (LOC=0.5).

Each of the hazard quotients summarized in Worksheet E04 involves a single exposure scenario. In some cases, individuals could be exposed by more than one route and in such cases risks can be approximated by simply adding the hazard quotients for different exposure scenarios summarized in Worksheet E03. For imazapic, considerations of multiple exposure scenarios has little impact on the risk assessment. For example, based on the upper ranges for typical levels of acute/accidental exposure for being directly sprayed on the lower legs, staying in contact with contaminated vegetation, eating contaminated fruit, drinking contaminated water from a stream, and consuming contaminated fish at rates characteristic of subsistence populations leads to a combined hazard quotient of 0.3532 (0.3 + 0.003 + 0.04 + 0.0002 + 0.01). Similarly, for all of the chronic exposure scenarios, the addition of all possible pathways lead to hazard quotient of approximately 0.0070002, with consumption of contaminated vegetation accounting for virtually all of the exposure.

3.4.4. Sensitive Subgroups. There is no information to suggest that specific groups or individuals may be especially sensitive to the systemic effects of imazapic. Due to the lack of data in humans, the likely critical effect of imazapic in humans cannot be identified clearly. As indicated in Section 3.1.2, imazapic exposures have been associated with changes in blood, bone marrow, muscle, and possibly the liver. However, it is unclear if individuals with pre-existing diseases of the hematological system, muscle, or liver would be particularly sensitive to imazapic exposure. Individuals with any severe disease condition could be considered more sensitive to

many toxic agents. Nonetheless, given the very low hazard quotients for imazapic, there is no basis for asserting that adverse effects in a specific subgroup is plausible.

3.4.5. Connected Actions. As discussed in Section 3.1.16, the manufacturer of imazapic has recommended tank mixtures of this herbicide with glyphosate. No data are available on the combined toxicity of these two herbicides. Studies have been conducted on mixtures of 2,4-D and imazapic. While these combinations are more toxic than imazapic alone, there appears to be no basis for asserting that synergistic effects are likely because the toxic action is probably due to 2,4-D alone.

Effects associated with connected actions could also occur by exposure to imazapic from other sources such as normal or incidental dietary or water contamination. The U.S. EPA (2001) has estimated that children in the age range of 1 year to 6 years are the highest exposed group and that dietary exposures resulting from residues of imazapic in crops could account for 0.000684% or a proportion of 0.00000684 of the 0.5 mg/kg/day RfD. This is equivalent to a daily dose of [0.00000684× 0.5 mg/kg/day = 0.00000342 mg/kg/day or 3.42e-06 mg/kg/day] and a hazard quotient of 6.84e-05. The addition of this hazard quotient to the hazard quotients associated with Forest Service programs (Worksheet E04) would have no impact on the characterization of risk.

3.4.6. Cumulative Effects. This risk assessment specifically considers the effect of repeated exposure in that the chronic RfD is used as an index of acceptable exposure even for acute exposure scenarios. Consequently, the risk characterizations presented in this risk assessment encompass the potential impact of long-term exposure and cumulative effects.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview. The available data appear to suggest that larger mammals, such as dogs and rabbits, may be more sensitive to imazapic than smaller mammals such as mice and rats. Essentially no toxic effects have been observed in rats and mice even at very high dietary concentrations of imazapic over prolonged periods of time. The chronic NOAEL in rats is about 1133 mg/kg bw/day. In dogs, however, imazapic has been associated with effects on muscle, blood, and liver at a dietary LOAEL of 5000 ppm, corresponding to an average daily dose of about 150 mg/kg bw over a period of two years. In rabbits, increased mortality has been noted after repeated oral (gavage) exposure to doses from 175 mg/kg bw/day to 700 mg/kg bw/day. The chronic toxicity of imazapic to birds is comparable to that in dogs with a NOAEL of 113 mg/kg bw/day and a LOAEL of 170 mg/kg bw/day. Only one bioassay is available on terrestrial invertebrates (i.e., the honey bee with an acute LD_{50} of greater than 1075 mg/kg bw).

The toxicity of imazapic to terrestrial plants has been assayed in both pre-emergence and post-emergence studies. In the pre-emergence study, no effects on emergence were noted for any plants (NOEC = 0.064 lb/acre) except ryegrass (NOEC = 0.032 lb/acre and EC_{25} of 0.055 lb/acre). NOEC values for survival were also 0.064 lb/acre except for ryegrass, which evidenced an NOEC of 0.016 lb/acre. Imazapic was much more toxic in the post-emergence assay, with 21-day NOEC values for visual injury of 0.001 lb/acre for cabbage, cucumber, and tomato; 0.002 lb ai/acre for onion, oat, and radish; 0.004 lb/acre for ryegrass, 0.008 for soybean, 0.016 for corn, and 0.032 for lettuce.

Aquatic animals appear to be relatively insensitive to imazapic exposures, with LC_{50} values of >100 mg/L for both acute toxicity and reproductive effects. Aquatic macrophytes may be much more sensitive, with an acute EC_{50} of 6.1 µg/L in duck weed (*Lemna gibba*). Aquatic algae appear to be much less sensitive, with EC_{50} values of greater than 45 µg/L. No toxicity studies have been located on the effects of imazapic on amphibians or microorganisms.

4.1.2. Toxicity to Terrestrial Organisms.

4.1.2.1. Mammals – As summarized in the human health risk assessment (Section 3.1), there are several standard toxicity studies in experimental mammals that were conducted as part of the registration process. Essentially no toxic effects have been observed in rats and mice even at very high dietary concentrations of imazapic over prolonged periods of time (Section 3.1.5). In dogs, however, dietary concentrations of imazapic have been associated with effects on muscle, blood, and liver. As discussed in Section 3.1.5., the most sensitive effect in dogs is damage to muscle tissue with a dietary LOAEL of 5000 ppm corresponding to an average daily dose of about 150 mg/kg bw.

The acute toxicity of imazapic is relatively low, with an oral LD_{50} of >5000 mg/kg in rats. Rabbits may be more sensitive to imazapic than rats, with increased mortality noted in a

developmental toxicity study with rabbits receiving gavage doses from 175 mg/kg bw/day to 700 mg/kg bw/day (MacKenzie 1992) (see Appendix 1).

The limited available data appear to suggest that larger mammals, such as dogs and rabbits, may be more sensitive to imazapic than smaller mammals. Because only one study supports this speculation (and the validity of the effect as an effect of imazapic, rather than a dosing error, has been questioned by U.S. EPA), allometric relationships will not be developed for interspecies extrapolation. Instead, it will be assumed that wildlife species may be as sensitive to imazapic as the most sensitive species (i.e., the dog). As detailed further in Section 4.4, this conservative assumption has relatively little impact on this risk assessment because the levels that are likely to be toxic to the dog are still far below levels of exposure that might occur in Forest Service programs.

4.1.2.2. Birds – Both acute and subchronic toxicity studies are available in mallard ducks and bobwhite (Appendix 2). These studies are required by the U.S. EPA for pesticide registration and were submitted to the U.S. EPA during the registration process.

Consistent with the gavage studies in rats (Section 3.1 and Appendix 1), the acute toxicity of imazapic to birds appears to be low, with no mortality observed after singe gavage doses of 2150 mg/kg in quail (Fletcher and Sullivan 1993a) and ducks (Fletcher and Sullivan 1993b). In ducks, however, there was a slight decrease in food consumption over the 20-day post-dosing observation period (Fletcher and Sullivan 1993b). After 8-day exposures to imazapic in the diet at concentrations of up to 5000 ppm, no effects were observed in either quail (Pedersen et al. 1993a) or ducks (Pedersen et al. 1993b).

Imazapic has also been assayed for subchronic toxicity and reproductive effects in both ducks (Mortensen et al. 1998) and quail (Miller et al. 1998). No signs of systemic toxicity or reproductive effects (egg production, hatchability, survival of hatchlings) were observed in ducks over a 22 week exposure to imazapic in the diet at a concentration of up to 1658 ppm (Mortensen et al. 1998). As indicated in Appendix 2, this dietary NOAEL of 1658 ppm corresponds to a dose of about 232 mg/kg/day. In quail, no signs of systemic toxicity were observed at dietary concentrations of imazapic up to 1907 ppm, corresponding to a NOAEL of approximately 170 mg/kg bw/day. At this concentration, however, there was a statistically significant decrease in 14-day body weights of hatchlings. No other signs of reproductive effects were observed. No effects on hatchling body weight were observed at the next lower dietary concentration (i.e., 1187 ppm corresponding to a dose of approximately 113 mg/kg bw/day) (Miller et al. 1998).

In addition to these toxicity studies, pharmacokinetic studies have been conducted in hens (Afzal 1994; Gatterdam 1993a,b). These studies are consistent with the pharmacokinetic studies in mammals (Section 3.1.15.2), indicating that imazapic is rapidly excreted unchanged and does not accumulate in body tissue. In addition, no detectable concentrations of imazapic were found in eggs (limit of detection of 0.01 ppm).

4.1.2.3. Terrestrial Invertebrates – Only one study has been encountered on the toxicity of imazapic to terrestrial invertebrates: a standard acute contact toxicity bioassay in honey bees (Hoxter et al. 1993). This type of study is required by the U.S. EPA for the registration of pesticides. In this study, imazapic dissolved in acetone was applied to the thorax of groups of 50 bees (1 to 7 days old) at levels of 0, 13, 22, 36, 60, or 100 µg/bee. Two groups of bees were used at each dose level (i.e., a total of 100 bees per dose group) and four groups of bees were used as controls (i.e., a total of 200 bees). Combined mortality rates were 11/200 (0 dose), 7/100 (13 µg/bee), 9/100 (22 µg/bee), 9/100 (36 µg/bee), 22/100 (60 µg/bee), and 25/100 (100 µg/bee). Using the Fisher exact test, the combined mortality in th e 36 µg/bee dose group was not statistically significant from the control response ($p=0.18$). The response in the 60 µg/bee dose group, however, was statistically significant ($p=0.000034$) relative to the control response.

4.1.2.4. Terrestrial Plants (Macrophytes) – The mechanism of action of imazapic in plants is well characterized. Imazapic inhibits acetolactate synthase (ALS), an enzyme that is required for the synthesis of essential branched chain amino acids (valine, leucine, and isoleucine). Imazapic may be effective in either pre-emergent or post-emergent applications and the time to response in the treated vegetation may be prolonged (Tu et al. 2000).

Two sets of phytotoxicity studies have been conducted to support the registration of imazapic: a seed germination and seedling emergence study (Chetram et al. 1994a) which essentially mimics pre-emergence applications and a vegetative vigor assay (Chetram et al. 1994b) which mimics post-emergence applications.

The pre-emergence study consisted of two assays: a petri dish assay and seedling emergence assay in treated soil. The seedling/petri assay used technical grade imazapic to assay effects on seed germination in soybeans, lettuce, radishes, tomatoes, cucumbers, cabbage, oats, ryegrass, corn, and onions. Imazapic was applied to blotter paper in petri plates (10 seeds per plate) at nominal rates of 0.004, 0.008, 0.016, 0.032, and 0.064 lb a.e./acre. At 0.064 lb ai/acre, the proportion of germinating onion seeds was 73%, compared to 95% in the matched control group (Chetram et al. 1994a, Table III, p. 30), a statistically significant decrease ($p<0.05$). No statistically significant effects were apparent in any other treatment groups.

In the seedling emergence assay, the same species were used with imazapic applied to the surface of soil at the same equivalent application rates used in the petri assay. Responses were assayed by a visual (0–5 scale) subjective evaluation on days 7, 14, and 21 and percent emergence was assayed on day 14, except for oats which were assayed on day 17. No effects on emergence were noted for any plants (NOEC = 0.064 lb/acre) except ryegrass (NOEC = 0.032 lb/acre and EC_{25} of 0.055 lb/acre). NOECs for survival were 0.064 lb/acre except for ryegrass, which evidenced an NOEC of 0.016 lb/acre (Chetram et al. 1994b).

In the post-emergence assay, 1–3 leaf stage soybeans, lettuce, radishes, tomatoes, cucumbers, cabbage, oats, ryegrass, corn, and onions were treated with imazapic at nominal application rates of 0.004, 0.008, 0.016, 0.032, and 0.064 lb ai/acre, as in the seed germination and emergence

assays. Because of greater than anticipated toxicity in radish, tomato, cucumber, cabbage, oat, and onion, an additional assay was run at nominal application rates of 0.00025, 0.0005, 0.001, 0.002, and 0.004 lb ai/acre. After 21 days, NOEC's for visual injury were 0.001 lb/acre for cabbage, cucumber, and tomato; 0.002 lb ai/acre for onion, oat, and radish; 0.004 lb/acre for ryegrass, 0.008 for soybean, 0.016 for corn, and 0.032 for lettuce.

4.1.2.5. Terrestrial Microorganisms **–** No information has been encountered in the published literature or in the U.S. EPA registration files on the toxicity of imazapic to terrestrial microorganisms.

4.1.3. Aquatic Organisms.

4.1.3.1. Fish **–** Standard toxicity bioassays to assess the effects of imazapic on fish are summarized in Appendix 3. In acute toxicity studies, all tested species (channel catfish, bluegill sunfish, trout, and sheepshead minnow) evidenced relatively low toxicity with 96-hour LC_{50} values of >100 mg/L (i.e., nominal concentrations of 100 mg/L caused less than 50% mortality over the 96-hour exposure period) (Barker and Skorczynski 1998; Yurk et al. 1992a,b). Similarly, no effects on reproductive parameters were seen in a 32-day egg and fry study using fathead minnow (Barker et al. 1998).

The very low toxicity of imazapic to fish is probably related to very low rate of uptake of this compound by fish. In a 28-day flow-through assay, the bioconcentration of imazapic was measured at 0.11 L/kg (Barker et al. 1998) indicating that the concentration of imazapic in the water was greater than the concentration of the compound in fish.

4.1.3.2. Amphibians **–** Neither the published literature nor the U.S. EPA files include data regarding the toxicity of imazapic to amphibian species.

4.1.3.3. Aquatic Invertebrates **–** Standard toxicity bioassays to assess the effects of imazapic on aquatic invertebrates are summarized in Appendix 3. As with fish, no adverse effects have been observed at nominal concentrations of imazapic of up to 100 mg/L in acute toxicity studies with aquatic invertebrates (Barker and Liu 1998a,b; Yurk et al. 1993b) as well as a life-cycle study in *Daphnia magna* (Barker et al. 1998).

4.1.3.4. Aquatic Plants **–** Standard toxicity bioassays to assess the effects of imazapic on aquatic plants were submitted to the U.S. EPA in support of the registration of imazapic and are summarized in Appendix 3. The most sensitive species on which data are available is the aquatic macrophyte, *Lemna gibba*, with an LC_{50} of 6.1 µg/L and an LC_{25} of 4.23 µg/L. Unicellular algae are much less sensitive with LC_{50} values greater than 45 µg/L (Hughes et al. 1994).

4.1.3.5. Other Aquatic Microorganisms **–** Neither the published literature nor the U.S. EPA files include data regarding the toxicity of imazapic to other aquatic microorganisms.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview. Terrestrial animals might be exposed to any applied herbicide from direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect dermal contact with contaminated vegetation. In acute exposure scenarios, the highest exposures for small terrestrial vertebrates will occur after a direct spray and could reach up to about 2.4 mg/kg at an application rate of 0.1 lb a.e./acre. There is a wide range of exposures anticipated from the consumption of contaminated vegetation by terrestrial animals: central estimates range from 0.125 mg/kg for a small mammal to 2.69 mg/kg for a large bird with upper ranges of about 0.27 mg/kg for a small mammal and 7.6 mg/kg for a large bird. The consumption of contaminated water leads to much lower levels of exposure. A similar pattern is seen for chronic exposures. Estimated daily doses for the a small mammal from the consumption of contaminated vegetation at the application site are in the range of about 0.0001 mg/kg to 0.01 mg/kg. The upper ranges of exposure from contaminated vegetation far exceed doses that are anticipated from the consumption of contaminated water, which range from 0.0000001 mg/kg/day to 0.00000044 mg/kg/day for a small mammal. Based on general relationships of body size to body volume, larger vertebrates will be exposed to lower doses and smaller animals, such as insects, to much higher doses than small vertebrates under comparable exposure conditions. Because of the apparently low toxicity of imazapic to animals, the rather substantial variations in the different exposure assessments have little impact on the assessment of risk to terrestrial animals.

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 considered in this risk assessment, 0.1 lb a.e./acre and should be regarded as an extreme/accidental form of exposure that is not likely to occur in most Forest Service applications. Estimates for the other routes of exposure are much less. All of these exposure scenarios are dominated by situational variability because the levels of exposure are highly dependent on site-specific conditions. Thus, the exposure estimates are intended to represent conservative but plausible ranges that could occur but these ranges may over-estimate or under-estimate actual exposures in some cases. Spray drift estimated using AgDRIFT. The proportion of the applied amount transported off-site from runoff is based on GLEAMS modeling of clay, loam, and sand. The amount of imazapic that might be transported off-site from wind erosion is based on estimates of annual soil loss associated with wind erosion and the assumption that the herbicide is incorporated into the top 1 cm of soil. Exposure from the use of contaminated irrigation water is based on the same data used to estimate human exposure from the consumption of contaminated ambient water and involves both monitoring studies as well as GLEAMS modeling.

Exposures to aquatic plants and animals is based on essentially the same information used to assess the exposure to terrestrial species from contaminated water. The peak concentrations of imazapic in contaminated water is estimated at 0.0005 mg/L (0.00005 to 0.01) mg a.e./L per 1 lb a.e./acre. For longer-term exposures, average estimated rate of contamination of ambient water associated with the normal application of imazapic is 0.00002 (0.00001 to 0.00003) mg a.e./L at

an application rate of 1 lb a.e./acre. For the assessment of potential hazards, these contamination rates are adjusted based on the application rates considered in this risk assessment.

4.2.2. Terrestrial Animals. Terrestrial animals might be exposed to any applied herbicide from direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect dermal contact with contaminated vegetation.

In this exposure assessment, estimates of oral exposure are expressed in the same units as the available toxicity data. As in the human health risk assessment, these units are usually expressed as mg of agent per kg of body weight and abbreviated as mg/kg. For dermal exposure, the units of measure usually are expressed in mg of agent per cm^2 of surface area of the organism and abbreviated as mg/cm^2. In estimating dose, however, a distinction is made between the exposure dose and the absorbed dose. The *exposure dose* is the amount of material on the organism (i.e., the product of the residue level in mg/cm^2 and the amount of surface area exposed), which can be expressed either as mg/organism or mg/kg body weight. The *absorbed dose* is the proportion of the exposure dose that is actually taken in or absorbed by the animal.

The exposure assessments for terrestrial animals are summarized in Worksheet G01. As with the human health exposure assessment, the computational details for each exposure assessment presented in this section are provided scenario specific worksheets (Worksheets F01 through F16b). Given the large number of species that could be exposed to herbicides and the varied diets in each of these species, a very large number of different exposure scenarios could be generated. For this generic – i.e., not site- or species-specific – risk assessment, an attempt is made to limit the number of exposure scenarios.

Because of the relationship of body weight to surface area as well as the consumption of food and water, small animals will generally receive a higher dose, in terms of mg/kg body weight, than large animals will receive for a given type of exposure. Consequently, most general exposure scenarios for mammals and birds are based on a small mammal or bird. For mammals, the body weight is taken as 20 grams, typical of mice, and exposure assessments are conducted for direct spray (F01 and F02a), consumption of contaminated fruit (F03, F04a, F04b), and contaminated water (F05, F06, F07). Grasses will generally have higher concentrations of herbicides than fruits and other types of vegetation (Fletcher et al. 1994; Hoerger and Kenaga 1972). Because small mammals do not generally consume large amounts of grass, the scenario for the assessment of contaminated grass is based on a large mammal – a deer (Worksheets F10, F11a, and F11b). Other exposure scenarios for a mammals involve the consumption of contaminated insects by a small mammal (Worksheet F14a) and the consumption of small mammals contaminated by direct spray by a large mammalian carnivore (Worksheet F16a). Exposure scenarios for birds involve the consumption of contaminated insects by a small bird (Worksheet F14b), the consumption of contaminated fish by a predatory bird (Worksheets F08 and F09), the consumption of small mammals contaminated by direct spray by a predatory bird and the consumption of contaminated grasses by a large bird (F12, F13a, and F13b).

While a very large number of other exposure scenarios could be generated, the specific exposure scenarios developed in this section are designed as conservative screening scenarios that may serve as guides for more detailed site-specific assessments by identifying the groups and routes of exposure that are of greatest concern.

4.2.2.1. Direct Spray – In the broadcast application of any herbicide, wildlife species may be sprayed directly. This scenario is 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 absorbed depends on the application rate, the surface area of the organism, and the rate of absorption.

For this risk assessment, three groups of direct spray exposure assessments are conducted. The first, which is defined in Worksheet F01, involves a 20 g mammal that is sprayed directly over one half of the body surface as the chemical is being applied. The range of application rates as well as the typical application rate is used to define the amount deposited on the organism. The absorbed dose over the first day (i.e., a 24-hour period) is estimated using the assumption of first-order dermal absorption. In the absence of any data regarding dermal absorption in a small mammal, the estimated absorption rate for humans is used (see Section 3.1.3). An empirical relationship between body weight and surface area (Boxenbaum and D'Souza 1990) is used to estimate the surface area of the animal. The estimates of absorbed doses in this scenario may bracket plausible levels of exposure for small mammals based on uncertainties in the dermal absorption rate of imazapic.

Other, perhaps more substantial, uncertainties affect the estimates for absorbed dose. For example, the estimate based on first-order dermal absorption does not consider fugitive losses from the surface of the animal and may overestimate the absorbed dose. Conversely, some animals, particularly birds and mammals, groom frequently, and grooming may contribute to the total absorbed dose by direct ingestion of the compound residing on fur or feathers. Furthermore, other vertebrates, particularly amphibians, may have skin that is far more permeable than the skin of most mammals. Quantitative methods for considering the effects of grooming or increased dermal permeability are not available. As a conservative upper limit, the second exposure scenario, detailed in Worksheet F02, is developed in which complete absorption over day 1 of exposure is assumed.

Because of the relationship of body size to surface area, very small organisms, like bees and other terrestrial insects, might be exposed to much greater amounts of imazapic per unit body weight, compared with small mammals. Consequently, a third exposure assessment is developed using a body weight of 0.093 g for the honey bee (USDA/APHIS 1993) and the equation above for body surface area proposed by Boxenbaum and D'Souza (1990). Because there is no information regarding the dermal absorption rate of imazapic by bees or other invertebrates, this exposure scenario, detailed in Worksheet F02b, also assumes complete absorption over the first day of exposure.

Direct spray scenarios are not given for large mammals. As noted above, allometric relationships dictate that large mammals will be exposed to lesser amounts of a compound in any direct spray scenario than smaller mammals. As detailed further in Section 4.4, the direct spray scenarios for the small mammal are substantially below a level of concern. Consequently, elaborating direct spray scenarios for a large mammal would have no impact on the characterization of risk.

4.2.2.2. Indirect Dermal Contact – As in the human health risk assessment (see Section 3.2.3.3), the only approach for estimating the potential significance of indirect dermal contact is to assume a relationship between the application rate and dislodgeable foliar residue. The study by Harris and Solomon (1992) (Worksheet A04) is used to estimate that the dislodgeable residue will be approximately 10 times less than the nominal application rate.

Unlike the human health risk assessment in which transfer rates for humans are available, there are no transfer rates available for wildlife species. As discussed in Durkin et al. (1995), the transfer rates for humans are based on brief (e.g., 0.5 to 1-hour) exposures that measure the transfer from contaminated soil to uncontaminated skin. Wildlife, compared with humans, are likely to spend longer periods of time in contact with contaminated vegetation.

It is reasonable to assume that for prolonged exposures an equilibrium may be reached between levels on the skin, rates of absorption, and levels on contaminated vegetation, although there are no data regarding the kinetics of such a process. The bioconcentration data on imazapic indicates that imazapic will not accumulate in the tissue of the fish. Thus, a plausible partition coefficient is unity (i.e., the concentration of the chemical on the surface of the animal will be equal to the dislodgeable residue on the vegetation).

Under these assumptions, the absorbed dose resulting from contact with contaminated vegetation will be one-tenth that associated with comparable direct spray scenarios. As discussed in the risk characterization for ecological effects (Section 4.4), the direct spray scenarios result in exposure levels below the estimated NOAEL (i.e., hazard quotients below one). Consequently, details of the indirect exposure scenarios for contaminated vegetation are not further elaborated in this document.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey – Since imazapic will be applied to vegetation, the consumption of contaminated vegetation is an obvious concern and separate exposure scenarios are developed for acute and chronic exposure scenarios for a small mammal (Worksheets F04a and F04b) and large mammal (Worksheets F10, F11a, and F11b) as well as large birds (Worksheets F12, F13a, and F13b).

For the consumption of contaminated vegetation, a small mammal is used because allometric relationships indicate that small mammals will ingest greater amounts of food per unit body weight, compared with large mammals. The amount of food consumed per day by a small mammal (i.e., an animal weighing approximately 20 g) is equal to about 15% of the mammal's total body weight (U.S. EPA/ORD 1989). When applied generally, this value may overestimate

or underestimate exposure in some circumstances. For example, a 20 g herbivore has a caloric requirement of about 13.5 kcal/day. If the diet of the herbivore consists largely of seeds (4.92 kcal/g), the animal would have to consume a daily amount of food equivalent to approximately 14% of its body weight [(13.5 kcal/day ÷ 4.92 kcal/g)÷20g = 0.137]. Conversely, if the diet of the herbivore consists largely of vegetation (2.46 kcal/g), the animal would have to consume a daily amount of food equivalent to approximately 27% of its body weight [(13.5 kcal/day ÷ 2.46 kcal/g)÷20g = 0.274] (U.S. EPA/ORD 1993, pp.3-5 to 3-6). For this exposure assessment (Worksheet F03), the amount of food consumed per day by a small mammal weighing 20 g is estimated at about 3.6 g/day or about 18% of body weight per day from the general allometric relationship for food consumption in rodents (U.S. EPA/ORD 1993, p. 3-6).

A large herbivorous mammal is included because empirical relationships of concentrations of pesticides in vegetation, discussed below, indicate that grasses may have substantially higher pesticide residues than other types of vegetation such as forage crops or fruits (Worksheet A04). Grasses are an important part of the diet for some large herbivores, but most small mammals do not consume grasses as a substantial proportion of their diet. Thus, even though using residues from grass to model exposure for a small mammal is the most conservative approach, it is not generally applicable to the assessment of potential adverse effects. Hence, in the exposure scenarios for large mammals, the consumption of contaminated range grass is modeled for a 70 kg herbivore, such as a deer. Caloric requirements for herbivores and the caloric content of vegetation are used to estimate food consumption based on data from U.S. EPA/ORD (1993). Details of these exposure scenarios are given in worksheets F10 for acute exposures as well as Worksheets F11a and F11b for longer-term exposures.

For the acute exposures, the assumption is made that the vegetation is sprayed directly – i.e., the animal grazes on site – and that100% of the animals diet is contaminated. While appropriately conservative for acute exposures, neither of these assumptions are plausible for longer-term exposures. Thus, for the longer-term exposure scenarios for the large mammal, two sub-scenarios are given. The first is an on-site scenario that assumes that a 70 kg herbivore consumes short grass for a 90 day period after application of the chemical. In the worksheets, the contaminated vegetation is assumed to account for 30% of the diet with a range of 10% to 100% of the diet. These are essentially arbitrary assumptions reflecting grazing time at the application site by the animal. Because the animal is assumed to be feeding at the application site, drift is set to unity - i.e., direct spray. This scenario is detailed in Worksheet 11a. The second sub-scenario is similar except the assumption is made that the animal is grazing at distances of 25 to 100 feet from the application site (lowing risk) but that the animal consumes 100% of the diet from the contaminated area (increasing risk). For this scenario, detailed in Worksheet F12b, AgDRIFT is used to estimate deposition on the off-site vegetation. Drift estimates from AgDRIFT are summarized in Worksheet A06 and this model is discussed further in Section 4.2.3.2.

The consumption of contaminated vegetation is also modeled for a large bird. For these exposure scenarios, the consumption of range grass by a 4 kg herbivorous bird, like a Canada Goose, is modeled for both acute (Worksheet F12) and chronic exposures (Worksheets F13a and

F13b). As with the large mammal, the two chronic exposure scenarios involve sub-scenarios for on-site as well as off-site exposure.

For this component of the exposure assessment, the estimated amounts of pesticide residue in vegetation are based on the relationship between application rate and residue rates on different types of vegetation. As summarized in Worksheet A04, these residue rates are based on estimated residue rates from Fletcher et al. (1994).

Similarly, the consumption of contaminated insects is modeled for a small (10g) bird and a small (20g) mammal. No monitoring data have been encountered on the concentrations of imazapic in insects after applications of imazapic. The empirical relationships recommended by Fletcher et al. (1994) are used as surrogates as detailed in Worksheets F14a and F14b. To be conservative, the residue rates from small insects are used – i.e., 45 to 135 ppm per lb/ac – rather than the residue rates from large insects – i.e., 7 to 15 ppm per lb/ac.

A similar set of scenarios are provided for the consumption of small mammals by either a predatory mammal (Worksheet 16a) or a predatory bird (Worksheet 16a). Each of these scenarios assume that the small mammal is directly sprayed at the specified application and the concentration of the compound in the small mammal is taken from the worksheet for direct spray of a small mammal under the assumption of 100% absorption (Worksheet F02a).

In addition to the consumption of contaminated vegetation and insects, imazapic may reach ambient water and fish. Thus, a separate exposure scenario is developed for the consumption of contaminated fish by a predatory bird in both acute (Worksheet F08) and chronic (Worksheet F09) exposures. Because predatory birds usually consume more food per unit body weight than do predatory mammals (U.S. EPA 1993, pp. 3-4 to 3-6), separate exposure scenarios for the consumption of contaminated fish by predatory mammals are not developed.

4.2.2.4. Ingestion of Contaminated Water – Estimated concentrations of imazapic in water are identical to those used in the human health risk assessment (Worksheet B06). The only major differences involve the weight of the animal and the amount of water consumed. There are well-established relationships between body weight and water consumption across a wide range of mammalian species (e.g., U.S. EPA 1989). Mice, weighing about 0.02 kg, consume approximately 0.005 L of water/day (i.e., 0.25 L/kg body weight/day). These values are used in the exposure assessment for the small (20 g) mammal. Unlike the human health risk assessment, estimates of the variability of water consumption are not available. Thus, for the acute scenario, the only factors affecting the variability of the ingested dose estimates include the field dilution rates (i.e., the concentration of the chemical in the solution that is spilled) and the amount of solution that is spilled. As in the acute exposure scenario for the human health risk assessment, the amount of the spilled solution is taken as 200 gallons. In the exposure scenario involving contaminated ponds or streams due to contamination by runoff or percolation, the factors that affect the variability are the water contamination rate, (see Section 3.2.3.4.2) and the application

rate. Details regarding these calculations are summarized in Worksheets F06 and Worksheet F07.

4.2.3. Terrestrial Plants. In general, 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.

4.2.3.1. Direct Spray – Unintended direct spray will result in an exposure level equivalent to the application rate. For many types of herbicide applications – e.g., rights-of-way management – 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 human health risk assessment for the consumption of contaminated vegetation.

4.2.3.2. Off-Site Drift – Because off-site drift is more or less a physical process that depends on droplet size and meteorological conditions rather than the specific properties of the herbicide, estimates of off-site drift can be modeled using AgDRIFT (Teske et al. 2001). AgDRIFT is a model developed as a joint effort by the EPA Office of Research and Development and the Spray Drift Task Force, a coalition of pesticide registrants. AgDRIFT is based on the algorithms in FSCBG (Teske and Curbishley 1990), a drift model previously used by USDA.

For aerial applications, AgDRIFT permits very detailed modeling of drift based on the chemical and physical properties of the applied product, the configuration of the aircraft, as well as wind speed and temperature. For ground applications, AgDRIFT provides estimates of drift based solely on distance downwind as well as the types of ground application: low boom spray, high boom spray, and orchard airblast. Representative estimates based on AgDRIFT (Version 1.16) are given in Worksheet A06. For the current risk assessment, the AgDRIFT estimates are used for consistency with comparable exposure assessments conducted by the U.S. EPA. In addition, AgDRIFT represents a detailed evaluation of a very large number of field studies and is likely to provide more reliable estimates of drift. Further details of AgDRIFT are available at http://www.AgDRIFT.com/.

Estimates of drift for ground and aerial applications is given in Worksheet A06. In ground broadcast applications, imazapic will typically be applied by low boom ground spray and thus these estimates are used in the current risk assessment.

Drift associated with backpack (directed foliar applications) are likely to be much less although studies quantitatively assessing drift after backpack applications have not been encountered. Drift distance can be estimated using Stoke's law, which describes the viscous drag on a moving sphere. According to Stoke's law:

$$v = \frac{D^2 \cdot g}{18n}$$

or

$$v = 2.87 \cdot 10^5 \cdot D^2$$

where ***v*** is the velocity of fall (cm sec^{-1}), ***D*** is the diameter of the sphere (cm), ***g*** is the force of gravity (980 cm sec^{-2}), and ***n*** is the viscosity of air ($1.9 \cdot 10^{-4}$ g sec^{-1} cm^{-1} at 20°C) (Goldstein et al. 1974).

In typical backpack ground sprays, droplet sizes are greater than 100 µ, and the distance from the spray nozzle to the ground is 3 feet or less. In mechanical sprays, raindrop nozzles might be used. These nozzles generate droplets that are usually greater than 400 µ, and the maximum distance above the ground is about 6 feet. In both cases, the sprays are directed downward.

Thus, the amount of time required for a 100 µ droplet to fall 3 feet (91.4 cm) is approximately 3.2 seconds,

$$91.4 \div (2.87 \cdot 10^5 (0.01)^2).$$

The comparable time for a 400 µ droplet to fall 6 feet (182.8 cm) is approximately 0.4 seconds,

$$182.8 \div (2.87 \cdot 10^5 (0.04)^2).$$

For most applications, the wind velocity will be no more than 5 miles/hour, which is equivalent to approximately 7.5 feet/second (1 mile/hour = 1.467 feet/second). Assuming a wind direction perpendicular to the line of application, 100 µ particles falling from 3 feet above the surface could drift as far as 23 feet (3 seconds · 7.5 feet/second). A raindrop or 400 µ particle applied at 6 feet above the surface could drift about 3 feet (0.4 seconds · 7.5 feet/second).

For backpack applications, wind speeds of up to 15 miles/hour are allowed in Forest Service programs. At this wind speed, a 100 µ droplet can drift as far as 68 feet (3 seconds · 15 · 1.5 feet/second). Smaller droplets will of course drift further, and the proportion of these particles in the spray as well as the wind speed and turbulence will affect the proportion of the applied herbicide that drifts off-site.

4.2.3.3. Runoff – Imazapic or any other herbicide may be transported to off-site soil by runoff or percolation. Both runoff and percolation are considered in estimating contamination of ambient water. For assessing off-site soil contamination, however, only runoff is considered. This approach is reasonable because off-site runoff will contaminate the off-site soil surface and could impact nontarget plants. Percolation, on the other hand, represents the amount of the herbicide

that is transported below the root zone and thus may impact water quality but should not affect off-site vegetation.

Based on the results of the GLEAMS modeling (Section 3.2.3.4.2), the proportion of the applied imazapic lost by runoff was estimated for clay, loam, and sand at rainfall rates ranging from 5 inches to 250 inches per year. These results are summarized in Worksheet G04 and indicate that runoff will be negligible in relatively arid environments as well as sandy or loam soils. In clay soils, which have the highest runoff potential, off-site loss may reach up to about 3.5% of the applied amount in regions with very high rainfall rates.

4.2.3.4. Contaminated Irrigation Water – Unintended direct exposures of nontarget plant species may occur through the use of contaminated ambient water for irrigation. Although there are no studies in the literature addressing the impact of imazapic in contaminated irrigation water, the effects of such exposure scenarios on nontarget vegetation have been observed with other herbicides (e.g., Bhandary et al. 1991). Furthermore, given the mobility of imazapic, the contamination of irrigation water is a plausible scenario.

The levels of exposure associated with this scenario will depend on the concentration of imazapic in the ambient water used for irrigation and the amount of irrigation water that is applied. As discussed in section 3.2.3.4, some contamination of ambient water may be anticipated and can be quantified [Worksheet B06].

The amount of irrigation water that may be applied will be highly dependent on the climate, soil type, topography, and plant species under cultivation. Thus, the selection of an irrigation rate is somewhat arbitrary. Typically, plants require 0.1 to 0.3 inch of water per day (Delaware Cooperative Extension Service 1999). In the absence of any general approach of determining and expressing the variability of irrigation rates, the application of one inch of irrigation water will be used in this risk assessment. This is somewhat higher than the maximum daily irrigation rate for sandy soil (0.75 inches/day) and substantially higher than the maximum daily irrigation rate for clay (0.15 inches/day) (Delaware Cooperative Extension Service 1999).

Based on the estimated concentrations of imazapic in ambient water and an irrigation rate of 1 inch per day, the estimated functional application rate of imazapic to the irrigated area is 1.13×10^{-6} (1.13×10^{-7} to 2.26×10^{-5}) lb a.e./acre (see Worksheet F15 for details of these calculations). This level of exposure is inconsequential relative to off-site drift and runoff. Specifically, off-site movement from runoff can result in functional offsite application rates of 5.07×10^{-2} lb a.e./acre (Worksheet G04) and offsite movement from drift can result in functional offsite application rates of about 1.87×10^{-3} lb a.e./acre at 25 feet from the application site after ground broadcast applications (Worksheet G05a).

4.2.3.5. Wind Erosion – Wind erosion is a major transport mechanism for soil (e.g., Winegardner 1996). Although no specific incidents of nontarget damage from wind erosion have been encountered in the literature for imazapic, this mechanism has been associated with the

environmental transport of other herbicides (Buser 1990). Numerous models have been developed for wind erosion (e.g., Strek and Spaan 1997; Strek and Stein 1997) and the quantitative aspects of soil erosion by wind are extremely complex and site specific. Field studies conducted on agricultural sites found that wind erosion may account for annual soil losses ranging from 2 to 6.5 metric tons/ha (Allen and Fryrear 1977). The upper range reported by Allen and Fryrear (1977) is nearly the same as the rate of 2.2 tons/acre (5.4 tons/ha) reported by the USDA (1998). The temporal sequence of soil loss (i.e., the amount lost after a specific storm event involving high winds) depends heavily on soil characteristics as well as meteorological and topographical conditions.

To estimate the potential transport of imazapic by wind erosion, this risk assessment uses average soil losses ranging from 1 to 10 tons/ha·year, with a typical value of 5 tons/ha·year. The value of 5 tons/ha·year is equivalent to 500 g/m^2 (1 ton=1000 kg and 1 ha = 10,000 m^2) or 0.05 g/cm^2 (1m^2=10,000 cm^2). Using a soil density of 2 g/cm^3, the depth of soil removed from the surface per year would be 0.025 cm [(0.05 g/cm^2)÷ (2 g/cm^3)]. The average amount per day would be about 0.00007 cm/day (0.025 cm per year ÷ 365 days/year). This central estimate is based on a typical soil loss rate of 5 tons/ha·year. Since the range of plausible rates of annual soil loss is 1 to 10 tons/ha·year, the range of soil loss per day may be calculated as 0.00001 cm/day (0.00007÷5 = 0.000014) to 0.0001 cm/day (0.00007×2 = 0.00014).

The amount of imazapic that might be transported by wind erosion depends on several factors, including the application, the depth of incorporation into the soil, the persistence in the soil, the wind speed, and the topographical and surface conditions of the soil. Under desirable conditions, like relatively deep (10 cm) soil incorporation, low wind speed, and surface conditions that inhibit wind erosion, it is likely that wind transport of imazapic would be neither substantial or nor significant. For this risk assessment, it will be assumed that imazapic is incorporated into the top 1 cm of soil. Thus, daily soil losses expressed as a proportion of applied amount would be 0.00007 with a range of 0.00001 to 0.001.

As with the deposition of imazapic in runoff, the deposition of the imazapic contaminated soil from wind erosion will vary substantially with local conditions and, for this risk assessment, neither concentration nor dispersion is considered quantitatively. Nonetheless, these factors together with the general and substantial uncertainties in the exposure assessment are considered in the risk characterization (see Section 4.4).

4.2.4. Soil Organisms. No data are available on effects of imazapic on soil invertebrates (Section 4.1.2.3) or soil microorganisms (Section 4.1.2.5). Consequently, an exposure assessment for these organisms is not required for the current risk assessment. Nonetheless, an exposure assessment for these groups is included in the event that data become available after the preparation of this risk assessment that may be used by individuals in region or site specific assessments.

For both soil microorganisms and soil invertebrates, the toxicity data are typically expressed in units of soil concentration – i.e., mg agent/kg soil which is equivalent to parts per million (ppm) concentrations in soil. The GLEAMS modeling discussed in Section 3.2.3.4 provides estimates of concentration in soil as well as estimates of off-site movement (runoff, sediment, and percolation). Based on the GLEAMS modeling, concentrations in clay, loam, and sand over a wide range of rainfall rates are summarized in Table 4-1. As indicated in this table, peak soil concentrations in the range of about 6 ppm are likely in relatively arid soils at an application rate of 1 lb a.e./acre. As rainfall rate increases, maximum soil concentrations are reduced somewhat because of losses from soil through percolation or runoff. Longer term concentrations in soil vary substantially with rainfall rates and range from about 1 to 2 ppm in very arid soils to about 0.01 ppm in regions with high rainfall rates.

4.2.5. Aquatic Organisms. The potential for effects on aquatic species are based on estimated concentrations of imazapic in water that are identical to those used in the human health risk assessment (Worksheet B06). As summarized in Worksheet B06, the peak estimated rate of contamination of ambient water associated with the normal application of imazapic is 0.0005 (0.00005 to 0.01) mg a.e./L at an application rate of 1 lb a.e./acre. For longer-term exposures, average estimated rate of contamination of ambient water associated with the normal application of imazapic is 0.00002 (0.00001 to 0.00003) mg a.e./L at an application rate of 1 lb a.e./acre. For the assessment of potential hazards, these contamination rates are adjusted based on the application considered in this risk assessment – i.e., 0.1 lb a.e./acre. The consequences of using higher application rates is discussed in the risk characterization (Section 4.4).

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview. For terrestrial mammals, the dose-response assessment is based on the same data as the human health risk assessment (i.e., an acute NOAEL of 350 mg/kg/day and a chronic NOAEL of 45 mg/kg/day). None of the exposure scenarios, acute or longer term, result in exposure estimates that exceed the applicable NOAEL. Birds appear to be somewhat less sensitive to imazapic than mammals. The 5-day dietary NOEL of 1100 mg/kg/day in bobwhite quail is used to characterize risks to birds associated with acute exposures. For chronic toxicity, NOAEL for birds is taken as 113 mg/kg bw/day from a dietary reproduction study. The only data available on terrestrial invertebrates is the standard bioassay in honey bees in which the NOAEL based on mortality was 387 mg/kg bw, very close to the NOAEL of 350 mg/kg bw in mammals.

The toxicity data for terrestrial plants involves standard bioassays for pre-emergent and post-emergent applications. For exposures involving the off-site drift of imazapic, the range of NOAEL values for post-emergence applications is 0.001 lb/acre for sensitive species and 0.032 for tolerant species. For exposures involving off-site runoff, the range of NOAEL values for pre-emergence applications is 0.032 lb/acre for sensitive species and 0.064 lb/acre for tolerant species.

Imazapic does not appear to be very toxic to aquatic fish or invertebrates. The available data are not sufficient to identify sensitive and tolerant species because the screening tests conducted at nominal concentrations 100 mg/L failed to demonstrated adverse effects in either acute or longer-term exposures. *Lemna gibba*, an aquatic macrophyte, is much more sensitive to imazapic than aquatic animals. An NOEC of 0.00127 mg/L in *Lemna minor* is used for quantifying effects in aquatic macrophytes. By comparison to *Lemna gibba*, unicellular aquatic algae appear to be relatively insensitive to imazapic and a concentration of 50 µg/L is taken as an LOEC for moderate growth inhibition and is used for the risk characterization.

4.3.2. Toxicity to Terrestrial Organisms.

4.3.2.1. Mammals – As summarized in the dose-response assessment for the human health risk assessment (Section 3.3.3.), the functional chronic NOAEL in experimental mammals is taken as 45 mg/kg/day. This is based on a LOAEL of 137 mg/kg/day from a six month feeding study in dogs (Wolford 1993) and the application of an uncertainty factor of 3 to extrapolate from the LOAEL to a NOAEL. None of the longer-term exposure scenarios for mammals approach this estimated NOAEL (Worksheet G01) and all of the resulting hazard quotients are substantially below a level of concern (Worksheet G01); thus, it is not necessary to elaborate on this dose-response assessment. For acute exposures, the acute NOAEL of 350 mg/kg/day from the teratology study in rabbits (MacKenzie 1992) will be used to characterize risk. This is also consistent with the acute NOAEL selected by U.S. EPA for the characterization of risks from short-term oral exposures (Section 3.3.3).

It should be noted that this approach – i.e., the selection of the lowest acute and chronic NOAELs – may substantially overestimate risk for small mammals for which substantially higher dietary NOAEL values have been noted (Appendix 1). This, however, has no material impact on the risk

assessment because, as detailed in Section 4.4.2.1, all of the exposures are substantially below the lowest acute and chronic NOAELs.

4.3.2.2. Birds - As discussed in Section 4.1.2.2 and detailed in Appendix 2, imazapic has a low order of acute toxicity in birds. After single gavage exposures, no mortality or signs of toxicity are apparent at doses of up to2150 mg/kg in bobwhite quail (Fletcher and Sullivan 1993a) and 1470 mg/kg in mallard ducks (Fletcher and Sullivan 1993b). Similarly, no adverse effects were noted in either bobwhite quail or mallard ducks at 5-day feeding studies at dietary concentrations of up to5000 ppm (Pedersen et al. 1993a,b). As noted in Appendix 2, the dietary concentration of 5000 ppm corresponds to about 1100 mg/kg/day in bobwhite quail and 1300 mg/kg/day in mallard ducks.

The somewhat lower NOAEL doses in the 5-day feeding studies compared to the gavage studies do not suggest gavage administration is less toxic than dietary administration but simply reflects the lower dose rates used in the dietary studies. Typically, gavage dosing leads to greater toxicity because all of the agent is inserted into the crop of the bird at one time. In dietary studies, the consumption of the compound is spread more evenly over the course of a day as the bird consumes food.

For this risk assessment, the 5-day dietary NOEL of 1100 mg/kg/day in bobwhite quail (Pedersen et al. 1993a) will be used to characterize risks to birds associated with acute exposures. This approach is taken because most of the acute exposure scenarios used in this risk assessment involve either dietary exposures or exposures that are similar to dietary exposures in that the exposure occurs over the course of a day rather than as a single event. Given the higher NOAEL values from gavage exposure, it is likely that the true NOAEL for dietary exposure is substantially higher than 1100 mg/kg/day. Because of the very low hazard quotients for acute exposures of birds (Worksheet G02), the underestimate of the acute NOAEL for birds has no impact on the risk characterization.

For chronic toxicity, the most sensitive endpoint for imazapic in birds appears to be decreased body weight gain in chicks after the subchronic oral administration of imazapic to quail (Miller et al. 1998). The NOAEL for this effect - a dietary concentration of 1187 ppm corresponding to a dose of approximately 113 mg/kg bw/day - is used to assess the consequences of longer term exposures to imazapic in birds. As with mammals, the estimated exposures of birds to imazapic are substantially below this NOAEL and further elaboration of the dose-response relationship is unnecessary.

4.3.2.3. Terrestrial Invertebrates - As discussed in Section 4.1.2.3, a standard bioassay was conducted on the toxicity of imazapic to honey bees (Hoxter et al. 1993). At the highest dose tested, 100 µg/bee, mortality was observed in 25% of the treated animals. At 36 µg/bee, mortality was not statistically significantly higher than controls. Using a body weight of 0.093 g for the honey bee (USDA/APHIS 1993), the 36 µg/bee dose corresponds to 387 mg/kg bw (0.036 mg/0.000093 kg). This value will be used in the risk characterization for assessing effects

on terrestrial invertebrates. Given the large number of species of terrestrial invertebrates, the use of this single study on a single species obviously leads to uncertainty in the risk assessment.

4.3.2.4. Terrestrial Plants (Macrophytes) – As discussed in Section 4.1.2.4, two studies are available on the toxicity of imazapic to nontarget plants, one study involving pre-emergence applications (Chetram et al. 1994a) and the other involving post-emergence application (Chetram et al. 1994b).

For exposures involving the off-site drift of imazapic, the range of NOAEL values for post-emergence applications is used in the risk characterization (i.e., 0.001 lb/acre for cabbage, cucumber, and tomato and 0.032 for lettuce). This 32-fold range is intended to represent plausible differences between the most sensitive and most resistant nontarget plant species. These NOAEL values are used to characterize risks associated with offsite drift from ground applications (Worksheet G05a) and aerial applications (Worksheet G05b).

For exposures involving off-site transport through runoff, direct deposition on the nontarget plants is less plausible and the exposures are more likely to occur through direct soil contamination. Therefore, the results of the seedling emergence assay (Chetram et al. 1994a) are used to characterize risks associated with runoff. As discussed in Section 4.1.2.4, there is a very narrow range between the most sensitive species (i.e., the lowest NOAEL) and the most tolerant species (i.e., the highest NOAEL). The NOAEL for the most sensitive species is taken as 0.032 lb/acre, the NOEC for ryegrass. The NOAEL for the most tolerant species is taken as 0.064 lb/acre, the highest application rate tested, in which no effects were noted in soybeans, lettuce, radishes, tomatoes, cucumbers, cabbage, oats, corn, and onions. These NOAEL values are entered into Worksheet G03 and used to characterize risk (Section 4.4).

4.3.2.5. Soil Organisms **-** As noted in Section 4.1.2, no information has been encountered on the effects of imazapic on soil microorganisms or soil invertebrates such as earthworms. Consequently, no dose-response relationship for these organisms can be established.

4.3.3. Aquatic Organisms.

4.3.3.1. Animals **–** Based on the low toxicity of imazapic to all species of fish on which data are available, there is no basis for selecting sensitive or tolerant species. For both acute and chronic exposures, the chronic concentration of 100 mg/L is used as the NOEC for all species. This is analogous to the application of the chronic RfD to both acute and chronic exposure scenarios for imazapic (Section 3.3.4). This value is entered into Worksheet G03 for all exposures involving fish. To maintain consistency with other Forest Service risk assessments and in the event that additional data may become available, Worksheet G03 designated sensitive and tolerant species but the same toxicity value is used for both groups.

As with fish, no adverse effects have been observed in acute and chronic exposures to nominal concentrations of imazapic of up to 100 mg/L. Thus, as with fish, there is no basis for identifying sensitive or tolerant species of aquatic invertebrates and the the concentration of

100 mg/L is used to characterize risks for all exposure scenarios involving aquatic invertebrates (Worksheet G03).

4.3.3.4. Aquatic Plants – Standard toxicity bioassays to assess the effects of imazapic on aquatic plants were submitted to the U.S. EPA in the registration of imazapic and are summarized in Appendix 3.

The most sensitive species on which data are available is the aquatic macrophyte, *Lemna gibba*, with an LC_{50} of 6.1 µg/L and an LC_{25} of 4.23 µg/L (Hughes et al. 1994). Two concentrations reported by Hughes et al. (1994) may be viewed as NOEC values. At 2.58 µg/L, growth inhibition was 4.2% and was not significantly different from the growth in the control group. Typically, this NOEC would be used to characterize risk. However, this value is relatively close to both the LC_{50} and the LC_{25} - i.e., the slope of the concentration-response curve appears to be very steep. At 1.27 µg/L, no growth inhibition was observed and this value is used in Worksheet G03 to characterize risks for aquatic macrophytes.

By comparison to *Lemna gibba*, unicellular aquatic algae appear to be relatively insensitive to imazapic. The magnitude of the difference, however, is difficult to quantify because the bioassays conducted by Hughes et al. (1994) on algae tested on a single concentration (about 50 µg/L) in each species. This approach was taken because the test concentrations were anticipated to be higher than concentrations that were likely to occur in the environment and these high concentrations did not result in substantial indications of toxicity – i.e., growth inhibition of <1% to about 12%. In any event, EC_{50} values cannot be determined and are characterized in Hughes et al. (1994) simply as greater than the highest concentration that was tested. For the current risk assessment, the concentration of 50 µg/L is taken as an LOEC and is used in Worksheet G03 to characterize risk to unicellular aquatic algae.

4.4. RISK CHARACTERIZATION

4.4.1. Overview. There is very little indication that the use of imazapic in Forest Service programs will lead to substantial unintended adverse effects. Imazapic is an effective herbicide and even tolerant plants that are directly sprayed with imazapic at normal application rates are likely to be damaged. Some sensitive plant species could be affected by the off-site drift of imazapic depending on local site-specific conditions within a relatively small distance from the application site – i.e., up to about 50 feet in ground applications and somewhat over 100 feet in aerial applications. Damage to terrestrial plants from runoff is possible in some areas but is not likely to be substantial. Under conditions in which runoff is favored – i.e., clay soils and relatively high rainfall rates – some aquatic macrophytes could also be affected by peak concentrations of imazapic. No effect in unicellular algae are anticipated.

Adverse effects in terrestrial or aquatic animals do not appear to be likely. The weight of evidence suggests that no adverse effects in mammals, birds, fish, and terrestrial or aquatic invertebrates are plausible using typical or worst-case exposure assumptions at the typical application rate of 0.1 lb/acre or the maximum application rate of 0.1875 lb/acre.

As in any ecological risk assessment, this risk characterization must be qualified. Imazapic has been tested in only a limited number of species and under conditions that may not well-represent populations of free-ranging nontarget animals. Notwithstanding this limitation, the available data are sufficient to assert that no adverse effects on animals are anticipated based on the information that is available.

4.4.2. Terrestrial Organisms.

4.4.2.1. Terrestrial Vertebrates – The quantitative risk characterization for mammals and birds is summarized in Worksheet G02. The toxicity values used for each group of animals is summarized at the bottom of Worksheet G02 and refer to values derived in the dose-response assessment (Sections 4.3.2.1 and 4.3.2.2). In this worksheet, risk is characterized as the estimated dose, taken from Worksheet G01, divided by toxicity value. This ratio is referred to as the hazard quotient (HQ). All exposures summarized in Worksheet G01 are based on the typical application rate of 0.1 lb a.e./acre. At this application rate, an HQ of one or less indicates that the estimated exposure is less than the toxicity value. When this is the case, there is no basis for asserting that adverse effects are plausible.

As discussed in Section 2 (Program Description), the maximum application rate that might be used in Forest Service programs is 0.1875 lb/acre. Because exposure is directly related to application rate, the level of concern for the hazard quotients given in Worksheet G02 for an application rate of 0.1875 lb/acre is about 0.5 [0.1 lb a.e./acre ÷ 0.1875 lb a.e./acre = 0.533].

As indicated in Worksheet G02, the highest hazard quotient for any acute exposure is 0.02 [2e-02], the upper range of the hazard quotient for the consumption of contaminated insects by a small mammal. The highest hazard quotient for any chronic exposure is also 0.02, the upper range of the hazard quotient for the consumption of contaminated vegetation on site by a large

mammal. This hazard quotient of 0.02 is below the level of concern by a factor of 50 at the typical application rate [1÷0.02=50] and below the level of concern by a factor of 25 at the highest application rate [0.5÷0.02=25]. Thus, there is no basis for asserting that adverse effects are likely from acute or longer term exposures from the application of imazapic at any application rate that might be used in Forest Service programs.

The simple verbal interpretation of this quantitative risk characterization is similar to that of the human health risk assessment: the weight of evidence suggests that no adverse effects in mammals or birds are plausible using typical or worst-case exposure assumptions at the typical application rate of 0.1 lb/acre or the maximum application rate of 0.1875 lb/acre. As with the human health risk assessment, this characterization of risk must be qualified. Imazapic has been tested in only a limited number of species and under conditions that may not well-represent populations of free-ranging nontarget terrestrial mammals or birds. Notwithstanding this limitation, the available data are sufficient to assert that no adverse effects are anticipated in terrestrial mammals or birds. As discussed below, imazapic is an effective herbicide and the control of undesirable vegetation and possible effects on nontarget vegetation may lead to secondary effects on terrestrial animals.

No toxicity data are available for reptiles or amphibians. Thus, no quantitative risk characterization for these animals can be made.

4.4.2.2. Terrestrial Invertebrates – Very little information is available on the toxicity of imazapic to terrestrial invertebrates. For the honey bee, the hazard quotient is based on the non-lethal acute dose level of 387 mg/kg from the study by Hoxter et al. (1993). Even at the exposure associated with a direct spray, the hazard quotient of 0.04 is below the level of concern by a factor of 25 [1 ÷ 0.04] at the typical application rate and a factor of 12.5 [0.5 ÷ 0.04] at the maximum application rate. Thus, there is no basis for expecting mortality in bees directly sprayed with imazapic.

4.4.2.3. Soil Microorganisms – Because of the lack of information on the toxicity of imazapic to terrestrial microorganisms (Section 4.3.2.3), no quantitative risk assessment for this group can be given. Nonetheless, imazapic has been used effectively to control unwanted vegetation in both crop and non-crop applications (Section 2). If imazapic 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.

4.4.2.4. Terrestrial Plants – A quantitative summary of the risk characterization for terrestrial plants is presented in Worksheet G04 for runoff and Worksheets G05a and G05b for drift. Analogous to the approach taken for terrestrial animals, risk in these worksheets is characterized as a ratio of the estimated exposure to a benchmark exposure (i.e., exposure associated with a defined response). For both worksheets, the benchmark exposure is a NOEC, as derived in Section 4.3.2.2, for both sensitive and tolerant species.

Imazapic is an effective herbicide and even tolerant plants that are directly sprayed with imazapic at normal application rates are likely to be damaged. As indicated in Worksheets G05a, off-site drift of imazapic associated with ground broadcast applications may cause damage to sensitive plant species at distances of 50 feet or less from the application site. After aerial applications, damage to sensitive nontarget species could be evident at over 100 feet from the application site. For both ground and aerial drift, the closer that the nontarget species is to the application site, the greater is the likelihood of damage. Whether or not damage due to drift would actually be observed after the application of imazapic would depend on a several site-specific conditions, including wind speed and foliar interception by the target vegetation. In other words, in some right-of-way applications conducted at low wind speeds and under conditions in which vegetation at or immediately adjacent to the application site would limit off-site drift, damage due to drift would probably be inconsequential or limited to the area immediately adjacent to the application site. Tolerant plant species would probably not be impacted by the drift of imazapic and might show relatively little damage unless they were directly sprayed.

As summarized in Worksheet G04, runoff could pose a slight risk to sensitive nontarget plant species (i.e., hazard quotients of up to 1.6) under conditions in which runoff is favored – i.e., clay soil at annual rainfall rates of over 100 inches. Higher application rates would result in hazard quotients which exceed the LOC of 0.5 at annual rainfall rates of 50 inches per year. Tolerant plants species would not likely be impacted at the typical application rate (an LOC of 1 in Worksheet G04) but might be affected at the maximum application rate (LOC=0.5) under conditions which favor runoff.

The situational variability in the exposure assessments for runoff, wind erosion, and irrigation water does impact the characterization of risk for nontarget plant species. All of these scenarios may overestimate or underestimate risk under certain conditions. For example, the exposure conditions involving runoff and contaminated irrigation water are plausible for applications in which relatively substantial rainfall occurs shortly after application and in which local topographic and/or hydrological conditions favor either runoff or percolation.

As summarized in Section 4.2.3.5, daily soil losses due to wind erosion, expressed as a proportion of an application rate, could be in the range of 0.00001 to 0.001. This is substantially less than off-site losses associated with runoff from clay at annual rainfall rates of 15 inches or more (Worksheet G04) and similar to off-site losses associated with drift at a distance of 500 feet or more from the application site (Worksheet G05a). As with the drift scenarios, wind erosion could lead to adverse effects in sensitive plant species. Wind erosion of soil contaminated with any herbicide is most plausible in relatively arid environments and if local soil surface and topographic conditions favor wind erosion.

The simple verbal interpretation for this quantitative risk characterization is that some sensitive plant species could be affected by the off-site drift of imazapic depending on local site-specific conditions within a relatively small distance from the application site – i.e., up to about 50 feet in

ground applications and somewhat over 100 feet in aerial applications. Damage from runoff is possible in some areas but is not likely to be substantial.

4.4.3. Aquatic Organisms.

4.4.3.1. Aquatic Animals – The risk characterization for aquatic animals is relatively simple and unambiguous. Imazapic appears to have a very low potential to cause any adverse effects in aquatic animals. As detailed in Section 4.2.3 and summarized in Worksheet G03, concentrations of imazapic in ambient water over prolonged periods of time are estimated to be no greater than 0.000003 mg/L and peak concentration of imazapic associated with runoff or percolation are estimated to be no more than 0.001 mg/L. As summarized in Worksheet G03, all of the hazard quotients for aquatic animals are extremely low, ranging from 0.00000001 (the lower range for longer term exposures in fish and invertebrates) to 0.00001 (the upper range for acute exposures for fish and invertebrates). Thus, there is no basis for asserting that effects on nontarget aquatic species are plausible. As detailed in Section 4.3.3.1, the available data do not permit an assessment of sensitive and tolerant species of fish or invertebrates. While the number of species of fish and invertebrates is not extensive, several species in each group have been tested and the failure to identify sensitive and tolerant species appears to be due simply to the very low toxicity of imazapic to both fish and aquatic invertebrates.

As with other risk characterization worksheets, Worksheet G03 is based on the typical application rate of 0.1 lbs/acre. At the maximum application rate of 0.1875 lbs/acre, all of the hazard quotients would be increased by a factor of about 2. This difference has no impact on the risk characterization for aquatic animals – i.e., the highest hazard quotient 0.00001 in Worksheet G03 would be increased to 0.00002, below the level of concern by a factor of 50,000.

As detailed in Section 3.2.3.4.1, an accidental spill scenario is used in the human health risk assessment as a very conservative screening scenario. While this scenario is not in Worksheet G03, the concentrations in water modeled for the accidental spill range from 0.9 mg/L to 4.5 mg/L with a central estimate of about 1.5 mg/L (Worksheet D05). The upper limit of this range is below the NOEC of 100 mg/L by a factor of about 67 [100 mg/L ÷ 1.5 mg/L] leading to a hazard quotient of 0.015. While this is an extremely arbitrary scenario and while the actual concentrations in the water after a spill would depend on the amount of compound spilled and the size of the water body into which it is spilled, this low hazard quotient underscores the very low order of toxicity of imazapic in aquatic animals.

4.4.3.2. Aquatic Plants – As with the risk assessment for terrestrial species, aquatic plants, particularly macrophytes, are much more sensitive than aquatic animals to imazapic exposure. Nonetheless, as indicated in Worksheet G03, hazard quotients for unicellular algae are substantially below a level of concern based either on peak concentration of imazapic in water associated with runoff (a hazard quotient of 0.02 at the upper range of exposure) as well as longer term concentrations that might be expected (hazard quotient of 0.00006 at the upper range of exposure). Thus, at both the typical application rate (LOC=1) and the maximum application rate (LOC=0.5), the upper ranges of the hazard quotients are substantially below the LOC.

Macrophytes appear to be more sensitive to imazapic than unicellular algae. For longer term exposures, the upper range of the hazard quotient (0.002) is substantially below the LOC. For peak exposures, however, the hazard quotient if 0.8. While this is below the LOC for the typical application rate, it exceeds the LOC for the maximum application rate by a factor of 1.6 [0.8 ÷ 0.5]. Thus, based on peak concentrations, some damage to macrophytes is plausible.

As noted above, accidental spills of large quantities of imazapic into relatively small bodies of water could lead to much higher concentrations – i.e., 0.9 mg/L to 4.5 mg/L as modeled in Worksheet D05. After spills of this magnitude, adverse effects on aquatic plants could be anticipated from imazapic as well as most other herbicides.

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Table 2-1. Selected physical and chemical properties of imazapic.

Synonyms	AC 263,222, CL 263,222, BAS 715 H (Leonard et al. 2002) Imazameth (rejected BSI name proposal) (Tomlin 2004)
U.S. EPA Reg. No.	241-365 (Plateau) (C&P Press 2003) 241-393 (Plateau DG) (BASF 2000)
Commercial Formulations	Plateau, Plateau DG, Contend
CAS number	104098-48-8 (ammonium salt) (American Cyanamid, 1997) 81334-60-3 (acid) (Birk 1999)
Smiles code	CC(C)C1(C)N=C(NC1=O)c2ncc(C)cc2C(=O)O (Tomlin 2004)
Molecular weight	275.31 (SRC 2003)
Specific Gravity	1.07-1.09 g/mL (American Cyanamid, 1997)
Appearance, ambient	clear liquid, pale yellow to green color (American Cyanamid, 1997)
Vapor pressure	not available (American Cyanamid, 1997) $<1 \times 10^{-2}$ mPa (60 degrees C) (Tomlin 2004) 7.75E-012 mm Hg,25 deg C (Meylan and Howard 2000)
pH	6.4-7.0 (American Cyanamid, 1997)
pK_a	pKa_1 2.0, pKa_2 3.6, pKa_3 11.1 (Tomlin 2004)
Water solubility (mg/L)	miscible (American Cyanamid, 1997) >2670 mg/L (Barker et al. 1998a) 36,000 mg/L at pH 7 and 25°C (Mangels. 1992, U.S. EPA 1995) 2,150 mg/L at pH 5 and 25°C (Mangels. 1992)
$K_{o/w}$	295 [experimental log $K_{o/w}$ of 2.47 from SRC 2003]
Soil adsorption, K_d (L/kg)	0.13 to 4.07 (U.S. EPA 1995) 0.13 to 4.05 (Mangels 1992)
Soil sorption, $K_{o/c}$	260 to 8140 (U.S. EPA 1995) 7 to 267 (Mangels 1992)
Field dissipation half-time (days)	256 days (prairiegrass) (Salzman and Nejad 1998, p.24) 410 days (bareground) (Salzman and Nejad 1998, p.24) 31 days (bareground) (Schaefer et al. 1994)
Foliar half-time (days)	<7 days (bermudagrass) (Hallman and Leonard 1999)
Soil half-time (days)	106 days (photolysis)(Ta 1994) 113 days (aerobic soil metabolism, sandy loam) (Ta 1997)
Anaerobic sediment (aqueous) half-time (days)	2440 days (Madsen 1993).
Water half-time (days)	30 (U.S. EPA 1995)

Table 2-2: Use of Imazapic by the Forest Service in 2001 (USDA/FS 2002).

Region	Use	Pounds	Acres	lbs/acre	Proportion by Pounds	Proportion by Acres
Region 1	Noxious Weed Control	297	2801	0.106	0.569	0.712
Region 2	Noxious Weed Control	78.18	545.13	0.143	0.150	0.139
Region 9	Rights-of-Way	147	589	0.250	0.282	0.150
Grand Total		**522.18**	**3935.1**	**0.133**		

Table 3-1: Chemical and site parameters used in GLEAMS Modeling for imazapic.

Chemical Specific Parameters

Parameter	Clay	Loam	Sand	Comment/ Reference
Halftimes (days)				
Aquatic Sediment	2400	2400	2400	Note 1
Foliar	4	4	4	Note 2
Soil	113	113	113	Note 3
Water	30	30	30	U.S. EPA 1995
Ko/c, mL/g	112	112	112	Note 4
K_d, mL/g	4.05	0.6	0.13	Note 5
Water Solubility, mg/L	36000	36000	36000	Note 6
Foliar wash-off fraction		0.8		Knisel and Davis 2000

Note 1 Based on study by Madsen (1993) of anaerobic aquatic metabolism in sandy loam sediment using ^{14}C-labeled imazapic. No studies available in other sediments.

Note 2 Approximate geometric mean of 1.2 and 12 days reported by Hallman and Leonard (1999). Knisel and Davis (2000) give a substantially longer halftime of 30 days. The value given by Hallman and Leonard (1999) is selected because it is a primary study and is well-documented.

Note 3 Aerobic metabolism in sandy loam soil from Ta (1997). Differences will occur in different soils but will be more dependent on microflora than soil types. The value from Ta (1997) is used for all soil types in the absence of specific data in other soil types. Close to reference value of 120 days given by Knisel and Davis (2000).

Note 4 Average value from 6 soils given by Mangels (1992). There was a wide range, 7 to 267, but no correlation with organic matter (Mangels 1992). The selected Ko/c value is somewhat higher than the reference value of 35 given in Knisel and Davis (2000). The value from Mangels (1992) is used because it is a primary study and is well-documented.

Note 5 Value of 4.05 measured in clay loam soil. Value of 0.13 measured in loamy sand. Value of 0.6 measured in loam (Mangels 1992).

Note 6 Solubility at pH 7 taken from Mangels (1992). The water solubility is only 2150 mg/L in acidic waters (pH 5) (Mangels 1992).

Table 3-2: Summary of modeled concentrations of imazapic in streams (all units are µg/L or ppb per lb/acre applied)

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
10	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
15	0.00067	0.04151	0.00000	0.00000	0.00000	0.00000
20	0.00125	0.09502	0.00000	0.00000	0.00030	0.00839
25	0.00182	0.15831	0.00000	0.00000	0.00116	0.02283
50	0.00386	0.49030	0.00025	0.00660	0.00589	0.08881
100	0.00556	1.01802	0.00179	0.09131	0.00905	0.21353
150	0.00589	1.36827	0.00248	0.12324	0.00902	0.28202
200	0.00577	1.61411	0.00265	0.12590	0.00824	0.31985
250	0.00550	1.79691	0.00262	0.11821	0.00743	0.33648

Table 3-3: Summary of modeled concentrations of imazapic in ponds (all units are µg/L or ppb per lb/acre applied)

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
10	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
15	0.00930	0.04412	0.00000	0.00000	0.00000	0.00000
20	0.01197	0.09054	0.00000	0.00000	0.00155	0.00381
25	0.01419	0.14009	0.00000	0.00000	0.00493	0.00970
50	0.02060	0.36630	0.00043	0.00097	0.01669	0.05081
100	0.02497	0.69134	0.00322	0.05034	0.02069	0.12888
150	0.02587	1.01783	0.00399	0.07328	0.02016	0.17853
200	0.02566	1.28333	0.00399	0.07754	0.01897	0.21139
250	0.02505	1.50269	0.00378	0.07520	0.01772	0.22983

Table 4-1: Summary of modeled concentrations of imazapic in soil (all units are mg/kg soil or ppm per lb/acre applied)

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	1.84478	6.30797	1.40592	5.57824	0.93398	4.35341
10	1.20420	5.72768	0.84613	4.83219	0.34470	3.56252
15	0.87343	5.40097	0.51629	4.24732	0.16047	3.53030
20	0.68304	5.12632	0.35863	3.77247	0.09574	3.52604
25	0.56984	4.90085	0.26787	3.52687	0.06469	3.52516
50	0.33222	4.10346	0.10512	3.52516	0.02281	3.52516
100	0.17219	3.99075	0.03750	3.52516	0.01433	3.52516
150	0.09590	3.99075	0.02151	3.52516	0.01299	3.52516
200	0.04758	3.99075	0.01538	3.52516	0.01239	3.52516
250	0.01349	3.99075	0.01293	3.52516	0.01205	3.52516

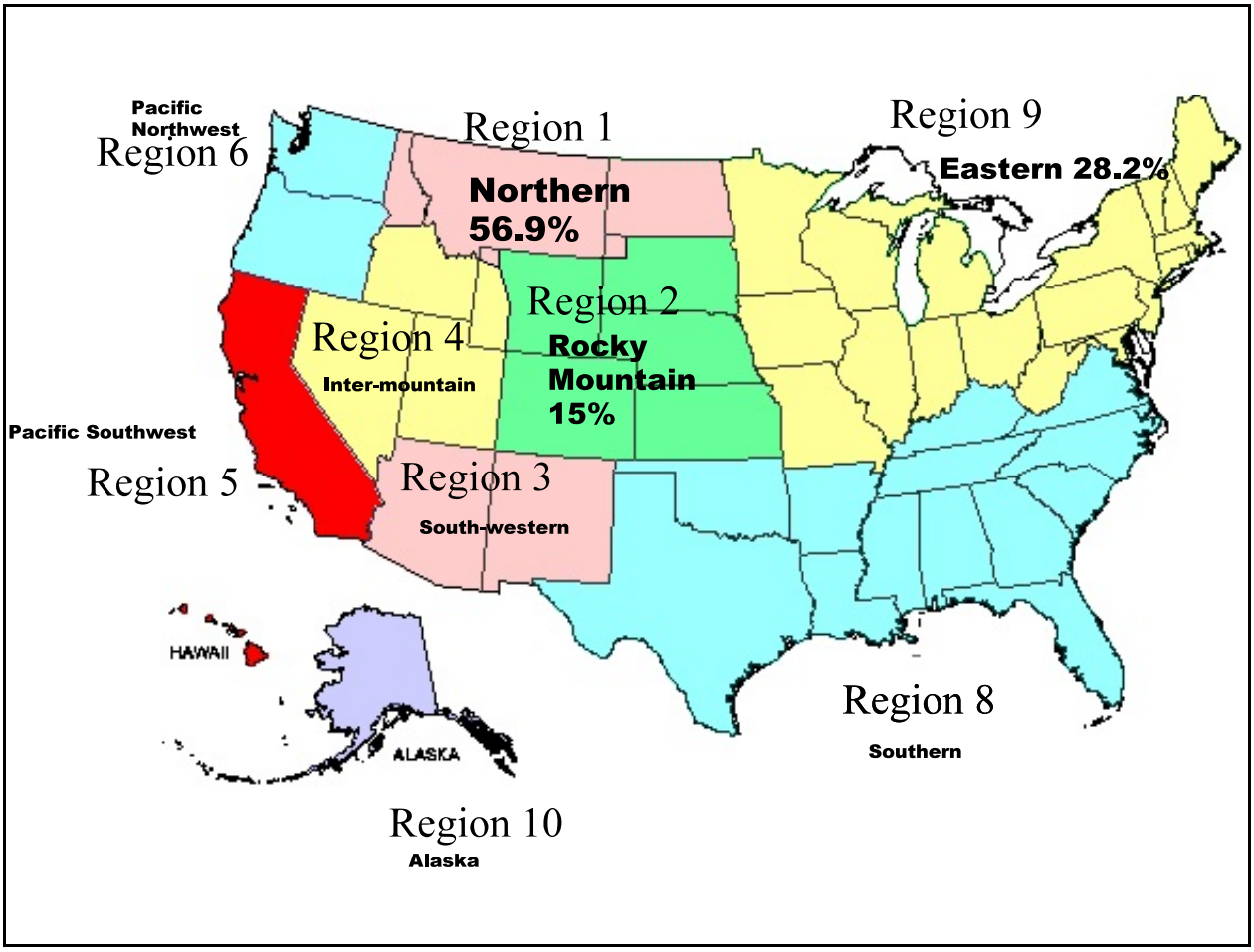

Figure 2-1. Use of imazapic by the USDA Forest Service in various regions of the United States based on percentages of total use by FS.

LIST OF APPENDICES

Appendix 1: Toxicity of Imazapic to Experimental Mammals

Animal	Dose/Exposure	Response	Reference
ORAL (acute)			
Rats, Sprague-Dawley, albino, 5/sex/dose group.	Single gavage dose of 5000 mg/kg bw AC 263,222 70 DG formulation in sterile distilled water. Observation period of 14 days.	Clinical signs included salivation during the first hour post-dosing in 2/5 males and 3/5 females. All animals recovered by 2 hours post-dosing. No effects on body weight gains and no gross pathological changes. LD_{50} = >5000 mg/kg bw	Bradley 1995b MRID No. 43888904
Rats, Sprague-Dawley, 5/sex/dose group, 8–9 weeks old at start of test.	Single exposure to 5000 mg/kg bw AC 263222 2 ASU formulation by gavage. Observation period of 14 days.	No overt signs of mortality or toxicity, no changes in body weight gain, and no significant gross lesions at necropsy. LD_{50} = >5000 mg/kg bw	Fischer 1993 MRID No. 42711413
Rats, Sprague-Dawley, albino, 5/sex, 7-weeks old at time of testing.	Single gavage dose of 5000 mg/kg bw of AC 263222 technical in corn oil. Observation period of 14 days.	No signs of toxicity, no effects on body weight gain, no gross pathological changes at time of termination. LD_{50} = >5000 mg/kg bw	Lowe 1992 MRID No. 42711407
ORAL (subchronic or chronic)			
Rats, Charles River, 4-weeks old, weighing 85–99 g (males) and 79–91 g (females), 20/sex/dose group.	0, 5000, 10,000, or 20,000 ppm AC 263222 in diet for 13 consecutive weeks. Average doses for both sexes combined were 0, 408, 804, or 1625 mg/kg bw.	No mortality; no overt signs of toxicity; no effects on food consumption or total body weight gain; no hematological effects; no significant ($p<0.05$) changes in absolute or relative organ weights; and no gross or microscopic changes associated with test material.	Fischer 1992 MRID No. 42711419
Mice, Charles River CD-1, 6-weeks old, weighing 23–37 g (males) and 21.6–30.8 g (females), 65/sex/dose group.	0, 1750, 3500, or 7000 ppm AC 263222 in the diet for 18 consecutive months (10/sex/dose group sacrificed at 12 months).	No overt signs of toxicity; no adverse effects on mortality, food consumption, total body weight gain, hematological parameters, absolute or relative organ weight changes, and no gross or microscopic changes attributable to treatment with AC 263222 in any tissue. NOEL for chronic toxicity or carcinogenicity >7000 ppm (equivalent to an average daily intake of >1134–1442 mg/kg bw).	Fischer 1994b MRID No. 43320306

Appendix 1: Toxicity of Imazapic to Experimental Mammals

Animal	Dose/Exposure	Response	Reference
ORAL (subchronic or chronic continued)			
Dogs, Beagle, 6–6.5 months old, 6/sex/group, weighing 8.3–10.9 kg (males) and 6.6–8.9 kg (females).	Dietary concentrations of 0, 5000, 20,000, or 40,000 ppm (equivalent to daily doses averaged for both sexes of 0, 158.5, 517.5, or 1116.5 mg/kg) AC 263222 for 1 year. Based on measured food consumption, these dietary concentrations corresponded to average daily doses of 0, 137, 501, and 1141 mg/kg/day in males and 0, 180, 534, and 1092 mg/kg/day in females.	At 40,000 ppm toxic effects included vomiting, increased salivation, decreased body weight, and food consumption. Degeneration of esophageal muscle in females. Decreased hemoglobin and increased macrocytes, poikilocytes, polychromatic cells, and target cells in blood as well as increased incidence of congestion of the bone marrow. Biochemical markers for liver damage. At 20,000 ppm, effects on the target organs were observed, but the effects were less severe than at the higher dose. At 5000 ppm, the only effect observed was minimal skeletal muscle effects determined microscopically in individual muscle fibers. These effects occurred in only a few fibers/tissue section and were not observed consistently in all skeletal muscle sites/ animal. Furthermore, the effects occurred in the absence of serum chemistry changes or associated clinical observations.	Wolford 1993 MRID No. 42711421
Rats, Sprague-Dawley, 5-weeks old, weighing 125–170 g (males) and 113–152 g (females), 65/sex/dose group.	0, 5000, 10,000, or 20,000 ppm AC 263222 in diet for 24 consecutive months (10/sex/dose group sacrificed at 12 months).	No overt signs of toxicity; no adverse effects on mortality, food consumption, total body weight gain, hematological parameters, absolute or relative organ weight changes, and no gross or microscopic changes attributable to treatment with AC 263222 in any tissue. NOEL for chronic toxicity and carcinogenicity >20,000 ppm (equivalent to an average daily intake of >1029–1237 mg/kg bw).	Fischer 1994a MRID No. 43320307

Appendix 1: Toxicity of Imazapic to Experimental Mammals

Animal	Dose/Exposure	Response	Reference
ORAL (reproduction/teratology)			
Rabbits, New Zealand white, inseminated females, 20/dose group.	0, 175, 350, 500, or 700 mg/kg bw AC 263222 in 0.4% carboxymethyl-cellulose on gestation days 7–19.	NOEL for maternal toxicity = 500 mg/kg based on increased mortality at highest dose level (i.e., 700 mg/kg). NOEL for embryo/fetotoxicity and teratogenicity = 700 mg/kg. NOEL for decreased maternal body weight = 350 mg/kg/day [Used by U.S. EPA 2001 for incidental short-term oral exposures.]	MacKenzie 1992 MRID No. 42711423
Additional notes on MacKenzie 1992: Survival rate: 95%(controls), 80% (175 mg/kg) 75% (350 and 500 mg/kg), and 40% (700 mg/kg). The U.S. EPA (1996b) summary gives somewhat different survival rates. The survival rates reported here are from Table 1, p. 23, of the full study. Overall pregnancy = 90–100% for study. At 700 mg/kg there was an increased incidence of "few or no feces," attributed to treatment. Food consumption was significantly lower in the 700 mg/kg group on days 9–19; at 500 mg/kg food consumption was significantly lower on days 15 and 16. *All treated animals that died during the study had one or a combination of the following effects: oral discharge, nasal discharge, fluid-filled trachea and or lungs, reddened trachea, and stomach lesions.*			
Rats, Charles River, mated females, 25/dose group.	0, 250, 500, or 1000 mg/kg/day AC 263222 in corn oil by gavage on gestation days 6–15 (single daily dose).	No maternal toxicity observed at any dose level. No evidence of fetotoxicity, embryotoxicity, or aberrant fetal development at any dose level. NOEL = 1000 mg/kg/day for developmental toxicity.	Shardein 1992 MRID No. 42711422

Appendix 1: Toxicity of Imazapic to Experimental Mammals

Animal	Dose/Exposure	Response	Reference
ORAL (reproduction/teratology) *(continued)*			
Rats, Sprague-Dawley, 56-days old, 30/sex/ dose group.	**P_1 generation**: dietary concentration of 0, 5000, 10,000, or 20,000 ppm AC 263222 for 14 weeks prior to mating and continuing until P_1 animals were sacrificed. **F_1 generation**: dietary concentration of 0, 5000, 10,000, or 20,000 ppm AC 263222 for 14 weeks prior to mating and continuing until F_1 animals were sacrificed.	No treatment related adverse effects on parental parameters (mortality, body weight, food consumption, physical examination data, gestation, body weight, food consumption data, and lactation body weights), reproductive performance or parturition data were observed in either generation (P_1, F_1) at dietary concentrations up to 20,000 ppm. Similarly, no adverse effect of treatment at a dietary level up to 20,000 ppm was observed during either litter interval (F_1, F_2) with respect to pup growth, survival, or development. NOEL (for parental and reproductive toxicity in 2-generation reproduction study) = 20,000 ppm (equivalent to 1205−1703 mg/kg/day). Used 1200 mg/kg bw as reproductive NOAEL in risk assessment.	Schroeder 1994 MRID No. 43320305
DERMAL			
Rats, Sprague-Dawley, albino, 5/sex/dose group.	2000 mg/kg bw of AC 263,222 70 DG formulation applied to intact skin (approxi-mately 10% of total body surface area) for continuous, occluded 24-hour contact.	No clinical signs of toxicity and all animals survived the 14-day observation period. No effects on body weight gains and no gross pathological changes. LD_{50} = >2000 mg/kg bw	Bradley 1995a MRID No. 43888905

Appendix 1: Toxicity of Imazapic to Experimental Mammals

Animal	Dose/Exposure	Response	Reference
DERMAL *(continued)*			
Guinea pigs, Hartley, males, 400−438 g, 10 treated, 10 naive controls, 10 positive controls (DNCP).	Induction phase: 0.43 g AC 263222 applied to intact skin 3 times a week for 6 hours (total of 9 applications to same test site). Challenge phase took place after 2-week respite. Test material was applied to clipped area on right flank for 6 hours.	AC 263222 is not a skin irritant, fatiguing agent, or skin sensitizer.	Costello 1992 MRID No. 42711412
Rabbits, New Zealand white, 5/sex, mean body weight 3.07 (males) and 2.85 (females) at start of test.	5000 mg/kg AC 263222 2ASU formulation applied to intact skin (approximately 10% of total body surface area) for continuous, occluded 24-hour contact.	LD_{50} = >5000 mg/kg bw Category = Class IV (nontoxic)	Fischer 1987a MRID No. 42711414
Rabbits, New Zealand white, 6 males.	0.5 mL AC 263222 2ASU formulation applied to intact skin covered with occlusive wrapping for 4 hours, after which remaining test material was removed with tap water. 72-hour observation period.	Two treated animals had diarrhea at 4 hours after dosing but not at any other observation period. There were no other overt signs of toxicity. AC 263222 2ASU formulation was not irritating to rabbit skin.	Fischer 1987c MRID No. 42711417
Rabbits, New Zealand white, 5/sex, 10−16 weeks old.	Single topical application of 2000 mg/kg bw AC 263222 technical to intact skin for 24 hours. Test site occluded for duration of exposure. 14-day observation period.	No overt signs of toxicity, no changes in body weight gain, and no gross pathological changes at termination of study. LD_{50} = >2000 mg/kg bw	Lowe 1993a MRID No. 42711408

Appendix 1: Toxicity of Imazapic to Experimental Mammals

Animal	Dose/Exposure	Response	Reference
DERMAL *(continued)*			
Rabbits, New Zealand white, 6 males, 10–16 weeks old at start of test.	0.5 g AC 263222 technical applied to intact, shaved skin using 1" square gauze pad for 4 hours, followed by tap water removal of testing material.	At 1 hour, erythema was barely perceptible in 2/6 animals. All signs of irritation resolved at 24 hours. There were no overt signs of toxicity during the course of the study.	Lowe 1993c MRID No. 42711411
Rabbits, New Zealand white, 2.44–3.27 g, 6/sex/dose group.	Topical application of 0, 250, 500, or 1000 mg/kg (adjusted level for 93.7% purity was 0, 266.8, 533.6, or 1067.2 mg/kg) AC 263222 to approximately 10% body surface (clipped) 5/days/week for 3 consecutive weeks.	No treatment related effects on any endpoints tested. NOEL = 1000 mg/kg bw (highest dose tested).	Moore 1992 MRID No. 42711420
Guinea pigs, Hartley, males, 362–600 g, 10 treated, 10 naive controls, 10 positive controls (DNCP).	Induction phase: 0.4 mL AC 263222 2ASU formulation applied to intact skin 3 times a week for 6 hours (total of 9 applications to same test site). Challenge phase took place after 2-week respite. Test material was applied to clipped area on right flank for 6 hours.	AC 263222 2ASU formulation is not a primary skin irritant or skin sensitizer in albino guinea pigs.	Reilly 1992 MRID No. 42711418

Appendix 1: Toxicity of Imazapic to Experimental Mammals

Animal	Dose/Exposure	Response	Reference
INHALATION			
Rats, outbred Sprague-Dawley, 231–298 g, 10/sex.	4-hour exposure to 3.65 or 4.83 mg/L (mass median aerodynamic diameter of 6.47 or 8.28 µm).	LC_{50} = >4.83 mg/L [Note: U.S. EPA (1996b) indicates that the concentration was 5.52 mg/L. The highest concentration reported in the study is 4.83 mg/L analytical corresponding to a gravimetric concentration of 5.31 mg/L. Table 1(b), p. 13 on fiche.] Animals evidenced signs of distress, eye clenching and huddling, and were covered with dust. No other signs of toxicity.	Hershman 1993a MRID No. 42711409
Rats, outbred Sprague-Dawley, 210–279 g, 10/sex.	4-hour exposure to 2.38 mg/L (mass median aerodynamic diameter of 1.97 µm).	LC_{50} = >2.38 mg/L. Congested lungs noted in 2 males and 1 female. No mortality or overt signs of toxicity.	Hershman 1993b MRID No. 42711415
Rats, Sprague-Dawley CD, 5/sex.	4-hour nose-only exposure of 2.3 mg of AC 263,222 70 DG formulation dust (mass median aerodynamic diameter of 3.5 µm). Observation period of 14 days.	No mortality resulted from exposure to the test substance. Clinical signs during exposure and for the next 2 days included secretory responses (chromodacryorrhea, nasal discharge, and dried material on facial area) as well as matted coat and wet fur. No effects on body weight gains and pathological findings included dermal effects (hair thinning, scabs) in 1 male. LC_{50} = >2.3 mg (analytical)	Hoffman 1995 MRID No. 43888906

Appendix 1: Toxicity of Imazapic to Experimental Mammals

Animal	Dose/Exposure	Response	Reference
OCULAR			
Rabbits, New Zealand white, 6 males.	Instillation of 0.1 g AC 263222 2ASU formulation into left conjunctival sac of each rabbit (right eyes served as controls) for 24-hour exposure. Eyes examined at -4 (pretreatment), 1, 24, 48, and 72 hours.	At 1 hour after treatment, 4/6 animals had slight redness of the conjunctivae; at 24 hours all irritation had resolved. No signs of irritation were observed at 48 or 72 hours. AC 263222 2ASU formulation was not irritating to the rabbit eye.	Fischer 1987b MRID No. 42711416
Rabbits, New Zealand white, 6 females, 10−16 weeks old.	Instillation of 0.1 g AC 263222 into left conjunctival sac of each rabbit (right eyes served as controls) for 24-hour exposure. Eyes examined at -4 (pretreatment), 1, 24, 48, and 72 hours.	No overt signs of toxicity. Eye irritation at 1 hour: slight (3/6) to moderate (3/6) redness of conjunctivae; slight (4/6) to moderate (2/6) chemosis; and moderate (5/6) to copious (1/6) ocular discharge. Eye irritation at 24 hours: scattered and diffuse areas of corneal involvement (2/6); moderate redness of the conjunctivae (3/6); slight redness of the conjunctivae (3/6); slight chemosis (6/6); and no ocular discharge (4/6) to slight ocular discharge (2/6). Eye irritation at 48 hours: scattered and diffuse corneal opacity (2/6); slight conjunctival irritation (6/6); and slight chemosis (1/6). At 72 hours, all signs of irritation had resolved. AC 263222 produced moderate irritation to the rabbit eye; category III.	Lowe 1993b MRID No. 42711410

Appendix 2: Toxicity of Imazapic to Birds

Organism	Exposure	Response	Reference
Animal	Dose/Exposure	Response	Reference
Quail, bobwhite, (*Colinus virginianus*), 23-weeks old, 10/dose group.	Single gavage dose of 0, 1470, or 2150 mg/kg bw AC 263222 technical in tap water. Observation period of 20 days.	No mortality; no clinical signs of toxicity; no statistically significant differences in body weight; no differences in food consumption. NOEL = 2150 mg/kg bw LD_{50} = >2150 mg/kg bw	Fletcher and Sullivan 1993a MRID No. 42711431
Ducks, Mallard (*Anas platyrhynchos*), 44−59 weeks old, 10/dose group.	Single gavage dose of 0, 1470, or 2150 mg/kg bw AC 263222 technical in tap water. Observation period of 20 days.	No mortality; no clinical signs of toxicity other than a slight decrease in food consumption at 2150 mg/kg. No gross pathological findings at necropsy. NOEL = 2150 mg/kg bw (based on mortality). NOEL = 1470 mg/kg bw (based on clinical signs [i.e., decreased food consumption]). LD_{50} = >2150 mg/kg bw	Fletcher and Sullivan 1993b MRID No. 42711430

Appendix 2: Toxicity of Imazapic to Birds

Organism	Exposure	Response	Reference
Animal	Dose/Exposure	Response	Reference
Quail, Northern bobwhite (*Colinus virginianus*), 20 weeks and 1-day old at start, weighing 180.2–271.5 g (males) and 185.7–274.5 g (females), 3 groups of 19/sex/group, 1 control group of 19/sex.	Dietary administration of imazapic (AC 263222) in nominal concentrations of 0, 650, 1300, or 1950 ppm (equivalent to mean measured concentrations of 607, 1187, or 1907 ppm) for 24 weeks and 2 days. Controls received acetone vehicle only in diet. Mean food consumption was about 20 g/bird with a range of about 15 to 30 g/bird over the 24 weeks (Table II, p. 26). Mean body weight was about 230 g/bird. Thus, the approximate fractional food consumption was 0.087 g food/g bw. This is used to convert ppm to mg/kg bw.	No mortality, no signs of toxicity, no treatment-related effects on body weight, food consumption, or gross pathology. Statistically significant reduction in 14-day hatchling body weights in the 1950 ppm group; no treatment-related effects on other reproduction endpoints (i.e., egg production, hatchability, survival of hatchlings). NOEC = 1300 ppm (approximately 113 mg/kg bw). LOAEL = 1950 ppm (approximately 170 mg/kg bw).	Miller et al. 1998 MRID No. 44638102

Appendix 2: Toxicity of Imazapic to Birds

Organism	Exposure	Response	Reference
Animal	Dose/Exposure	Response	Reference
Ducks, Mallard, 20 weeks and 1-day old at start, weighing 875−1390 g (males) and 841−1208 g (females), 3 groups of 16/sex/group, 1 control group of 16/sex.	Dietary administration of imazapic (AC 263222) in nominal concentrations of 0, 650, 1300, or 1950 ppm (equivalent to mean measured concentrations of 538, 994, or 1658 ppm) for 22 weeks and 3 days. Average body weight over course of study of about 1150 g (Table 1, p. 27). Average food consumption of about 160 g/day (Table 2, p. 28). Thus, the approximate fractional food consumption was 0.14 g food/g bw.	No mortality, no signs of toxicity, no treatment-related effects on body weight, food consumption, or gross pathology. No treatment-related effects on reproduction endpoints (i.e., egg production, hatchability, survival of hatchlings). NOEC = 1658 ppm (about 232 mg/kg/day)	Mortensen et al. 1998 MRID No. 44638101
Quail, bobwhite, (*Colinus virginianus*), 10-days old, 10/dose group.	Nominal dietary concentrations of 0, 312, 625, 1250, 2500, or 5000 ppm AC 263222 for 5 consecutive days; test terminated after 8 days. Measured food consumption (Table 2, p. 21) was about 0.22 g food/g bw. Thus, dietary concentrations correspond to doses of 0, 68.6, 138, 275, 550, and 1100 mg/kg bw.	No mortalities; no clinical signs of toxicity, no gross or pathological findings at necropsy. NOEC = 5000 ppm LC_{50} (dietary) = >5000 ppm (>1100 mg/kg bw)	Pedersen et al. 1993a MRID No. 42711432

Appendix 2: Toxicity of Imazapic to Birds

Organism	Exposure	Response	Reference
Animal	Dose/Exposure	Response	Reference
Ducks, Mallard (*Anas platyrhynchos*), 7-days old, 10/dose group.	Nominal dietary concentrations of 0, 312, 625, 1250, 2500, or 5000 ppm AC 263222 for 5 consecutive days; test terminated after 8 days. Measured food consumption (Table 2, p. 20) was about 0.26 g food/g bw. Thus, dietary concentrations correspond to doses of 0, 81.1, 163, 325, 650, and 1300 mg/kg bw.	No mortality; no clinical signs of toxicity; no unusual gross pathological findings. NOEC = 5000 ppm LC_{50} = >5000 ppm (>1300 mg/kg bw)	Pedersen et al. 1993b MRID No. 42711433

Appendix 3: Toxicity of Imazapic to Fish, Aquatic Invertebrates, and Aquatic Plants

Organism	Exposure	Response	Reference
Fish			
Sheepshead minnow (*Cyprinodon variegatus*), juvenile, 13−22 mm long, wet weight of 0.05−0.32 g.	Nominal concentrations of 0, 6.25, 12.5, 25.0, 50.0, or 100 mg/L AC 263222 (equivalent to mean measured concentrations of 4.74, 10.4, 24.4, 47.3, or 98.7 mg/L) for 96 hours under flow-through conditions.	No effects observed at any concentration.	Barker and Skorczynski 1998 MRID No. 44817702
Fathead minnow (*Pimephales promelas*), less than 24-hours old at start, 5 groups of 80 minnows plus negative control group.	Nominal concentrations of 0, 6.3, 13, 25, 50, or 100 mg a.i./L (equivalent to mean measured concentrations of 5.7, 12, 25, 46, or 96 mg a.i./L) AC 263222 for 32 days.	No treatment related effects on time to hatch, hatching success, survival, or growth of minnow for 28-days post-hatch. NOEC = 100 mg a.i./L LOEC and MATC = >100 mg a.i./L	Barker et al. 1998 MRID No. 44728202
Bluegill sunfish (*Lepomis macrochirus*).	0.5 ppm ^{14}C-CL 263222 for 28 days under flow-through conditions.	^{14}C-CL 263222 does not bioaccumulate in fish. BCF 0.11 ± 0.02. Time to 90% steady state 3 days. K_1 = 0.081 mg/kg fish per mg/L. K_2 = 0.77 per day. Time to 50% depuration 0.91 days.	Robinson 1994 MRID No. 433320315
Bluegill sunfish (*Lepomis macrochirus*), juvenile, −0.44 g, 25−34 mm long, 10/replicate. 3 replicated per concentration.	nominal concentration of 0 or 100 mg/L AC 263222 for 96 hours under static test conditions.	At 100 mg/L, 2/30 fish died by 96 hours. No mortality (0/30) in controls. Mortality not statistically significant (p=0.23). No signs of toxicity.	Yurk et al. 1992a MRID No. 42711434
Rainbow trout (*Oncorhynchus mykiss*), juvenile, −2.11 g, 36−60 mm long, 10//replicate. 3 replicated per concentration.	nominal concentration of 0 or 100 mg/L AC 263222 for 96 hours under static test conditions.	At 100 mg/L, 3/30 fish died by 96 hours. In controls, 1/30) fish died. Mortality not statistically significant (p=0.306). No signs of toxicity reported.	Yurk et al. 1993a MRID No. 42711435

Appendix 3: Toxicity of Imazapic to Fish, Aquatic Invertebrates, and Aquatic Plants

Organism	Exposure	Response	Reference
Fish *(continued)*			
Channel catfish (*Ictalurus punctatus*), juvenile, −0.78 g, 34−47 mm long, 10//replicate. 3 replicated per concentration.	nominal concentration of 0 or 100 mg/L AC 263222 for 96 hours under static test conditions.	No mortality (0/30) in controls or exposed fish over 96 hours. In one replicate from the 100 mg/L group, lethargic behavior was observed and associated with low oxygen concentrations.	Yurk et al. 1992b MRID No. 42711436
Aquatic Invertebrates			
Shrimp, Mysid (*Mysidopsis bahia*), post-larval, <24-hours old.	Nominal concentrations of 0, 6.25, 12.5, 25.0, 50.0, or 100 mg/L (equivalent to mean measured concentrations of 4.63, 10.1, 21.9, 46.7, or 97.7 mg/L) AC 263222 for 96 hours under flow-through conditions.	NOEC = 97.7 mg/L	Barker and Liu 1998a MRID No. 44817704
Oysters, Eastern (*Crassostrea virginica*), umbo to distal valve edge length 33−49 mm, wet tissue weight 0.92−2.64 g, 20/group.	Nominal concentrations of 0, 6.25, 12.5, 25.0, 50.0, or 100 mg/L (equivalent to mean measured concentrations of 4.43, 9.70, 21.5, 47.2, or 99.2 mg/L) AC 263222 for 96 hours under flow-through conditions.	No statistical differences in new shell deposition in treated oysters compared with controls. NOEC = 99.2 mg/L	Barker and Liu 1998b MRID No. 44817703
Water flea (*Daphnia magna*), <24-hours old, 10/dose group.	Nominal concentration of 0 or 100 mg/L AC 263222 for 48 hours under static test conditions.	48-hour NOEC = 100 mg/L	Yurk et al. 1993b MRID No. 42711437
Water flea (*Daphnia magna*)	Concentration of 96 mg/L	NOEC for effects on survival and reproduction.	Barker et al. 1998 MRID No. 44728201

Appendix 3: Toxicity of Imazapic to Fish, Aquatic Invertebrates, and Aquatic Plants

Organism	Exposure	Response	Reference
Aquatic Plants			
Freshwater blue-green algae (*Anabaena flos-aquae*).	Nominal concentration of 50.8 µg/L (mean measured concentration 49.9 µg/L) AC 263222 (equivalent to direct application of maximum label rate of 0.064 lbs a.i./acre to 15 cm column of water) for 5 days.	Test substance resulted in 11.9% growth inhibition, compared with controls. There were no treatment related effects on the size of shape of algal cells. EC_{50} = >67.4 µg/L (mean measured concentration).	Hughes et al. 1994 MRID No. 43320310
Algae (*Selenastrum capricomutum*).	Nominal concentration of 50.8 µg/L (mean measured concentration 49.9 µg/L) AC 263222 (equivalent to direct application of maximum label rate of 0.064 lbs a.i./acre to 15 cm column of water) for 5 days.	Test substance resulted in 0.18% growth inhibition. EC_{50} = >52.3 µg/L (mean measured concentration).	Hughes et al. 1994 MRID No. 43320310
Algae (*Navicula pelliculosa*).	Nominal concentration of 50.4 µg/L (mean measured concentration 49.9 µg/L) AC 263222 (equivalent to direct application of maximum label rate of 0.064 lbs a.i./acre to 15 cm column of water) for 5 days.	Test substance resulted in 32.9% growth inhibition, if data from all 4 replicates are used. If outlier data are omitted, growth inhibition is 11.1%. EC_{50} = >67.3 µg/L (mean measured concentration).	Hughes et al. 1994 MRID No. 43320310
Algae (*Skeletonema costatum*).	Nominal concentration of 50.0 µg/L (mean measured concentration 49.9 µg/L) AC 263222 (equivalent to direct application of maximum label rate of 0.064 lbs a.i./acre to 15 cm column of water) for 5 days.	Test substance resulted in 0.777% growth stimulation. EC_{50} = >45.0 µg/L (mean measured concentration).	Hughes et al. 1994 MRID No. 43320310

Appendix 3: Toxicity of Imazapic to Fish, Aquatic Invertebrates, and Aquatic Plants

Organism	Exposure	Response	Reference
Aquatic Plants *(continued)*			
Duckweed (*Lemna gibba*), macrophyte.	Active ingredient concentrations of AC 263222 ranging from 1.27 to 20.1 µg/L (mean measure concentrations ranged from 1.22 to 12.5 µg/L) for 14 days. Static test.	Frond counts: NOEC's: 2.58 µg/L (4.2% inhibition not statistically different from controls) 1.27 µg/L (no inhibition) EC_{25} = 4.23 µg/L (3.82–4.69 µg/L = 95% confidence limit). EC_{50} = 6.10 µg/L (5.69–6.53 µg/L = 95% confidence limit).	Hughes et al. 1994 MRID No. 43320310