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Imazapyr - Human Health and Ecological Risk Assessment – Final Report

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LIST OF WORKSHEETS

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
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
NAWQA	National Water Quality Assessment
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 the herbicide, imazapyr, in its vegetation management programs. This document provides risk assessments for human health effects and ecological effects to support an assessment of the environmental consequences of using imazapyr in current and future Forest Service programs. This is an update to the risk assessment conducted for the USDA Forest Service in 1999.

Imazapyr is an effective herbicide and even tolerant plants that are directly sprayed with imazapyr at normal application rates are likely to be damaged. Some sensitive plant species could be affected by the off-site drift or by off-site movement in runoff of imazapyr depending on local site-specific conditions. When applied to areas in which runoff is favored, damage from runoff appears to pose a greater hazard than drift. Residual soil contamination with imazapyr could be prolonged in some areas. In relatively arid areas in which microbial degradation may be predominant factor in the decline of imazapyr residues in soil, residual toxicity to sensitive plant species could last for several months to several years. In areas of relatively high rainfall rates, residual toxicity to sensitive plant species would be much shorter. Some effects are also plausible in aquatic plants. Aquatic macrophytes appear to be more sensitive to imazapyr than unicellular algae. Peak concentrations of imazapyr in surface water could be associated with adverse effects in some aquatic macrophytes. Longer term concentrations of imazapyr, however, are substantially below the level of concern.

Adverse effects in workers, members of the general public, as well as terrestrial or aquatic animals do not appear to be likely. The weight of evidence suggests that no adverse effects in these organisms are plausible using typical or worst-case exposure assumptions at the typical application rate of 0.45 lb/acre or the maximum application rate of 1.25 lb/acre.

PROGRAM DESCRIPTION

Imazapyr is a herbicide that is used in the control a variety of grasses, broadleaf weeds, vines, and brush species, site preparation and conifer release, and rights-of-way maintenance. Four formulations of imazapyr may be used in Forest Service programs: Arsenal, Arsenal AC (applicators concentrate), Chopper, and Stalker, all of which contain imazapyr as the isopropylamine salt. While imazapyr formulations can be used in pre-emergence applications, the most common and effective applications are post-emergent when the vegetation to be controlled is growing vigorously. The most common methods of ground application for Arsenal or Chopper formulations involve backpack (selective foliar) and boom spray (broadcast foliar) operations. Cut surface treatment methods may also be used by the Forest Service in applications of Stalker and Arsenal AC and could be used with other imazapyr formulations. Boom spray applications are used primarily in rights-of-way management. Arsenal is registered for aerial applications and aerial applications in Forest Service programs are restricted to helicopter only. Forest Service uses imazapyr primarily in conifer or hardwood release, conifer release, wildlife

habitat improvement, and rights-of-way management. Lesser amounts are used in noxious weed control, hardwood release, and housekeeping/facilities maintenance.

For this risk assessment, application rates used to construct the various exposure scenarios range from 0.03 lb a.e./acre to 1.25 lb a.e./acre with a typical rate taken as 0.45 lb a.e./acre. The typical application rate is about the average application rate that the Forest Service used in 2001 for noxious weed control and is near the geometric mean of the recommended range of application rates, 0.125 to 1.25 lbs/acre. The lower range of the application rate is near to the average application rates used by the Forest Service for conifer and/or hardwood release. The upper end of the application rate is taken at the maximum rate recommended on the product labels for Arsenal, Arsenal AC, and Chopper. The total use of imazapyr by the Forest Service nation-wide in 2001 was about 221 lbs. Comparable nation-wide statistics on the total use of imazapyr have not been encountered. The 2001 use of imazapyr by the Forest Service, however, is about 1% of the total use of imazapyr in California during 2001. Thus, it appears that the use of imazapyr by the Forest Service is insubstantial relative to the total use of this herbicide.

HUMAN HEALTH RISK ASSESSMENT

Hazard Identification **–** The toxicity of imazapyr has been relatively well-characterized in experimental mammals. All of the mammalian information is contained in unpublished studies that were submitted to the U.S. EPA as part of the registration process for imazapyr and were obtained and reviewed as part of this risk assessment. Some clinical cases reports of intentional (attempted suicide) or accidental ingestion of large amounts of Arsenal have been reported. Symptoms include vomiting, impaired consciousness, and respiratory distress. requiring intubation. No fatal cases of imazapyr ingestion have been encountered.

Although the mode of action of imazapyr in humans or other mammals is unclear, this is at least partially a reflection of the apparently low and essentially undetectable acute and chronic systemic toxicity of this compound. The acute oral LD_{50} of unformulated imazapyr is greater than 5000 mg/kg and the chronic dietary NOAEL for imazapyr is 10,000 ppm in dogs, rats, and mice. In the dog, this dietary concentration is equivalent to a daily dose of 250 mg a.i./kg/day. In the other species, the equivalent daily doses are higher than 250 mg/kg/day. An adequate number of multi-generation reproductive and developmental studies have been conducted and no adverse effects on reproductive capacity or normal development have been demonstrated. Tests of carcinogenic and mutagenic activity are consistently negative, and the U.S. EPA has categorized the carcinogenic potential of imazapyr as *Class E: evidence of non-carcinogenicity*.

Increased food consumption has been reported in chronic toxicity studies in which imazapyr was added to the diets of male and female mice as well as female rats. It is unclear if this effect can be attributed to a toxicologic effect of imazapyr, since it may be due to an increase in palatability of the chow. The weight of evidence suggests that imazapyr is not directly neurotoxic, and the available data do not suggest that systemic toxic effects are plausible after dermal or inhalation exposures to imazapyr. Similarly, while the available data are limited, there is no basis for

asserting that impurities or adjuvants in or metabolites of imazapyr are likely to impact the assessment of risk.

Imazapyr and imazapyr formulations can be mildly irritating to the eyes and skin. From a practical perspective, this is probably the effect that is most likely to be observed in the application of this compound if proper personal protection practices are not employed.

Exposure Assessment – Exposure assessments are conducted for both workers and members of the general public for the typical application rate of 0.45 lb/acre. The consequences of using the maximum application rate that might be used by the Forest Service, 1.25 lb/acre, are discussed in the risk characterization.

For workers, three types of application methods are modeled: directed ground, broadcast ground, and aerial. The central estimates of exposure for broadcast ground spray workers is about 0.01 mg/kg/day. The central estimates of exposures for backpack and aerial workers are somewhat lower, about 0.006 mg/kg/day. Upper range of exposures are approximately 0.04 mg/kg/day for backpack and aerial applications and 0.07 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 estimates of acute exposures range from approximately 0.000002 mg/kg associated with the lower range for the consumption of contaminated water from a stream by a child to 0.9 mg/kg associated with the upper range for consumption of contaminated water by a child following an accidental spill of imazapyr into a small pond. High dose estimates are also associated with the direct spray of a child (an upper range of 0.116 mg/kg/day). Other acute exposures are lower by about an order of magnitude or greater. For chronic or longer term exposures, the modeled exposures are much lower than for acute exposures, ranging from approximately 0.0000000003 mg/kg/day (0.3 billionths of a mg/kg) associated with the lower range for the normal consumption of fish to approximately 0.04 mg/kg/day associated with the upper range for consumption of contaminated fruit.

Dose-Response Assessment – The dose-response assessment for imazapyr is relatively straightforward and the toxicity data base is reasonably complete and unambiguous. The U.S. EPA has derived a chronic RfD of 2.5 mg/kg/day using a dog NOAEL of 250 mg/kg/day and an uncertainty factor of 100. The NOAEL selected by the U.S. EPA appears to be the most appropriate and is supported by additional NOAELs in rats and mice as well as a number of studies on potential reproduction and developmental effects. Consistent with the approach taken by U.S. EPA, no acute RfD is derived in this risk assessment and the chronic RfD of 2.5 mg/kg/day is used to characterize the risks of both acute and longer term exposures.

Risk Characterization – For both workers and members of the general public, risk is characterized quantitatively using a hazard quotient, the ratio of the exposure estimate to the

chronic RfD. Because all exposure assessments are based on the typical application rate of 0.45 lb/acre, the level of concern for the hazard quotient is one (1) at the typical application rate. Because the maximum application rate is 1.25 lb/acre, the level of concern at the maximum application rate is 0.36 – i.e., 0.45 lb/acre ÷ 1.25 lb/acre.

Typical exposures to imazapyr do not lead to estimated doses that exceed a level of concern for either workers or members of the general public at either the typical or highest application rate. 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 longer-term exposure to imazapyr 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 imazapyr. From a practical perspective, eye irritation is likely to be the only overt effect as a consequence of mishandling imazapyr. This effect can be minimized or avoided by prudent industrial hygiene practices – e. g., exercising care to reduce splashing and wearing goggles – during the handling of the compound.

ECOLOGICAL RISK ASSESSMENT

Hazard Identification – As with the human health risk assessment, a limitation in the identification of potential hazards to terrestrial or aquatic animals is that the great majority of the toxicity studies have failed to demonstrate any significant or substantial association between imazapyr exposure and toxicity. In addition, few wildlife species have been assayed relative to the large number of non-target animal species that might be exposed to imazapyr. Within these admittedly substantial reservations, imazapyr appears to be relatively non-toxic to terrestrial or aquatic animals. In other words, no hazards associated with the direct toxic action of imazapyr can be identified for either terrestrial or aquatic animals.

The toxicity of imazapyr to terrestrial plants is relatively well characterized. Imazapyr is practically non-toxic to conifers, but it is toxic to many other non-target plants. As with several sulfonylurea, imidazolinone, and triazolopyrimidine herbicides, imazapyr inhibits acetolactate synthase (ALS), an enzyme that catalyzes the biosynthesis of three branched-chain amino acids, all of which are essential for plant growth. Although post-emergence application is more effective than pre-emergence application, toxicity can be induced either through foliar or root absorption. Imazapyr is not metabolized extensively in plants but is transported rapidly from treated leaves to root systems and may be exuded into the soil from the roots of treated plants.

Imazapyr is relatively non-toxic to soil microorganisms, aquatic invertebrates, and fish. Imazapyr is not expected to bioaccumulate in the food chain. In terrestrial animals and birds, imazapyr is practically non-toxic. A number of standard bioassays are available on the toxicity

of imazapyr to aquatic plants. The most sensitive species appears to be aquatic macrophytes, *Lemna minor* and *Myrophyllium sibiricum*, with reported EC_{25} values of 0.013 mg/L in both species. Some aquatic algae appear to be substantially less sensitive, with EC_{50} values on the order of about 0.2 mg/L. In tolerant species, concentrations of up to 100 mg/L may cause either no effect or be associated with a stimulation rather than inhibition of growth.

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 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 11 mg/kg at an application rate of 0.45 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 0.6 mg/kg for a small mammal to 12 mg/kg for a large bird with upper ranges of about 1.2 mg/kg for a small mammal and 34 mg/kg for a large bird. The consumption of contaminated water leads to much lower levels of acute exposure and 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 0.00004 mg/kg to 0.1 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 0.0000007 mg/kg/day to 0.00007 mg/kg/day for a small mammal. Because of the apparently low toxicity of imazapyr 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, 0.45 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 based on estimates modeled 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 imazapyr 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 are based on essentially the same information used to assess the exposure to terrestrial species from contaminated water. Peak estimated rate of contamination of ambient water associated with the normal application of imazapyr is 0.002

(0.0001 to 0.08) 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 imazapyr is 0.0001 (0.00001 to 0.001) 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, a chronic NOAEL of 250 mg/kg/day that is applied to both acute and longer term exposures. For birds, a 5-day dietary NOEL of 674 mg/kg/day used to characterize risks associated with acute exposures and an 18-week dietary NOAEL of 200 mg/kg/day based on reproductive endpoints is used to characterize risk associated with longer term exposures. The only data available on terrestrial invertebrates is the standard bioassay in honey bees in which the NOAEL based on mortality was 1000 mg/kg bw.

The toxicity data for terrestrial plants involves standard bioassays for pre-emergent and post-emergent applications. For exposures involving the off-site drift of imazapyr, the range of NOAEL values for post-emergence applications is 0.00049 lb/acre for sensitive species and 0.018 lb/acre for tolerant species. For exposures involving off-site runoff, the range of NOAEL values for pre-emergence applications is 0.002 lb/acre for sensitive species and 1 lb/acre for tolerant species.

Imazapyr does not appear to be very toxic to aquatic fish or invertebrates. For tolerant species of fish, an NOEC of 100 mg/L, supported by a large number of studies submitted to U.S. EPA is used to assess risks associated with acute exposures. For sensitive species, the lowest LC_{50} value encountered in the open literature, 2.71 mg/L, is used. Three longer term studies in fish suggest no substantial differences between the acute and chronic toxicity of imazapyr, with a life-cycle NOEC of about 100 mg/L. No chronic toxicity studies are available on the presumably sensitive species and the 2.71 mg/L concentration use for acute exposure is also applied to chronic exposures for sensitive species. Aquatic invertebrates do not appear to be any more sensitive to imazapyr than fish. An NOEC value of 100 mg/L from both an acute study and a life cycle study in daphnids is used to characterize risks of both acute and chronic exposures. There is no basis for identifying tolerant and sensitive species of aquatic invertebrates.

Lemna gibba, an aquatic macrophyte, is much more sensitive to imazapyr than aquatic animals. An EC_{25} of 0.013 mg/L in *Lemna minor* is used for quantifying effects in aquatic macrophytes. By comparison to *Lemna gibba*, unicellular aquatic algae appear to be less sensitive to imazapyr and a concentration of 0.2 mg/L is taken as an EC_{50} for sensitive species and an NOEC of 100 mg/L is taken as an NOEC for tolerant species of algae.

Risk Characterization – Imazapyr is an effective herbicide and even tolerant plants that are directly sprayed with imazapyr at normal application rates are likely to be damaged. Some sensitive plant species could be affected by the off-site drift or by off-site movement in runoff of imazapyr depending on site-specific conditions. When applied to areas in which runoff is

favored, damage from runoff appears to pose a greater hazard than drift. Residual soil contamination with imazapyr could be prolonged in some areas. In relatively arid areas in which microbial degradation may be predominant factor in the decline of imazapyr residues in soil, residual toxicity to sensitive plant species could last for several month to several years. In areas of relatively high rainfall rates, residual toxicity to sensitive plant species would be much shorter. This characterization of risk for residual soil contamination is general rather than site-specific. The persistence and movement of imazapyr in soil is highly complex and substantially different estimates of persistence and transport could be made if different site-specific factors were considered. Thus, these estimates of risk should be considered only as crude approximations of environmentally plausible consequences.

Some effects are also plausible in aquatic plants. Aquatic macrophytes appear to be more sensitive to imazapyr than unicellular algae. Peak concentrations of imazapyr in surface water could be associated with adverse effects in some aquatic macrophytes. Longer term concentrations of imazapyr, however, are substantially below the level of concern.

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 0.45 lb/acre or the maximum application rate of 1.25 lb/acre.

As in any ecological risk assessment, the risk characterization must be qualified. Imazapyr has been tested in only a limited number of species and under conditions that may not well-represent populations of free-ranging non-target organisms. 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, imazapyr, in its vegetation management programs. The Forest Service generally uses aqueous formulations of imazapyr (Arsenal or Arsenal AC) although emulsifiable concentrates (Chopper and Stalker) may be used in some rights-of-way applications. The present document provides risk assessments for human health effects and ecological effects to support an assessment of the environmental consequences of using imazapyr in current and future Forest Service programs. This is an update to the risk assessment conducted for the USDA Forest Service in 1999 (SERA 1999).

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 imazapyr, 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 2001). Some of the more complicated terms and concepts are defined, as necessary, in the text.

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. Brief reviews regarding the human health or ecological effects of imazapyr have been published and were used in the preparation of this risk assessment (Cox 1996; Gagne et al. 1991; Peoples 1984). Almost all of the mammalian toxicology studies and most of the ecotoxicology studies, however, are unpublished reports submitted to the U.S. EPA as part of the registration process for this compound. Because of the lack of the preponderance of unpublished relevant data in U.S. EPA files, a complete search of the U.S. EPA files was conducted. Full text copies of relevant studies were kindly provided by the U.S. EPA Office of Pesticide Programs. These studies were reviewed, discussed in Sections 3 and 4 as necessary, and synopses of the most relevant studies are provided in the Appendices 1 through 4 of this document.

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 (2001).

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 imazapyr 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

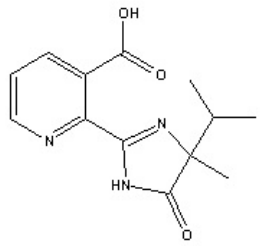
2.1. OVERVIEW

Imazapyr is a herbicide that is used in the control a variety of grasses, broadleaf weeds, vines, and brush species, site preparation and conifer release, and rights-of-way maintenance. Four formulations of imazapyr may be used in Forest Service programs: Arsenal, Arsenal AC (applicators concentrate), Chopper, and Stalker, all of which contain imazapyr as the isopropylamine salt. While imazapyr formulations can be used in pre-emergence applications, the most common and effective applications are post-emergent when the vegetation to be controlled is growing vigorously. The most common methods of ground application for Arsenal or Chopper formulations involve backpack (selective foliar) and boom spray (broadcast foliar) operations. Cut surface treatment methods may also be used by the Forest Service in applications of Stalker and Arsenal AC and could be used with other imazapyr formulations. Boom spray applications are used primarily in rights-of-way management. Arsenal is registered for aerial applications and aerial applications in Forest Service programs are restricted to helicopter only. Forest Service uses imazapyr primarily in conifer or hardwood release, conifer release, wildlife habitat improvement, and rights-of-way management. Lesser amounts are used in noxious weed control, hardwood release, and housekeeping/facilities maintenance.

For this risk assessment, application rates used to construct the various exposure scenarios range from 0.03 lb a.e./acre to 1.25 lb a.e./acre with a typical rate taken as 0.45 lb a.e./acre. The typical application rate is about the average application rate that the Forest Service used in 2001 for noxious weed control and is near the geometric mean of the recommended range of application rates, 0.125 to 1.25 lbs/acre. The lower range of the application rate is near to the average application rates used by the Forest Service for conifer and/or hardwood release. The upper end of the application rate is taken at the maximum rate recommended on the product labels for Arsenal, Arsenal AC, and Chopper. The total use of imazapyr by the Forest Service nation-wide in 2001 was about 221 lbs. Comparable nation-wide statistics on the total use of imazapyr have not been encountered. The 2001 use of imazapyr by the Forest Service, however, is about 1% of the total use of imazapyr in California during 2001. Thus, it appears that the use of imazapyr by the Forest Service is insubstantial relative to the total use of this herbicide.

2.2. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS

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



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

The previous risk assessment on this compound (SERA 1999) covered four formulations of imazapyr that were used by the Forest Service: Arsenal, Arsenal AC (applicators concentrate), Chopper, and Stalker, all of which were produced by American Cyanamid. The most recent labels for all of the imazapyr formulations, obtained at www.cdms.net, indicate that all formulations covered in the previous risk assessment are currently available but are now supplied by BASF : Arsenal Herbicide (BASF 2000a), Arsenal AC (BASF 2000b), Chopper (BASF 2001), and Stalker (BASF 2000c).

The Arsenal, Chopper, and Stalker formulations contain imazapyr 2 lb a.e./gallon. Arsenal AC is more concentrated (4 lbs a.e./gallon) and Chopper RTU is less concentrated (0.255 lbs a.e./gallon). All formulations contain imazapyr as the isopropylamine salt. Information on inerts and impurities in imazapyr formulations have been reviewed as part of this risk assessment (e.g., American Cyanamid 1983a,b, 1989; Arendt and Comisky 1995; Arthur 2000; Beardmore 1987a; Cortes and Chiarello 1994; Danishevsky and Cortes 1994; Garber 1984, 1988; Stellar 1998a,b). This information is considered proprietary under FIFRA Section 10. The potential significance of inerts in imazapyr can be inferred based on differences in the toxicity of the formulations and technical grade imazapyr. In addition, a limited amount of information on inerts in some imazapyr formations can be disclosed. These topics are discussed further in Section 3.1.14.

Arsenal is labeled for use only in non-crop areas to control a variety of grasses, broadleaf weeds, vines, and brush species. Recommended uses include the control of undesirable vegetation on rights-of-way, fence rows, storage areas, non-irrigation ditchbanks, wildlife openings, and the release of unimproved bermudagrass. Both preemergence and postemergence applications are recommended on the label. Arsenal may not be used in crop areas and may not be directly applied to water (BASF 2000a). The uses for Arsenal AC are similar to those for Arsenal. Unlike Arsenal, however, Arsenal AC is labeled for forestry sites - i.e., site preparation and conifer release (BASF 2000b). Chopper is also labeled for forestry uses including site

preparation (BASF 2001) but is more typically used by the Forest Service in rights-of-way maintenance. Stalker is labeled for application as a spray to cut stumps or to the basal bark of brush and trees but is not labeled for broadcast applications (BASF 2000c).

While imazapyr formulations can be used in pre-emergence applications, the most common and effective applications are post-emergent when the vegetation to be controlled is growing vigorously. This is detailed further in Section 4.3.2.4 (dose-response assessment for terrestrial plants). In postemergence applications, imazapyr formulations may require the use of an adjuvant. Recommended adjuvants for Arsenal include silicone or nonionic surfactants as well as seed or vegetable oils (BASF 2000a). Arsenal AC is generally applied without a surfactant although nonionic surfactants may be used (BASF 2000b). In cut stump or basal bark treatments, the product labels for Chopper and Stalker indicate that the product may be mixed with diesel oil, some other penetrating oil, or a surfactant (BASF 2000c; BASF 2001). The Forest Service, however, does not use diesel oil.

2.3. APPLICATION METHODS

The most common methods of ground application for Arsenal or Chopper formulations involve backpack (selective foliar) and boom spray (broadcast foliar) operations. In selective foliar applications, the herbicide sprayer or container is carried by backpack and the herbicide is applied to selected target vegetation. Application crews may treat up to shoulder high brush, which means that chemical contact with the arms, hands, or face is plausible. To reduce the likelihood of significant exposure, application crews are directed not to walk through treated vegetation and not to spray above shoulder height. Usually, a worker treats approximately 0.5 acre/hour with a plausible range of 0.25-1.0 acre/hour.

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

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

Arsenal is registered for aerial applications, fixed-wing or helicopter (BASF 2000a) and Arsenal AC is labeled for aerial applications, helicopter only (BASF 2000b). In Forest Service programs, aerial applications for imazapyr are restricted to helicopter only. Arsenal is applied

under pressure through specially designed spray nozzles and booms. The nozzles are designed to minimize turbulence and maintain a large droplet size, both of which contribute to a reduction in spray drift. In aerial applications, approximately 40-100 acres may be treated per hour.

2.4. MIXING AND APPLICATION RATES

The specific application rates used in ground applications vary according to the formulation as well as local conditions and the nature of the target vegetation.

Arsenal - Application rates of 1-6 pints Arsenal/acre are recommended on the product label (BASF 2000a). This is equivalent to ½ to 3 quarts Arsenal per acre or 0.125-0.75 gallons Arsenal per acre. Given that there is 2 lb a.e./gallon in Arsenal, these rates correspond to 0.25 to 1.5 lb a.e./acre. In rights-of-way application, the recommended application rates range from 1 to 3 pints Arsenal/acre or about 0.25 to 0.75 lbs a.e./acre. In low volume ground applications, Arsenal may be applied in 5 to 20 gallons of water per acre. High volume ground applications may involve up to 100 gallons of water per acre. In aerial applications, Arsenal should be applied in solutions that result in 5 to 30 gallons of water per acre (BASF 2000a).

Arsenal AC - The product label for Arsenal AC recommends application rates of 12-40 fl oz/acre for site preparation, 4-10 fl oz per acre for herbaceous weed control, 6-32 fl oz/acre for conifer release. The overall range of 4-40 fl oz Arsenal AC/acre is equivalent to 0.03125-0.3125 gallons Arsenal AC/acre [128 fl oz/gallon]. Given that there is 4 lb imazapyr a.e./gallon in Arsenal AC, these rates correspond to 0.125 to 1.25 lb a.e./acre. Arsenal AC is typically diluted with 5 to 100 gallons of water per acre in ground applications with high volume ground applications (75-100 gallons/acre) recommended for the control of kudzu, an invasive plant common in the southeastern United States. In aerial applications, Arsenal AC is diluted in 5 to 30 gallons of water per acre (BASF 2000b).

Chopper – Chopper is an emulsifiable concentrate that may be mixed with water or penetrating oils. Application rates for site preparation range from 24-80 fl oz per acre in application volumes of 5-40 gallons per acre for ground applications and 5-20 gallons per acre for aerial applications. Somewhat lower application rates (12-40 fl oz/acre) are used for conifer release in ground application volumes of 10 gallons/acre of less. Understory broadcast applications – i.e., applications under a tree canopy – may range from 32-64 fl oz/acre (BASF 2001). The overall range of 12-80 fl oz Chopper/acre is equivalent to 0.09375-0.625 gallons Chopper/acre [128 fl oz/gallon]. Given that there is 2 lb imazapyr a.e./gallon in Chopper, these rates correspond to 0.1875 to 1.25 lb a.e./acre.

Stalker - Stalker is also an emulsifiable concentrate that is typically mixed with penetrating oils and applied as a spray to stumps, stubble, or basal bark. In general, 8-12 fluid ounces of Stalker are mixed with one gallon of water and penetrating oils and applied as a spray to stumps, stubble, or basal bark. For such applications, rates expressed in lb a.e./acre are not specified on the product label (BASF 2000c).

The use of imazapyr in Forest Service Programs for fiscal year 2001, the most recent year for which data are available, is summarized in Table 2-2. Imazapyr is used currently in Forest Service Programs in a number of different types of applications. As a proportion of the total Forest Service use of imazapyr in pounds, the predominant uses include conifer or hardwood release (0.308), conifer release (0.249), wildlife habitat improvement (0.19), and rights-of-way management (0.141). Lesser amounts are used in noxious weed control (0.05) hardwood release (0.045), and housekeeping/facilities maintenance (0.016). Based on the total amount used and total number of acres treated, the average application rate is about 0.051 lb/acre. This is substantially below the the lower range of application rates recommended on the product formulations and probably reflects sporadic spot applications over relatively large areas.

For this risk assessment, the typical application rate will be taken as 0.45 lb a.e./acre. The typical application rate is about the average application rate that the Forest Service used in 2001 for noxious weed control – i.e., 0.451 lb/acre in Table 2-3 – and is near the geometric mean of the recommended range of application rates [$(0.125 \times 1.25)^{0.5} = 0.39$]. The range of application rates will be taken as 0.03 lb a.e./acre to 1.25 lb a.e./acre. The lower range of the application rate is near to the average application rates used by the Forest Service for conifer and/or hardwood release. The upper end of the application rate is taken at the maximum rate recommended on the product labels for Arsenal, Arsenal AC, and Chopper. The worksheets that accompany this risk assessment are based on the typical application rate of 0.45 lb/acre rather than the full range of application rates. The consequences of varying application rates within the range of 0.03 lbs a.e./acre to 1.25 lbs a.e./acre is considered in the risk characterization for human health (Section 3.4) and ecological effects (Section 4.4).

The extent to which imazapyr formulations are diluted prior to application primarily influences dermal and direct spray scenarios, both of which are dependent on the 'field dilution' - i.e., the concentration of imazapyr in the applied spray. In all cases, the higher the concentration of imazapyr, the greater the risk. For this risk assessment, the lowest dilution will be taken at 5 gallons/acre. The highest dilution - i.e., that which results in the lowest risk - will be based on 20 gallons of water per acre. This is a conservative approach in that some applications of imazapyr formulations will involve more dilute solutions that consequently present a lesser risk. The central estimate will be taken as 10 gallons of water per acre, the geometric mean of the range of 5 to 20 gallons per acre. These values are entered into Worksheet B01.

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. The worksheets that accompany this risk assessment are based on the typical application rate of 0.45 lb/acre rather than the full range of application rates (Worksheet B01). The consequences of varying application rates within the range of 0.03 lb a.e./acre to 1.25 lb a.e./acre is considered in the risk characterization for human health (Section 3.4) and ecological effects (Section 4.4).

2.5. USE STATISTICS

The USDA Forest Service (USDA/FS 2002) tracks and reports its use of pesticides by geographical areas referred to as "*Regions*". As illustrated in Figure 2-1, 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 by region in Table 2-3, the greatest proportion of imazapyr used by the Forest Service occurs in Region 8 (Southern, 80.2%) with a lesser proportion used in Region 9 (Eastern, 10.5%). Very small proportions of the total use are associated with Region 2 (Rocky Mountain, 2.6%), Region 4 (Inter-mountain, 4.1%), and Region 6 (Pacific Northwest, 2.7%).

National production and use data on imazapyr have not been encountered in the open literature. In California, approximately 15,800 pounds of the isopropylamine salt imazapyr were applied in 2001 (California Department of Pesticide Regulation 2002). About 93% of the imazapyr was applied to timberland and about 7% was applied in rights-of-way management. Other uses were minor (<0.1%). While imazapyr was not used by the Forest Service in California during 2001, it should be noted that the total use of imazapyr by the Forest Service in 2001 was about 221 lbs (Table 2-3), about 1% of the total use of imazapyr in California during 2001.

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview. The toxicity of imazapyr has been relatively well-characterized in experimental mammals. All of the mammalian information is contained in unpublished studies that were submitted to the U.S. EPA as part of the registration process for imazapyr and were obtained and reviewed as part of this risk assessment. Some clinical cases reports of intentional (attempted suicide) or accidental ingestion of large amounts of Arsenal have been reported. Symptoms include vomiting, impaired consciousness, and respiratory distress. requiring intubation. No fatal cases of imazapyr ingestion have been encountered.

Although the mode of action of imazapyr in humans or other mammals is unclear, this is at least partially a reflection of the apparently low and essentially undetectable acute and chronic systemic toxicity of this compound. The acute oral LD_{50} of unformulated imazapyr is greater than 5000 mg/kg and the chronic dietary NOAEL for imazapyr is 10,000 ppm in dogs, rats, and mice. In the dog, this dietary concentration is equivalent to a daily dose of 250 mg a.i./kg/day. In the other species, the equivalent daily doses are higher than 250 mg/kg/day. An adequate number of multi-generation reproductive and developmental studies have been conducted and no adverse effects on reproductive capacity or normal development have been demonstrated. Tests of carcinogenic and mutagenic activity are consistently negative, and the U.S. EPA has categorized the carcinogenic potential of imazapyr as *Class E: evidence of non-carcinogenicity*.

Increased food consumption has been reported in chronic toxicity studies in which imazapyr was added to the diets of male and female mice as well as female rats. It is unclear if this effect can be attributed to a toxicologic effect of imazapyr, since it may be due to an increase in palatability of the chow. The weight of evidence suggests that imazapyr is not directly neurotoxic, and the available data do not suggest that systemic toxic effects are plausible after dermal or inhalation exposures to imazapyr. Similarly, while the available data are limited, there is no basis for asserting that impurities or adjuvants in or metabolites of imazapyr are likely to impact the assessment of risk.

Imazapyr and imazapyr formulations can be mildly irritating to the eyes and skin. From a practical perspective, this is probably the effect that is most likely to be observed in the application of this compound if proper personal protection practices are not employed.

3.1.2. Mechanism of Action. In plants, imazapyr inhibits acetolactate synthase, an enzyme that is required for the synthesis of essential amino acids (valine, leucine, and isoleucine). This enzyme is not present in animals, and the mechanism of toxic action in animals and man is not known.

3.1.3. Kinetics and Metabolism. The metabolism and kinetics of imazapyr has been studied in rats (Mallipudi et al. 1983b) and lactating goats (Zdybak 1992). The available data in these species suggest that orally administered imazapyr is well absorbed and that the majority of the

administered dose is rapidly excreted, unchanged, in urine and feces. In rats, ^{14}C-imazapyr labeled on the carboxy group, dissolved in ethanol/water, was administered to 15 male Sprague Dawley rats (225 g) by gavage at a dose of 4.4 mg/kg. Imazapyr was excreted in the urine and feces, 87.2% and 93.3% of the administered dose was recovered from urine and feces on days 1 and 2 (respectively) after dosing. Approximately 98% of the administered dose was recovered in the urine and feces after 8 days as parent compound with no residues in liver, kidneys, muscle, or blood (Mallipudi et al. 1983b; Miller et al. 1991). No metabolites were identified (Mallipudi et al. 1983b). A similar pattern was noted in lactating goats administered ^{14}C-imazapyr acid in gelatin capsules in amounts equivalent to dietary exposures of 0, 17.7, or 42.5 ppm for 7 days (Zdybak 1992). Most of the radioactivity, 60–65% of the administered dose, was excreted in the urine as parent compound; a smaller portion, 16–19% of the administered dose, was recovered from feces. Only very small amounts were recovered from milk, blood, kidneys, liver, muscle, and fat.

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

3.1.4. Acute Oral Toxicity. Information on the toxicity of imazapyr in humans is available from reports of six cases of acute poisoning in Taiwan (Lee et al. 1999). Five of the cases were adults (4 men, 1 woman) who attempted suicide by ingesting concentrated (undiluted) Arsenal herbicide formulation (23.1% w/w imazapyr as the isopropylamine salt) in approximate amounts of 75, 100, 120, 300, and 500 mL. These ingested amounts are reported estimates based on patient history (e.g., number of mouthfuls ingested) and/or physical evidence such as the size of the bottle and remaining contents. The sixth case was a 4-year-old boy who was forced to swallow approximately 2 mL of Arsensal. There were no deaths; all six cases experienced copious vomiting following ingestion. Three of the five adults had severe symptoms including impaired consciousness and respiratory distress requiring intubation. Other effects in the adults included oral mucosal and gastrointestinal irritation and transient liver and renal dysfunction. Vomiting was the only effect observed in the child. It was concluded that the clinical observations constituted a toxic syndrome resulting from ingestion of a large amount (>100 mL) of Arsenal herbicide, although the specific component(s) in the Arsensal formulation that is responsible for the toxic effects is unknown.

Little information is available on the acute toxicity of imazapyr to experimental mammals. As part of the pesticide registration process, an acute oral toxicity study is required. As summarized in Appendix 1, single oral doses of 5000 mg/kg of a 2 lbs a.e./gallon formulation of imazapyr—corresponding to 25 mL formulation/kg body weight—was administered to groups of five male and female rats. Over the 14-day observation period, one male rat died. Abnormal findings in this rat included congestion of liver, kidney, and intestinal tract, as well as hemorrhagic lungs (Fischer 1983). None of the surviving rats showed signs of toxicity. It is unclear if the death of the one male rat was associated with treatment. In a similar study using a mixture of imazapyr and a related herbicide, imazethapyr, at a total dose of 5000 mg/kg, no

effects were noted (Lowe 1988). A review of unpublished studies of imazapyr sponsored by American Cyanamid (Peoples 1984) indicates that the oral LD_{50} of unformulated imazapyr (i.e., presumably technical grade imazapyr) is greater than 5000 mg/kg. No further information on the acute oral toxicity of imazapyr has been encountered in U.S. EPA's files on this compound or other reviews in the published literature (Cox 1996; Gagne et al. 1991).

3.1.5. Subchronic or Chronic Systemic Toxic Effects. Chronic toxicity studies on imazapyr have been conducted in three species: dogs (Shellenberger 1987), mice (Auletta 1988; Hess 1992), and rats (Daly 1988; Hess 1992). These studies were submitted to the U.S. EPA in support of the registration of imazapyr; none of the studies are published in the open peer-reviewed literature. In the preparation of this risk assessment, full copies of these studies were obtained from the U.S. EPA and reviewed (Appendix 1).

For the most part, these studies do not suggest any specific signs of frank toxicity at dietary concentrations of up to 10,000 ppm. In the rat feeding study (Daly 1988), a slight decrease in survivorship is apparent with increasing dose. Nonetheless, these changes are not statistically significant, using the Fischer exact test, at any of observation intervals (i.e., 6 months, 12 months, 18 months, and 24 months). Consequently, the dietary NOAEL of 10,000 ppm from the one-year dog feeding study (Shellenberger 1987) is used as the basis for the U.S. EPA's RfD, as discussed further in Section 3.3.2. U.S. EPA (1997) calculated that the dietary concentration of 10,000 ppm resulted in an average daily dose of about 250 mg/kg/day in dogs, calculated by based on midpoint food consumption and body weights reported by Shellenberger (1987).

The food consumption rates in the rat (Daly 1988) and mouse (Auletta 1988) chronic dietary studies are somewhat unusual. In both studies, there was a slight, and in some cases statistically significant, increase in food consumption with no corresponding increase in body weight. Three classes of mechanisms could produce this effect: a biochemical basis, such as uncoupling of oxidative phosphorylation; an endocrine basis – e.g. changes in thyroid hormone secretion, or increased corticosteroid levels – or a neurological basis involving hyperactivity. Imazapyr has been implicated in the development of thyroid tumors (Section 3.1.10). While a detailed review of the carcinogenicity studies do not support the assertion that imazapyr is carcinogenic, changes in appetite could be associated with effects on the thyroid. Without additional mechanistic studies, however, the basis for the observed effects on food consumption remain speculative.

A subchronic (13-week) study (Hess 1992) was conducted in rats exposed to imazapyr at dietary concentrations higher than the maximum tested in the chronic studies summarized above. Exposure to levels of 15,000 or 20,000 ppm caused no toxicity in either sex as evaluated by a comprehensive range of endpoints. The 13-week study establishes a subchronic dietary NOAEL at the highest dose tested 20,000 ppm in rats, which corresponded to daily doses of about 1700 mg/kg/day according to Hess (1992). This NOAEL dose in rats is several-fold higher than the NOAEL in dogs established by Shellenberger (1987).

Two standard teratology studies in Charles River rats involving gavage administration (discussed further in Sections 3.1.6 and 3.1.9), reported dose-related increases in salivation in treated dams (Salamon et al. 1983c,d). Salivation can be a sign of a neurologic involvement (e.g., Anthony et al. 1996). This effect, however, was not reported in a dietary reproduction study involving Sprague-Dawley rats (Robinson 1987) and was not noted in any of the acute toxicity studies summarized in Section 3.1.4 or in the chronic toxicity studies discussed above. Thus, while the results of Salamon et al. (1983c,d) are suggestive of a potential neurotoxic effect, this suggestion is not supported by the weight of the evidence (see Section 3.1.6).

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. This is the case for imazapyr. At high doses that produce a broad spectrum of toxicologic effects, clinical signs of poisoning include neurotoxicity, manifest as impaired consciousness and respiratory distress in humans (Lee et al. 1999), decreased activity in rats (Fischer 1986b), and loss of equilibrium and inactivity in fish (Cohle and McAllister 1984b,c). These reports from acute high-dose exposures, however, do not implicate imazapyr as a direct neurotoxicant.

As described in Appendix 1, two standard teratology studies reported dose-related increases in salivation in treated rats (Salamon et al. 1983c,d). While speculative and tenuous, this could suggest a possible neurologic effect. In addition, general pharmacology studies with imazapyr isopropylamine revealed central nervous system (CNS) effects following oral exposure (Medical Scientific Research Laboratory 1992, as cited by Cyanamid 1997). Male mice or male rabbits were orally administered imazapyr isopropylamine at levels of 1000, 3000, and l0,000 mg/kg to define the effect on gross behavior, central nervous system, and digestive system. In addition, male rabbits or male rats were administered intravenously imazapyr isopropylamine at 100, 300, 1000, and 3000 mg/kg to define the effect on skeletal muscle and respiratory and circulatory systems. Administration of imazapyr isopropylamine produced a stimulant effect on gross behavior and increased the sleeping time induced by hexobarbital at high doses in mice, slightly increased muscle contractility in rats, depressed gross behavior at high doses in rabbits, slightly changed respiratory rate, blood pressure, and heart rate in rabbits, and increased the volume of urine at high doses in both mice and rabbits. No effect on the digestive system was observed. These data suggest that exposure to imazapyr isopropylamine at these levels produces CNS effects.

Schwarcz et al. (1983) noted that quinolinic acid, a photolytic (though not metabolic) breakdown product of imazapyr, causes neurotoxic effects at very low doses when injected directly into the brains of rats (i.e., intracerebral injection). It is possible that the neurologic effect identified by these studies (Medical Scientific Research Laboratory 1992, as cited by Cyanamid 1997;

Salamon et al. 1983c,d) resulted from contamination of the administered dose by a photolytic breakdown product, rather than as a result of imazapyr administration. However, as noted in Section 3.1.15.1, quinolinic acid levels in the brain are regulated by an active transport system and it does not seem likely that sufficient quinolinic acid would be present in imazapyr to cause frank signs of toxicity. This supposition is supported by the fact that signs of neurotoxicity have not been noted in other studies on reproductive or developmental effects and neurotoxicity has not been noted in standard acute and chronic toxicity studies. In addition, none of the studies in the imazapyr database reported histopathological changes in nervous tissue. Thus, the weight of evidence does not support the assertion that imazapyr is likely to have neurotoxic potential.

No studies designed specifically to detect impairments in motor, sensory, or cognitive functions in animals or humans exposed to imazapyr have been reported in the open literature or in the studies submitted to the U.S. EPA to support the registration of imazapyr. 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 imazapyr. This is not surprising, since the undertaking of such studies on a substance such as imazapyr, 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 imazapyr. The only studies specifically related to the effects of imazapyr on immune function are skin sensitization studies (Section 3.1.11). While these studies provide information about the potential for imazapyr to act as a skin sensitizer, they provide no information useful for directly assessing the immunoactive potential of imazapyr. The toxicity of imazapyr 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 observed 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). Imazapyr 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 imazapyr exposures. Thus, any judgments concerning the potential effect of imazapyr 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 discussed in Section 3.1.5, the increased food consumption noted in some chronic feeding studies in rodents (Auletta 1988; Daly 1988) could be associated with endocrine function – i.e., a change in thyroid status. However, none of the animal studies reported abnormal thyroid histology or hormone levels in the standard clinical chemistry results that were attributed to imazapyr exposure. The study by Auletta (1988) also noted an increase in the incidence of elevated seminal vesicle weight. While Auletta (1988) suggests that this is a *"common findings in old mice"*, the response appears to be dose-related and the development of the seminal vesicles is stimulated by androgenic hormones. These observations suggest that imazapyr may impact some aspects of endocrine function.

3.1.9. Reproductive and Teratogenic Effects. As reported by Cox (1996), no studies on potential reproductive or teratogenic effects are available in the published literature. Nonetheless, several studies, summarized in Appendix 1, on the reproductive effects of imazapyr in rats and rabbits have been conducted and submitted to the U.S. EPA in support of the registration of imazapyr. As with the chronic studies, full copies of these studies were obtained from the U.S. EPA and reviewed in the preparation of this risk assessment. These studies were also reviewed by the U.S. EPA (1997) in the derivation of the U.S. EPA/OPP RfD for imazapyr and were classified as acceptable and adequate. Even at dose levels that cause signs of maternal toxicity (including death), imazapyr does not cause adverse reproductive or developmental effects.

3.1.10. Carcinogenicity and Mutagenicity. The U.S. EPA (1997) has reviewed a number of assays for mutagenicity, as well as chronic studies in mice (Auletta 1988) and rats (Daly 1988), that can be used to assess carcinogenic potential. As reviewed by Cox (1996), some of the observations from the chronic rat study (Daly 1988) raise concerns for potential carcinogenic activity. While this study was reviewed by the U.S. EPA (1997), it was further reviewed as part of this risk assessment. As summarized in Table 3-1, microscopic pathology did reveal an increased incidence of C-cell carcinomas of the thyroid gland in male rats exposed to10,000 ppm for up to 2 years, compared with male rats in the middle-dose, low-dose (1000 ppm), and matched control (0 ppm) groups. Nonetheless, the incidences of C-cell carcinomas for all groups of male rats in the Daly (1988) study are within the range of the historical control data (13.7%) (Table 3-2), although the incidence in high-dose male rats (7.69%) is almost twice the average incidence (4.10%) reported in the historical control data (Daly 1988; Daly et al. 1991).

According to Daly (1988) and consistent with the interpretation of the U.S. EPA (1997), the increased incidence of C-cell carcinoma in the thyroid gland of high-dose male rats is an incidental finding, based on the following observations: first, the combined incidences of C-cell adenoma and carcinoma in all male rats in the matched control study are within the range reported in the historical control data (17.14%); moreover, the incidences in the control (4.62%) and low-dose (6.15%) groups are below the average incidence reported in the historical control data (9.13%); second, a comparison of the combined incidences of C-cell hyperplasia, adenoma, and carcinoma reveals higher than average incidences in the control (26.15%) and middle-dose

group (33.33%), compared with the historical data (25.71%), whereas the low-dose (18.46%) and high-dose (23.08%) groups fall within the range of the historical control data; and, finally, the overall incidences of C-cell proliferative lesions in the Daly (Daly 1988; Daly et al. 1991) studies, in general, do not demonstrate a clear dose-response relationship or a clear progression from C-cell hyperplasia to adenoma to carcinoma (Table 3-1).

Support for this argument was provided by another pathologist hired by the sponsor of the study to review the data on 260 thyroid glands from male rats in the study. The consultant concluded that the difference in C-cell carcinomas between the treated and untreated rats is not statistically significant at $p<0.05$ and that the difference between the control and high-dose male rats with respect to the incidence of C-cell carcinomas is of no biological significance because it is consistent with that reported in other studies conducted at the same laboratory as the Daly (1988) study and in studies published in the open literature. The apparent increase in the incidence of the C-cell carcinomas in the high-dose males is viewed as a consequence of the 'extremely low' incidence of C-cell carcinomas in the matched control group. Finally, in summarizing the microscopic evaluation of the thyroid glands from rats exposed to 1000, 5000, or 10,000 ppm for up to 2 years, the consulting pathologist concluded that there is no evidence of treatment-related effects on the incidence or progression of proliferative lesions in the Daly (1988) study (i.e, no indication of a carcinogenic effect). Again, this is consistent with the interpretation by the U.S. EPA (1997) and is consistent with the available data from the study.

Two gene mutation studies (*Salmonella typhimurium/Escherichia coli* and Chinese hamster ovary cell gene mutation) and one chromosomal aberration study (Chinese hamster ovary cells) were classified as acceptable and negative for potential mutagenic activity. An additional chromosomal aberration study (dominant lethal assay) was also negative but had been classified as inadequate because the complete spermatogenic cycle had not been evaluated. In a re-review of this study, however, the U.S. EPA (1997) has recommended that the study be upgraded to acceptable. Based on these studies, the U.S. EPA (1997) has categorized imazapyr as *Class E: evidence of non-carcinogenicity*. Further support for lack of genotoxic activity comes from other mutagenicity studies that have been conducted and submitted to the U.S. EPA in support of the registration of imazapyr (Allen et al. 1983; Cortina 1984; Enloe et al. 1985; Johnson and Allen 1984; Sernau 1984). All of these demonstrated a negative response. More recently, imazapyr was negative in a mouse micronucleus assay, a common screening test for mutagenic activity (Grisolia 2002). While it is impossible, by definition, to prove the negative, the available data appear to be of sufficient quality and detail to assert that no potential carcinogenic risk from exposure to imazapyr can be identified at this time.

3.1.11. Irritation and Sensitization (Effects on the Skin and Eyes). Imazapyr and its formulations can be irritating to the eyes and skin. The published reviews on imazapyr (Cox 1996; Gagne et al. 1991; Peoples 1984) all appear to cite the study on ocular and dermal toxicity (Fischer 1983) summarized in Appendix 1. This study was conducted and submitted to the U.S. EPA in support of the registration of imazapyr and a copy of the study was obtained from the U.S. EPA and reviewed in the preparation of this risk assessment. Other studies available from

the U.S. EPA involve a mixture of imazapyr and imazethapyr. These mixture studies, while summarized in Appendix 1, are not further detailed in this risk assessment.

In a standard assay of skin irritation, an imazapyr formulation was classified as mildly irritating, causing redness in intact or abraded skin and edema (swelling) only in abraded skin (Fischer 1989d). When the formulation was instilled directly into the eyes of rabbits, transient eye irritation was observed with complete recovery by day 7 after administration (Fischer 1983; Fischer 1986a,b; Fischer 1989b). The extent of irritation was substantially less in eyes that had been rinsed with water one hour after instillation of the imazapyr formulation (Fischer 1983).

3.1.12. Systemic Toxic Effects from Dermal Exposure. Several studies, summarized in Appendix 1, on the effects of dermal exposure to imazapyr in experimental animals have been conducted and submitted to the U.S. EPA in support of the registration of imazapyr. The available toxicity studies summarized in Appendix 1 suggest that dermal exposure to 2000 mg/kg imazapyr was not associated with any signs of systemic toxicity in rabbits based on standard acute/single application bioassays with 14-day observation periods. It is not clear if the mottled and pale liver and congestion of the lungs, each observed in 1 of 9 rabbits after the dermal application of an imazapyr formulation, were incidental or treatment related (Fischer 1983). A single dose of Arsenal AC at 5000 mg/kg was not associated with mortality, signs of toxicity or changes in body weight (Lowe and Bradley 1996). Effects on the lungs have been observed in rabbits after dermal application of a mixture of imazapyr and imazethapyr (Lowe 1988), but these effects were apparently due to a respiratory infection in the treated group rather than a direct effect of the imazapyr/imazethapyr mixture.

Although there are no data concerning the dermal absorption kinetics of imazapyr, dermal absorption is typically less rapid than absorption after oral exposure and dermal LD_{50}'s are typically higher than oral LD_{50}'s (e.g., Gaines 1969). Since the acute oral LD_{50} of imazapyr is more than 5000 mg/kg (Fischer 1983), the lack of apparent toxicity at dermal doses of up to 2000 mg/kg/day is to be expected and these studies add little to the assessment of risk for imazapyr after dermal contact.

Nonetheless, the dermal exposure route is important to this and other similar risk assessments. 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 with 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 imazapyr is likely to be absorbed from the surface of the skin.

As discussed in SERA (2001), 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. Because no kinetic data are available on the dermal absorption of imazapyr, the method for estimating a zero-order absorption rate (U.S. EPA 1992)

is used in this risk assessment. Using this method, a dermal permeability coefficient for imazapyr is estimated at 0.000056 cm/hour with a 95% confidence interval of 0.000028–0.00011 cm/hour. These estimates are used in all exposure assessments that are based on Fick's first law. The calculations for these estimates are presented in Worksheet B05.

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 Durkin et al. (1998), the estimated first-order dermal absorption coefficient is 0.0011 hour-1 with 95% confidence intervals of 0.00044–0.0029 hour-1. The calculations for these estimates are presented in Worksheet B04.

3.1.13. Inhalation Exposure. Compared with oral exposure data, data regarding the inhalation toxicity of imazapyr are limited to three studies (see Appendix 1). All three studies on the effects of inhaled imazapyr in rats have been conducted and submitted to the U.S. EPA in support of the registration of imazapyr. No toxic effects were observed during or after 4-hour exposures to either imazapyr or imazapyr formulations at aerosol concentrations of >5 mg/L (Peoples 1984).

Although inhalation of imazapyr is not a typical route of exposure, it may occur during brown-and-burn operations. The post-treatment burns in brown-and-burn operations are conducted 30 to 180 days after treatment with the herbicide (McMahon and Bush 1992). McMahon and Bush (1992) found no detectable levels of imazapyr in the breathing zone of workers during brown-and-burn operations in plots that had been treated with imazapyr 69 or 106 days earlier at application rates of up to 3.5 L/ha (0.92 gal/ha or 1.84 lbs imazapyr a.e./ha or about 0.77 lb a.e./acre).

3.1.14. Inerts and Adjuvants. As noted in Section 2, information on inerts in imazapyr formulations have been reviewed as part of this risk assessment. Specific notes are included in Appendix 1 concerning those toxicity studies in which information on inerts is specified. This information, however, is considered proprietary under FIFRA. Other than to state that no apparently hazardous materials have been identified, this information cannot be detailed.

All of the technical formulations of imazapyr covered in this risk assessment involve the isopropyl or isopropanolamine salts of imazapyr. Little toxicity information is available on these compounds. Isopropanolamine is classified by the U.S. EPA (1998) as a List 3 inert. These are compounds that the U.S. EPA cannot classify as hazardous or non-hazardous based on the available information. Isopropyl alcohol, isopropylamine, and a large number of other derivatives of isopropanol are used as food additives and classified as GRAS (generally recognized as safe) compounds (Clydesdale 1997). Isopropyl alcohol is classified as a List 4B inert and isopropanolamine as well as a large number of related compounds are classified by U.S. EPA as List 3 inerts (U.S. EPA/OPP 2003).

The Northwest Coalition for Alternatives to Pesticides (NCAP) has obtained information on the identity of the inerts in Arsenal AC from U.S. EPA under the Freedom of Information Act and

has listed this information on the NCAP web site (http://www.pesticide.org/FOIA). The only inert listed at this site other than water is glacial acetic acid (CAS No. 64-19-7). Dilute acetic acid is an approved food additive and is also classified as a GRAS compound (Clydesdale 1997). Acetic acid is a major component of vinegar and is a List 4B inert (U.S. EPA/OPP 2003).

The minimal testing requirements for compounds that have been used as inerts or adjuvants for many years is a general problem in many pesticide risk assessments. For new inerts, the U.S. EPA does require more extensive testing (Levine 1996). Notwithstanding this uncertainty, none of the inerts used in any of the imazapyr formulations have been classified by the U.S. EPA as hazardous (List 1 or List 2).

3.1.15. Impurities and Metabolites.

3.1.15.1. Impurities **–** No information has been encountered in the published literature on the manufacturing impurities in imazapyr. Nonetheless, virtually no chemical synthesis yields a totally pure product. Technical grade imazapyr, as with other technical grade products, contains some impurities. These impurities have been disclosed to U.S. EPA and have been reviewed as part of the current risk assessment (i.e., American Cyanamid 1983a,b; Arthur 2000; Beardmore 1987a; Cortes and Chiarello 1994; Danishevsky and Cortes 1994; Garber 1984; Stellar 1998a,b). Because specific information concerning impurities may provide insight into the manufacturing process used to synthesize imazapyr, such information is considered proprietary, is protected under FIFRA (Section 10), and cannot be specifically discussed in this risk assessment.

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

As stated earlier, quinolinic acid is a photolytic breakdown product of imazapyr that has been associated with neurologic effects in experimental animals (Schwarcz et al. 1983). Quinolinic acid is a metabolite of tryptophan, a naturally occurring and essential amino acid in mammals. Levels of quinolinic acid are controlled in mammals by an active transport system which helps to regulate the concentrations of a large number of weak acids in the central nervous system as well as transport systems involved in the urinary excretion of weak acids (e.g., Morrison et al. 1999).

3.1.15.2. Metabolites **–** The metabolism and kinetics of imazapyr has been studied in rats (Mallipudi et al. 1983b), lactating goats (Zdybak 1992), and white leghorn chickens (Tsalta 1995). The only significant component in excreted residues was the parent compound (i.e., imazapyr). These studies do not rule-out the formation of minor metabolites. Nonetheless, there is no basis for asserting that metabolites may be formed that would have any substantial impact on this risk assessment.

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 0.45 lb/acre. The consequences of using the maximum application rate that might be used by the Forest Service, 1.25 lb/acre, are discussed in the risk characterization.

For workers, three types of application methods are modeled: directed ground, broadcast ground, and aerial. The central estimates of exposure for broadcast ground spray workers is about 0.01 mg/kg/day. The central estimates of exposures for backpack and aerial workers are somewhat lower, about 0.006 mg/kg/day. Upper range of exposures are approximately 0.04 mg/kg/day for backpack and aerial applications and 0.07 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 estimates of acute exposures range from approximately 0.000002 mg/kg associated with the lower range for the consumption of contaminated water from a stream by a child to 0.9 mg/kg associated with the upper range for consumption of contaminated water by a child following an accidental spill of imazapyr into a small pond. High dose estimates are also associated with the direct spray of a child (an upper range of 0.116 mg/kg/day). Other acute exposures are lower by about an order of magnitude or greater. For chronic or longer term exposures, the modeled exposures are much lower than for acute exposures, ranging from approximately 0.0000000003 mg/kg/day (i.e., 0.3 billionths of a mg/kg) associated with the lower range for the normal consumption of fish to approximately 0.04 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 imazapyr that accompany this risk assessment (Supplement 1). This section on workers and the following section on the general public provides are plain verbal description of the worksheets and discuss imazapyr 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 imazapyr 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 0.45 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 (2001), 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 imazapyr were found in the literature. As described in SERA (2001), worker exposure rates are expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical handled. These exposure rates 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 imazapyr is 261.3 and the $K_{o/w}$ is 1.3, which corresponds to a log $K_{o/w}$ of 0.11. These values are within the range of the herbicides used in SERA (2001). As described in SERA (2001), 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. These values are taken from previous USDA risk assessments (USDA 1989a,b,c). 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.

Imazapyr is a mild skin and eye irritant (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 2001). 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 summarized 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 imazapyr is not available. Thus, the Kp for imazapyr is estimated using the algorithm from U.S. EPA (1992), which is detailed in Worksheet A07b. The application of this algorithm to imazapyr, 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 on to 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 imazapyr.

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 imazapyr. 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 these exposure scenarios and the quality of the data supporting the exposure scenarios.

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 imazapyr. 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 imazapyr 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 the compound in ambient water are acute/accidental exposure from an accidental spill and longer-term exposure to imazapyr 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 imazapyr 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 imazapyr in a small pond is estimated to range from about 2 mg/L to 8.3 mg/L with a central estimate of about 4.1 mg/L (Worksheet D05).

The other acute exposure scenario for the consumption of contaminated water involves runoff into a small stream. Two monitoring studies are available on the concentrations of imazapyr in streams after aerial applications (Michael and Neary 1993; Rashin and Graber 1993). In the Michael and Neary (1993) study, a liquid formulation of imazapyr was applied at a rate of 2.2 kg a.i./ha, which is equivalent to 1.96 lbs a.i./acre. While Michael and Neary (1993) do not specify the formulation, they indicate that it was a formulation produced by American Cyanamid. Thus, it will be assumed that an Arsenal formulation of the isopropylamine salt of imazapyr was applied. Consequently, correcting for differences in molecular weight (Table 2-1), an application rate of 1.96 lbs a.i./acre corresponds to 1.59 lbs a.e./acre [1.96 lbs a.i. × (MW acid 261÷MW 320 salt)]. The broadcast aerial applications were made in two similar watersheds in Alabama (designated as Sites 12 and 13 in Michael and Neary 1993). At one site (13), a buffer zone was maintained along streams. The maximum surface water concentration in the site with the buffer zone was 130 µg/L. The maximum surface water concentration in the site without the buffer zone (site 12) was 680 µg/L, but this was associated with imazapyr "falling directly into the stream during application" (Michael and Neary 1993, Table 3, p.407). The maximum levels of imazapyr occurred as a pulse immediately after a 30 mm (about 1.2 inches) rainfall and decreased to trace or non-detectable levels within 9 hours. Subsequent rainfalls of (>10 mm or about 0.4 inches) resulted in maximum imazapyr concentrations of 6 µg/L which decreased to non-detectable or trace levels within 1.5 hours.

The study by Rashin and Graber (1993) involved the aerial application of imazapyr at 0.1 a.i. kg/ha or 0.0892 lb a.i./acre to two watersheds in Washington state. Again correcting for molecular weight, this application rate corresponds to 0.073 lb a.e./acre [0.0892 lbs a.i. × (MW acid 261÷MW 320 salt)]. At both sites, buffer zones were used around surface water and the maximum concentrations detected in surface water was 1 µg/L at both sites. It is not clear from the review by Neary and Michael (1996) if this concentration was an actual maximum observed measurement or simply represented the limit of detection.

Additional monitoring studies have not been located in the literature. The National Water Quality Assessment (NAWQA) of the U.S. Geological Survey is a large scale monitoring effort to characterize pesticides in surface and ground water (USGS 2003). Imazapyr, however, is not included in the specific pesticides examined in this program.

While monitoring data provide practical and documented instances of water contamination, monitoring studies may not encompass a broad range of conditions which may occur during program applications – e.g., extremely heavy rainfall – or they may reflect atypical applications that do not reflect program practices. Consequently, for this component of the exposure assessment, the monitored levels in ambient water are compared to modeled estimates based on GLEAMS (Groundwater Loading Effects of Agricultural Management Systems). 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).

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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 3-3. The GLEAMS modeling yielded estimates runoff, sediment and percolation that were in turn 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 3-4 and the corresponding values for the small pond are summarized in Table 3-5. 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 3-4, no stream contamination is estimated in very arid regions – i.e., annual rainfall of 5 or less to25 inches depending on soil type. The modeled maximum concentrations in the stream range from about 0.1 µg/L or less (in loam) to somewhat over 2 µg/L (clay) at annual rainfall rates from 150 to 250 inches per year, with the highest concentrations associated with clay at annual rainfall rates of 200 inches or more. While not detailed in Table 3-4, the losses from clay are associated almost exclusively with runoff (about 84%), with the remaining amount due to sediment loss. For loam, about 88% of the loss is associated with percolation and most of the remaining loss with runoff. For sand, the pesticide loss is associated exclusively with

percolation. For both clay and loam, the maximum losses occur with the first rainfall after application. For sand, time to maximum loss is attenuated.

The stream concentrations based on the GLEAMS modeling appear to underestimate concentrations in streams noted in the monitoring studies. For example, as discussed above, the data from Michael and Neary (1993) indicate peak concentrations of 130 µg/L to 680 µg/L in streams after an application of 1.59 lbs a.e./acre following a rainfall of about 1.2 inches. The higher concentration of 680 µg/L, however, was associated with direct spray of the stream and is thus not appropriate as a comparison to the GLEAMS modeling. The peak concentration 130 µg/L may be normalized for the application rate to a water contamination rate of about 80µg/L per lb a.e. applied [680 µg/L ÷ 1.59 lbs a.e./acre = 81.76 µg/L per lb/acre]. The highest concentration in streams based on the GLEAMS modeling is only about 2 µg/L. Based on the every tenth day storm pattern used in the GLEAMS modeling, the rainfall rate of 1.2 inches would correspond to an annual rain fall of about 44 inches [1.2 inches/event × 36.5 events/year]. Based on the GLEAMS modeling for clay soil, the estimated peak concentration in streams at an annual rainfall of 44 inches would be about 0.4 µg/L, a factor of about 200 below the normalized peak concentration of 80µg/L per lb a.e./acre from Michael and Neary (1993).

The reasons for this discrepancy cannot be clearly determined from the available data. One critical factor in the modeling based on the GLEAMS output is the stream flow rate. As specified in Table 3-3, the GLEAMS modeling is based on a mean stream flow rate 4.42 million L/day with a flow velocity of 0.08 m/second. Some streams, however, have much smaller flow rates and flow rates for any single stream may be highly variable over time. For example, a discussed in SERA (2003b), the flow rate of 4.420 million L/day used in the GLEAM modeling is based on the lower 5th percentile of a database of 55,701 stream reaches, including only thus streams with mean flow volumes >1,000 liters/day. For this database, the lower 0.1 percent of streams have a mean flow rate of 0.158 million liters per day, a factor of about 28 less than the value used in the GLEAMS modeling. In addition to variations in mean flow rates among streams, flow rates will vary more substantially over time for an individual stream. For example, the stream with a mean flow rate of 4.420 million L/day has a low flow rate of less than 1,000 liters/day. Thus, if the stream monitored by Michael and Neary (1993) had a very low flow volume, the higher concentrations could be expected.

The GLEAMS modeling for the stream may be compared to a similar modeling effort by Garrett et al. (1999) using PRZM/EXAMS. PRZM, like GLEAMS, is a root zone model that gives edge-of-field pesticide losses that are generally comparable to GLEAMS (see SERA 2003, Section 1). EXAMS is a model used by U.S. EPA which uses outputs from PRZM to estimate concentrations in surface water. Garrett et al. (1999) modeled concentrations in streams after the application of imazapyr at a rate of 1.5 lb a.e./acre. Peak concentrations of up to 24 µg/L were modeled but concentrations were generally in the range of 1 to 10 µg/L, equivalent to water contamination rates of about 0.7 to 7 µg/L per lb a.e./acre. These are only modestly higher than the peak of 2 µg/L per lb a.e./acre for clay in Table 3-4. The concentration of 24 µg/L is

equivalent to 16 µg/L per lb a.e./acre, a factor of 5 below the 80µg/L per lb a.e./acre value from the study by Michael and Neary (1993).

The estimated peak concentrations in ponds based on the GLEAMS modeling (Table 3-5) are generally similar to those in streams, ranging from about 0.05 or less to1.7 µg/L in clay soil, up to about 0.4 µg/L in sand, and less than 0.07 µg/L in loam. Modeled average concentrations in ponds, however, are substantially higher than those in streams. The highest average concentration is estimated at about 0.2 µg/L – i.e., sandy soil at a rainfall rate of 50 to 100 inches per year. Over all soil types, typical concentrations are in the range of 0.01 or less to 0.2 µg/L. As with the stream modeling, virtually no contamination is modeled in very arid regions for clay and sand. For loam, no water contamination is estimated at rainfall rates of 25 inches per year or less

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]. As indicated in Table 3-4, the expected peak concentrations from runoff or percolation in streams are below this value by a factor of about 5 or more.

For the the current risk assessment, the upper range for the short-term water contamination rate will be taken as 80 µg/L per lb/acre based on the monitoring data from Michael and Neary (1993). This value is substantially higher than the estimates from GLEAMS (Table 3-4) or the similar modeling effort by Mangels et al. (2000) and may have involved an application to a very small stream or some other factors such as incidental contamination from aerial drift. Nonetheless, this monitoring study is analogous to the types of applications that could be made in Forest Service programs. The value of 80 µg/L per lb/acre converted to 0.08 mg/L per lb/acre and is entered into Worksheet B06. The central estimated will be taken as 2 µg/L (0.002 mg/L), about the maximum concentration for clay at annual rainfall rates of 100 to 250 inches. While this is the upper range of modeled values, the discrepancies between the modeled estimates and monitoring data suggest that this conservative approach is appropriate for imazapyr. The lower range will be taken as 0.1 µg/L (0.0001 mg/L), concentrations that might be expected in relatively arid regions with clay soil – i.e., annual rainfall of 20 inches. Note that lesser concentrations are modeled for loam and sand and this may need to be considered in any site-specific application of GLEAMS.

3.2.3.4.2. LONGER-TERM EXPOSURE – The scenario for chronic exposure 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 on the modeled estimates from GLEAMS, discussed in the previous section.

As noted in the previous section, imazapyr is not included in the NAWQA program of the U.S. Geological Survey (USGS 2003) and no other longer-term monitoring studies have been encountered. Thus, the longer term estimates will be based solely on the GLEAM modeling.

For this risk assessment, the typical longer term WCR is taken as 0.1 µg/L or 0.0001 mg/L per lb/acre. This is about the average concentration that modeled in a pond using GLEAMS at a rainfall rate of 50 to about 250 inches per year in clay soil as well as average concentrations modeled for sand at a rainfall rate of about 25 inches per year (Table 3-5). The upper range of the WCR could be taken as 0.2 µg/L or 0.0002 mg/L per lb/acre. This is the highest average concentration modeled from sandy soil at an rainfall rate of 50 inches per year. However, as noted in the previous section, the peak values from GLEAMS did not encompass the available monitoring data. Thus, the peak level is set of 0.001 mg/L – a factor of 5 higher than the highest modeled average concentration – because of concerns that concentrations higher than those modeled could be plausible under some conditions. 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).

As part of the registration process, experimental bioconcentration factors are required and one such study has been submitted to U.S. EPA (McAllister et al. 1985). McAllister et al. (1985) exposed bluegill sunfish to 14C-labeled imazapyr for 28 days and found no indication of bioconcentration. The measured bioconcentration factor was less than 0.5. In other words, the concentration of imazapyr in the fish was less than the concentration of imazapyr in the water. For exposure assessments based on the consumption of contaminated fish, the measured BCF of 0.5 is used (i.e., the concentration in the fish will be one-half that of the concentration in the water).

For both the acute and longer-term exposure scenarios involving the consumption of contaminated fish, the water concentrations of imazapyr 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 worksheets D08a (general public) and D08b (subsistence populations). The chronic exposure scenario is constructed in a similar way, as detailed in worksheets D09a and D09b, except that estimates of imazapyr concentrations in ambient water are based on the estimates of longer term concentrations given in Section 3.2.3.4.

3.2.3.6. Oral Exposure from Contaminated Vegetation – None of the Forest Service applications of imazapyr 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 imazapyr 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 imazapyr (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 imazapyr 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 Michael and Neary (1993), who report a range of halftimes from 15 to 37 days. This range is used as the upper and lower limit and the arithmetic mean, 26 days, is taken as the central estimate. 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 dose-response assessment for imazapyr is relatively straightforward and the toxicity data base is reasonably complete and unambiguous. The U.S. EPA has derived a chronic RfD of 2.5 mg/kg/day using a dog NOAEL of 250 mg/kg/day and an uncertainty factor of 100. The NOAEL selected by the U.S. EPA appears to be the most appropriate and is supported by additional NOAELs in rats and mice as well as a number of studies on potential reproduction and developmental effects. Consistent with the approach taken by U.S. EPA (2003c), no acute RfD will be derived in this risk assessment and the chronic RfD of 2.5 mg/kg/day will be used to characterize the risks of both acute and longer term exposures.

3.3.2. Existing Guidelines for Chronic Exposure. The U.S. EPA has not derived an agency-wide RfD for imazapyr – i.e., there is no RfD for imazapyr listed on the U.S. EPA Integrated Risk Information System (http://www.epa.gov/iriswebp/iris/index.html).

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

As discussed in Section 3.1.3, no adverse effects attributable to treatment were noted in any treatment group. As reported by U.S. EPA (1997), the highest dietary concentration corresponded to reported daily doses of 250 mg/kg/day. In deriving the RfD, the U.S. EPA (1997) used an uncertainty factor of 100 (10 for species-to-species extrapolation and 10 for sensitive subgroups in the human population) [250 mg/kg/day ÷ 100 = 2.5 mg/kg/day]. Because the available data on reproductive toxicity and teratogenicity do not indicate that young animals are more sensitive than adults to imazapyr, no additional uncertainty factor for infants or children was applied. This approach and the resulting RfD have been maintained in the pesticide tolerances for imazapyr that have recently been published by Office of Pesticide Programs (U.S. EPA 2003c).

No other criteria for imazapyr have been found on INTERNET sites of any of the organizations responsible for setting environmental or occupational exposure recommendations, criteria or standards (i.e., WHO, OSHA, NIOSH, or ACGIH). No published recommendations from these agencies or organizations were encountered in the literature search, which included databases covering the Federal Register.

3.3.3. Acute RfD. The U.S. EPA has not derived an acute RfD for imazapyr. In the recent pesticide tolerances for imazapyr, the U.S. EPA (2003c) states that: *An acute dietary endpoint was not selected based on the absence of an appropriate endpoint attributable to a single dose* (U.S. EPA 2003c, p. 55478). The U.S. EPA also derives incidental oral risk values that cover a range of 1 to 30 days. For imazapyr, the U.S. EPA (2003c) specifies a NOAEL of 250 mg/kg/day, identical to that used for the chronic RfD, and a margin of exposure of 100, identical to the uncertainty factor used for the chronic RfD. While not explicitly identifying this as an

"acute RfD", this approach is functionally equivalent to setting the acute RfD for incidental oral exposure to the chronic RfD of 2.5 mg/kg/day.

As discussed in Section 3.1.3 and detailed in Appendix 1, the dog study (Shellenberger 1987) is supported by chronic oral toxicity studies in both rats (Daly 1988) and mice (Auletta 1988) as well as several studies designed to detect adverse effects on reproduction and development (Section 3.1.4). The teratology studies (e.g., Salamon et al. 1983a,b,c,d summarized in Appendix 1) typically involve gavage doses over a relatively short period of time, in the range of 10 to 14 days and can be considered as a basis for deriving short term RfDs. However, for imazapyr, a clear acute NOAEL value that is substantially above 250 mg/kg/day cannot be identified. Thus, consistent with the approach taken by U.S. EPA (2003c), no acute RfD will be derived in this risk assessment and the chronic RfD of 2.5 mg/kg/day will be used to characterize the risks of both acute and longer term exposures.

3.4. RISK CHARACTERIZATION

3.4.1. Overview. For both workers and members of the general public, risk is characterized quantitatively using a hazard quotient, the ratio of the exposure estimate to the chronic RfD. Because all exposure assessments are based on the typical application rate of 0.45 lb/acre, the level of concern for the hazard quotient is one (1) at the typical application rate. Because the maximum application rate is 1.25 lb/acre, the level of concern at the maximum application rate is 0.36 – i.e., 0.45 lb/acre ÷ 1.25 lb/acre.

Typical exposures to imazapyr do not lead to estimated doses that exceed a level of concern for either workers or members of the general public at either the typical or highest application rate. 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 longer-term exposure to imazapyr 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 imazapyr. From a practical perspective, eye irritation is likely to be the only overt effect as a consequence of mishandling imazapyr. This effects can be minimized or avoided by prudent industrial hygiene practices – e. g., exercising care to reduce splashing and wearing goggles – during the handling of the compound.

3.4.2. Workers. A quantitative summary of the risk characterization for workers associated with exposure to imazapyr 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 2.5 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 0.45 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 1.25 lb a.e./acre, the highest labeled application rate, the level of concern would be 0.36 – i.e., 0.45 lb/acre ÷ 1.25 lb/acre.

The highest hazard quotient for workers based on general exposures given in Worksheet E02 is 0.03 – the upper range for broadcast ground spray. 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 12 [0.36 ÷ 0.03].

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 0.006 – 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 about 166 consecutive hours [1÷0.006 = 166.666...] or a about 7 days would be required to reach a level of concern (a hazard quotient of one) at the typical application rate. Based on the highest application rate, the hazard quotient of 0.006 is below the level of concern (i.e., 0.36) by a factor of 60. Thus, at the highest application rate, a worker would have to wear contaminated gloves for 60 hours or 2.5 days to reach a 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 imazapyr that are regarded as unacceptable and no exposure scenario approaches a level of concern.

Confidence in this risk characterization for acute worker exposures is diminished by the lack of experimental data on the dermal absorption kinetics of imazapyr (Section 3.1) and confidence in risk characterization for general exposures is diminished by the lack of a worker exposure study (Section 3.2.2.1). Nonetheless, uncertainties in the estimated dermal absorption rates and worker exposure rates are incorporated into the exposure assessment and risk characterization and these estimates would have to be in error by a factor of about 100 or more to impact in the qualitative risk characterization.

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

3.4.3. General Public. The quantitative hazard characterization for the general public associated with exposure to imazapyr 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 2.5 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 imazapyr even if the level of concern is set to 0.36 – i.e., that associated with the maximum application rate considered in this risk

assessment. The upper bound of the hazard quotient for the consumption of contaminated vegetation is 0.02, a factor of 50 below the level of concern at the typical application rate [1÷0.02] and about 18 [0.36÷0.02] below the level of concern at the maximum application rate.

For the acute/accidental scenarios, none of the central estimates of the hazard quotients in Worksheet E04 exceed the level of concern at the typical application rate of 0.45 lb/acre – i.e., a hazard quotient of 1 – or the level of concern at the highest application rate of 1.25 lb/acre – i.e., a hazard quotient of 0.36. Thus, even at the highest application rate that might be used, none of the exposure scenarios reach a level of concern based on central estimates of exposure. At the upper range of the hazard quotients, the scenario for drinking contaminated water after an accidental spill into a small pond slightly exceeds a level of concern at the highest application rate – i.e., a hazard quotient of 0.4 in Worksheet E04 compared to a level of concern of 0.36 at the highest application rate. At the typical application rate of 0.45 lb/acre, this scenario is below the level of concern by a factor of 2.5 [1÷0.4]. 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 imazapyr, all of the hazard quotients would be a factor of 10 less. This accidental spill scenario is used consistently in Forest Service risk assessments simply to serve as a guide in the case of a substantial accidental spill. For imazapyr as well as most other chemicals, a large spill into a small body of water should lead to steps to prevent the consumption of the contaminated water.

The direct spray of a small child yields a hazard quotient of 0.05, 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 imazapyr, 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=0.36).

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 imazapyr, consideration 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 0.058 (0.005 + 0.001 + 0.03 + 0.002 + 0.02). This is below the level of concern by a factor of about 17 at the typical application rate [1÷0.058] and about 6 at the highest application rate [0.36÷0.058]. Similarly, for all of the chronic exposure scenarios, the addition of all possible pathways lead to hazard quotient of approximately 0.02000611, with consumption of contaminated vegetation [0.02] accounting for virtually all of the totaled risk.

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 imazapyr. Due to the lack of data in humans, the likely critical effect of imazapyr in humans cannot be identified clearly. As indicated in Section 3.1, the mechanism of action for imazapyr is not well understood. Imazapyr does not appear to specifically affect the nervous system (Section 3.1.6) or the immune system (Section 3.1.7) but there is suggestive evidence for effects on endocrine function (3.1.8). Given the very low hazard quotients for imazapyr, there appears to be no basis for asserting that adverse effects in a specific subgroup are plausible. The U.S. EPA (1997, 2003c) has judged that infants and children are not likely to be more sensitive to imazapyr than adults. Given the number of studies available on reproductive and developmental effects and the unremarkable findings from these studies, this judgement appears appropriate.

3.4.5. Connected Actions. Imazapyr may be applied in combination with other herbicides. No data have been encountered in the literature that permit a characterization of the joint action of imazapyr (i.e., synergism, antagonism, or additivity) with most herbicides. The limited information encountered in the U.S. EPA files on mixtures of imazapyr with imazethapyr (Lowe 1988 as summarized in Appendix 1) does not indicate any substantial interaction.

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. As with the human health risk assessment, a limitation in the identification of potential hazards to terrestrial or aquatic animals is that the great majority of the toxicity studies have failed to demonstrate any significant or substantial association between imazapyr exposure and toxicity. In addition, few wildlife species have been assayed relative to the large number of non-target animal species that might be exposed to imazapyr. Within these admittedly substantial reservations, imazapyr appears to be relatively non-toxic to terrestrial or aquatic animals. In other words, no hazards associated with the direct toxic action of imazapyr can be identified for either terrestrial or aquatic animals.

The toxicity of imazapyr to terrestrial plants is relatively well characterized. Imazapyr is practically non-toxic to conifers, but it is toxic to many other non-target plants. As with several sulfonylurea, imidazolinone, and triazolopyrimidine herbicides, imazapyr inhibits acetolactate synthase (ALS), an enzyme that catalyzes the biosynthesis of three branched-chain amino acids, all of which are essential for plant growth. Although post-emergence application is more effective than pre-emergence application, toxicity can be induced either through foliar or root absorption. Imazapyr is not metabolized extensively in plants but is transported rapidly from treated leaves to root systems and may be exuded into the soil from the roots of treated plants.

Imazapyr is relatively non-toxic to soil microorganisms, aquatic invertebrates, and fish. Imazapyr is not expected to bioaccumulate in the food chain. In terrestrial animals and birds, imazapyr is practically non-toxic. A number of standard bioassays are available on the toxicity of imazapyr to aquatic plants. The most sensitive species appears to be aquatic macrophyte, *Lemna minor* and *Myrophyllium sibiricum*, with reported EC_{25} values of 0.013 mg/L in both species. Some aquatic algae appear to be substantially less sensitive, with EC_{50} values on the order of about 0.2 mg/L. In tolerant species, concentrations of up to 100 mg/L may cause either no effect or be associated with a stimulation rather than inhibition of growth.

4.1.2. Toxicity to Terrestrial Organisms.

4.1.2.1. Mammals – The toxicity studies used to assess the potential hazards of imazapyr to humans (Appendix 1) can also be applied to the risk assessment for mammalian wildlife. Perhaps the most substantial limitation in the identification of potential hazards relates to the lack of information on dose levels that are harmful to mammals. As discussed in Section 3.1 and further detailed in Appendix 1, virtually all of the studies on imazapyr are negative (i.e., no effects clearly attributable to the compound have been identified). Thus, while the toxicity of imazapyr to plants is understood relatively well (Section 4.1.2.4), it is not clear what, if any, specific toxicity imazapyr may cause in mammalian wildlife. While this may be considered an uncertainty or a lack of knowledge, it has a relatively minor impact on this risk assessment because the available toxicity studies are relatively complete—chronic studies in three mammalian species (dogs, rats, and mice) and several reproduction studies in two mammalian

species (rats and rabbits)—and indicate that imazapyr is not likely to be associated with adverse effects at relatively high-dose levels.

Only one field study relevant to assessing potential effects of imazapyr on terrestrial mammals has been encountered. Brooks et al. (1995) examined the impact of imazapyr, as well as picloram, triclopyr, and hexazinone, all used in site preparation, on small mammal and avian communities. The study area was located in Georgia and consisted of a 157-ha tract of residual hardwoods. Imazapyr (Arsenal) was applied at 4.1 kg a.e./ha. After herbicide treatment and a prescribed burn, loblolly pine were planted. Data on small mammals was collected by trapping and data on birds involved visual surveys. Observations were made at pre-treatment and three times per year at 1, 2, and 3 years after treatment. No substantial differences were noted among the different herbicides. With all herbicides, the number of small animals trapped after treatment was diminished compared to pre-treatment levels. Because no non-herbicide treated sites (i.e., control sites) were used in this study, observed changes in populations of small mammals or birds cannot be clearly associated with herbicide treatment.

4.1.2.2. Birds – While toxicity studies on birds (Appendix 2) are less extensive than those on mammals, both ducks and quail have been assayed in 5 day acute toxicity studies and 18 week reproduction studies. As with the mammalian studies, no adverse effects have been noted in birds. In the acute studies (Fletcher 1983a,b), no mortality was observed at imazapyr concentrations of up to 5000 ppm in the diet. These acute exposures were equivalent to average daily doses of 674 mg/kg in quail (Fletcher 1983b) and 1149 mg/kg in ducks (Fletcher 1983a). Similarly, in the 18-week dietary studies, no effects on reproductive endpoints (i.e., egg production, hatchability, survival of hatchlings) were observed at dietary concentrations of up to 2000 ppm. These 18-week exposures were equivalent to average daily doses of 200 mg/kg in both quail and ducks (Fletcher et al. 1995a,b). The LD_{50} for Bobwhite quail and Mallard ducks is >2150 mg/kg (Fletcher et al. 1984a,b). Acute toxicity studies (5-day) in Bobwhite quail and Mallard ducks found no adverse effects at dietary concentrations up to 5000 ppm (Fletcher et al. 1984c,d).

4.1.2.3. Terrestrial Invertebrates – The only information on the toxicity of imazapyr to a terrestrial invertebrate is provided by the honey bee studies by Atkins (1984) and Atkins and Kellum (1983). Atkins and Kellum (1983) identifies an oral LD_{50} in the honey bee of >100 μg/bee, equivalent to >0.1 mg/bee. Taking an average weight of 0.093 g/bee or 0.000093 kg/bee (USDA/APHIS 1993) and making the very conservative assumption of 100% absorption, this would correspond to an LD_{50} greater than 1000 mg/kg bw [0.1 mg imazapyr/bee ÷ 0.000093 kg bw/bee = 1075 mg/kg]. This order of toxicity is comparable to the LD_{50} values reported in experimental mammals (Appendix 1) and birds (Appendix 2). This suggests that the toxicity of imazapyr to terrestrial invertebrates may be similar to the toxicity of this compound to terrestrial vertebrates. On the other hand, there are a very large number of terrestrial invertebrates in any diverse environment. Typically, as with imazapyr, information is available on only a single terrestrial invertebrate species, the honey bee. Thus, the ability to characterize potential effects in other species is limited.

4.1.2.4. Terrestrial Plants (Macrophytes) – The toxicity of imazapyr to terrestrial plants is relatively well characterized (Appendix 3). As with several sulfonylurea, imidazolinone, and triazolopyrimidine herbicides, imazapyr inhibits acetolactate synthase (ALS), an enzyme that catalyzes the biosynthesis of three branched-chain amino acids, all of which are essential for protein synthesis and plant growth (Boutsalis and Powles 1995). Post-emergence application is more effective than pre-emergence application and time to complete kill may require several weeks (Peoples 1984).

Several types of weed species have developed resistance to imazapyr. In some plant species, resistance is based on a modified form of ALS that is associated with a single nuclear gene (Boutsalis and Powles 1995). Resistant strains of common chickweed, perennial ryegrass, and Russian thistle have also been associated with a less sensitive ALS (Saari et al. 1992). Based on a comparison of different levels of resistance to various herbicides, including imazapyr, Burnet et al. (1994) have suggested that there is likely to be more than one mechanism involved in the development of resistance to imazapyr and other similarly acting herbicides.

After foliar application, imazapyr as well as other structurally similar herbicides (e.g., picloram, clopyralid, and other imidazolinone herbicides) are transported via the phloem and thus are able to control deeply rooted weeds. The efficacy of imazapyr appears to be particularly strongly related to its transport in phloem, which is more rapid than would be expected from simple structure-activity correlations (Chamberlain et al. 1995). Although a number of herbicides inhibit ALS, the kinetics of inhibition and thus the mechanisms are not necessarily identical. For example, imazapyr acts as an uncompetitive inhibitor of ALS in *Arabidopsis thaliana* whereas chlorsulphuron acts as a non-competitive inhibitor (Chang and Duggleby 1997).

Rapid transport from treated leaves to root systems has also been noted by Nissen et al. (1995) using liquid growth cultures of leafy spurge (*Euphordia esula*) after foliar treatments with ^{14}C-imazapyr. By day 8 after application, 14% of the applied imazapyr remained in the leaf tissue but 17% was transported to the root system. In terms of total absorption, 62.5% of the applied radioactivity was absorbed by day 2 and 80.0% by day 8. Under the assumption of simple first-order absorption, the absorption rate, k_a, should be constant over time and can be calculated as the natural logarithm of the proportion of the unabsorbed dose divided by the duration of exposure:

$$ka = \ln(1- Pa)/t$$

where *Pa* is the proportion absorbed over the time interval *t*.

The k_a values calculated for day 2 and day 8 are 0.49 day^{-1} [ln(1-0.625)/2] and 0.20 day^{-1} [ln(1-0.8)/8], respectively. Thus, at least in this species, the rate of absorption may not be constant with time and first order absorption kinetics may not apply. Alternatively, these differences may simply reflect random variation in the responses of the plants or the

measurements taken during the study. The data reported by Nissen et al. (1995) do not include a sufficient number of time points to evaluate either possibility.

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

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

Some herbicides may be absorbed by plant foliage, translocated to the roots of plants, and subsequently exuded from the roots to the surrounding soil, posing a risk to neighboring plants. This process, referred to as allelopathy, has been demonstrated for picloram, 2,4-D, and 2,4,5-T (Reid and Hurtt 1970; Webb and Newton 1972). These herbicides, like imazapyr, are weak acids with pK_a values between 1.9 and 2.8 (Willis and McDowell 1987) and are poorly soluble in non-polar liquids (Bromilow et al. 1990). Although reports of allelopathic effects for imazapyr have not been reported in field studies, Nissen et al. (1995) found that about 3% of absorbed imazapyr may be exuded from the root system of leafy spurge into a liquid culture medium by day 8 after treatment. This report combined with the fact that herbicides with similar physical and chemical properties generally translocate similarly in plants (Bromilow et al. 1990) suggests that imazapyr has the potential to induce allelopathic effects. Nonetheless, given the relatively rapid movement of imazapyr in soil, the potential for allelopathic effects may not have a practical or substantial impact on potential risk to non-target plants.

4.1.2.5. Terrestrial Microorganisms – Relatively little information is available on the toxicity of imazapyr to terrestrial microorganisms. In pure culture laboratory assays, imazapyr inhibited the growth of two strains of plant-associated bacteria, *Bacillus subtilis* and *Bacillus circulans*, both isolated from wheat. LC_{50} values ranged from about 10 to 100 µM (see Forlani et al. 1995, Figure 1, p. 248). Three other species of *Bacillus* as well as several additional soil bacteria were not affected at concentrations up to 1000 µM (Forlani et al. 1995). Thus, effects on bacteria appear to be highly species specific with variations in sensitivity of up to a factor of 100. Consequently, imazapyr does appear to have the potential to shift bacterial soil populations that contain sensitive species of bacteria. In addition, imazapyr has been shown to inhibit rates of cellulose decomposition and carboxymethyl cellulase activity in peat soil with 59% organic carbon (Ismail and Wong 1994). These investigators speculate that *"the reduction in cellulose*

degradation is likely to be only a temporary effect" (Ismail and Wong 1994, p. 122) and that the activity of imazapyr on terrestrial microorganisms may decline as the herbicide is adsorbed to soil and thus unavailable to microorganisms. This may be a reasonable speculation for peat. Imazapyr is likely to bind relatively strongly to peat. On the other hand, imazapyr may persist in soil for a prolonged period of time, particularly in relatively arid regions, and will not bind tightly to alkaline soils with low organic matter. Thus, in at least some areas, a potential for longer term effects on soil microorganisms seems plausible. As with effects on both terrestrial and aquatic plants, the plausibility and magnitude of any such effects are likely to be highly site-specific.

4.1.3. Aquatic Organisms.

4.1.3.1. Fish – Standard toxicity bioassays to assess the effects of imazapyr on fish and other aquatic species are summarized in Appendix 4. For fish, standard 96-hour acute toxicity bioassays indicate that the LC_{50} is greater than 100 mg/L. Other research suggests that imazapyr is moderately toxic to other fish species. Foreign studies found that the silver barb (*Barbus gonionotus*) and Nile Tilapia (*Sarotherodon niloticus*) are more sensitive to the acute toxic effects of imazapyr with 96-hour LC_{50} values of 2.71 mg/L (2.66–2.75 mg/L) and 4.36 mg/L (4.21–4.53 mg/L), respectively (Supamataya et al. 1981). This study is published in Thai with an English abstract and a full text copy of this study was not obtained and translated for the current risk assessment. As discussed in Section 4.2, the concentrations reported in this study as LC_{50} values are substantially above concentrations that may be expected in the normal use of imazapyr. Nonetheless, the results from these studies are further considered in the dose-response assessment for fish (Section 4.3) and risk characterization (Section 4.4).

The longer term toxicity of imazapyr has also been tested in an early life-stage bioassay using rainbow trout at concentrations of 0, 6.59, 12.1, 24.0, 43.1, or 92.4 mg/L for 62 days. At the highest concentration, a "*nearly significant effect on hatching*" was observed (Manning 1989b). The investigator judged that this effect was not toxicologically significant. A review of the data tables provided in the study does not contradict this assessment. Nonetheless, the classification of 92.4 mg/L as a NOAEL is questionable. For this risk assessment, the next lower dose, 43.1 mg/L, will be taken as the NOAEL. As discussed in Section 4.4, any of these concentrations are far in excess of concentrations that are plausible in the environment. Thus, any uncertainty concerning the classification of the 92.4 mg/L concentration has no impact on the risk characterization.

Tilapia rendalli, a herbivorous fish native to Africa, evidenced positive activity in a micronucleus assay, a screening test for mutagenic activity (Grisolia 2002). After intra-abdominal injections of imazapyr at 20, 40, and 80 mg/kg, a statistically significant increase was seen in erythrocyte micronuclei in the 80 mg/kg dose groups but not in the two lower dose groups. As noted in Section 3.1.10, imazapyr does not appear to be mutagenic or carcinogenic in mammals. Because of the atypical route of exposure and because a positive response was seen only at the maximum tolerated dose of 80 mg/kg, this report does not have a substantial impact on the hazard identification for fish.

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

4.1.3.3. Aquatic Invertebrates – Three standard aquatic toxicity studies are available on the common test species, *Daphnia magna*. As with fish, the 48-hour LC_{50} is greater than 100 mg/L (Forbis et al. 1984; Kintner and Forbis 1983b). In addition, a 21-day chronic study noted no effects on reproduction or growth at concentrations of up to 97.1 mg/L (Manning 1989c).

In mollusks, the available data on imazapyr show no bioconcentration (Christensen et al. 1999; Drotter et al. 1996) and no effect in the growth of oyster shell (Drotter et al. 1997).

4.1.3.4. Aquatic Plants – A number of standard bioassays are available on the toxicity of imazapyr to aquatic plants. The most sensitive species appears to be the aquatic macrophytes *Lemna gibba*, with a reported EC_{25} of 0.013 (0.009–0.019) mg/L (Hughes 1987), and *Myrophyllium sibiricum*, with a reported EC_{25} of 0.013 mg a.i./L (95% CI not provided) for shoot growth and 0.0079 mg a.i./L (95% CI not provided) for root growth (Roshon et al. 1999). As detailed in Appendix 4, aquatic algae appear to be substantially less sensitive. The most sensitive species of algae appears to be *Chlorella emersonii*, with an EC_{50} of about 0.2 mg/L (Landstein et al. 1993). The growth of other species of algae is stimulated rather than inhibited by imazapyr at concentrations of up to 100 mg/L (Hughes 1987).

As with terrestrial plants, some species of aquatic plants may develop resistance to imazapyr. Bioassays conducted on *Chlorella emersonii* indicate that resistant strains may be less sensitive to imazapyr by a factor of about 10 (Landstein et al. 1993).

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview. Terrestrial animals might be exposed to any applied herbicide from direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. In acute exposure scenarios, the highest exposures for small terrestrial vertebrates will occur after a direct spray and could reach up to about 11 mg/kg at an application rate of 0.45 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 0.6 mg/kg for a small mammal to 12 mg/kg for a large bird with upper ranges of about 1.2 mg/kg for a small mammal and 34 mg/kg for a large bird. The consumption of contaminated water leads to much lower levels of acute exposure and 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 0.00004 mg/kg to 0.1 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 0.0000007 mg/kg/day to 0.00007 mg/kg/day for a small mammal. Because of the apparently low toxicity of imazapyr 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, 0.45 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 based on estimates 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 imazapyr 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 are based on essentially the same information used to assess the exposure to terrestrial species from contaminated water. Peak estimated rate of contamination of ambient water associated with the normal application of imazapyr is 0.002 (0.0001 to 0.08) 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 imazapyr is 0.0001 (0.00001 to 0.001) 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 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-specific 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 mammals involve the consumption of contaminated insects by a small mammal (Worksheet F14a) and the consumption of small mammals 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 by a predatory bird (F16b), 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 and species-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 imazapyr.

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 imazapyr 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 imazapyr 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 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 a steady state 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 imazapyr indicates that imazapyr 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 imazapyr 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 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 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 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 (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 imazapyr in insects after applications of imazapyr. 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, imazapyr 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 imazapyr 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 non-target 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 non-target 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.

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, imazapyr 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:

$$v = D^2 \times g \div 18n = 28{,}700\ D^2$$

where $\boldsymbol{v}$ is the velocity of fall (cm sec^{-1}), $\boldsymbol{D}$ is the diameter of the sphere (cm), $\boldsymbol{g}$ is the force of gravity (ca. 980 cm sec^{-2}), and $\boldsymbol{n}$ 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 – Imazapyr 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 non-target 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 imazapyr 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 60% of the applied amount in sites with very runoff potential – i.e., clay soil and high rates of rainfall.

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 imazapyr in contaminated irrigation water, the effects of such exposure scenarios on non-target vegetation have been observed with other herbicides (e.g., Bhandary et al. 1991). Furthermore, given the mobility of imazapyr, the contamination of irrigation water is a plausible scenario.

The levels of exposure associated with this scenario will depend on the concentration of imazapyr 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 imazapyr in ambient water and an irrigation rate of 1 inch per day, the estimated functional application rate of imazapyr to the irrigated area is 2.04×10^{-5} (1.02×10^{-6} to 8.14×10^{-4}) 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 0.261 lb a.e./acre (Worksheet G04) and offsite movement from drift can result in functional offsite application rates of about 8.4×10^{-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 imazapyr, 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 imazapyr 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 imazapyr 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 imazapyr would be neither substantial or nor significant. For this risk assessment, it will be assumed that imazapyr 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 imazapyr in runoff, the deposition of the imazapyr 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. Although no data are available on effects of imazapyr on soil invertebrates (Section 4.1.2.3), limited data are available on the toxicity of imazapyr to soil microorganisms (Section 4.1.2.5). For both soil microorganisms, the toxicity data are expressed in units of concentration – i.e., mg agent/kg soil or culture media – and may be compared to estimates of 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 0.2 to 1 ppm in very arid soils to about 0.01 ppm in regions with high rainfall rates.

In a field study conducted by Vizantinopoulos and Lolos (1994), imazapyr was applied to clay loam soil at an application rate of 1 kg a.i./ha. Using a salt to acid conversion factor of 0.816 (Table 2-1) the rate of 1 kg a.i./ha is equivalent to 0.816 kg a.e./ha or 0.728 lb a.e./acre. By day 3 after application and with three simulated rainfall event of 27 mm per day, the concentrations in

the 0–10, 10–20, and 20–30 cm soil layers were about 0.24 ppm, 0.12 ppm, and 0.06 ppm, respectively, for an overall average of 0.14 ppm. This average corresponds to a residue rate of about 0.2 ppm per lb/acre [0.14 ppm ÷ 0.728 lb/acre].

The 27 mm per event of simulated rainfall corresponds to 2.7 cm or about 1.1 inches per event. In terms of the GLEAMS modeling, which uses a 10 day rainfall cycle or 36.5 rainfall events per year (SERA 2003b), the 1.1 inches of rainfall used by Vizantinopoulos and Lolos (1994) corresponds to an annual rainfall of about 40 inches. Based on the average values given in Table 4-1 and interpolating, the estimated average concentration in clay at a rainfall rate of 40 inches per year is about 0.3 ppm and the value for loam is about 0.13 ppm. The average of these two values is about 0.22 ppm, close to the 0.2 ppm per lb/acre value noted by Vizantinopoulos and Lolos (1994).

4.2.5. Aquatic Organisms. The potential for effects on aquatic species are based on estimated concentrations of imazapyr 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 imazapyr is 0.002 (0.0001 to 0.08) 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 imazapyr is 0.0001 (0.00001 to 0.001) 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., 0.45 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, a chronic NOAEL of 250 mg/kg/day that is applied to both acute and longer term exposures. For birds, a 5-day dietary NOEL of 674 mg/kg/day used to characterize risks associated with acute exposures and an 18-week dietary NOAEL of 200 mg/kg/day based on reproductive endpoints is used to characterize risk associated with longer term exposures. The only data available on terrestrial invertebrates is the standard bioassay in honey bees in which the NOAEL based on mortality was 1000 mg/kg bw.

The toxicity data for terrestrial plants involves standard bioassays for pre-emergent and post-emergent applications. For exposures involving the off-site drift of imazapyr, the range of NOAEL values for post-emergence applications is 0.00049 lb/acre for sensitive species and 0.018 lb/acre for tolerant species. For exposures involving off-site runoff, the range of NOAEL values for pre-emergence applications is 0.002 lb/acre for sensitive species and 1 lb/acre for tolerant species.

Imazapyr does not appear to be very toxic to aquatic fish or invertebrates. For tolerant species of fish, an NOEC of 100 mg/L, supported by a large number of studies submitted to U.S. EPA is used to assess risks associated with acute exposures. For sensitive species, the lowest LC_{50} value encountered in the open literature, 2.71 mg/L, is used. Three longer term studies in fish suggest no substantial differences between the acute and chronic toxicity of imazapyr, with a life-cycle NOEC of about 100 mg/L. No chronic toxicity studies are available on the presumably sensitive species and the 2.71 mg/L concentration use for acute exposure is also applied to chronic exposures for sensitive species. Aquatic invertebrates do not appear to be any more sensitive to imazapyr than fish. An NOEC values of 100 mg/L from both an acute study and a life cycle study in daphnids is used to characterize risks of both acute and chronic exposures. There is no basis for identifying tolerant and sensitive species of aquatic invertebrates.

*A*quatic macrophytes appear to be much more sensitive to imazapyr than aquatic animals. An EC_{25} of 0.013 mg/L in both *Lemna minor* and *Myriophyllum sibricium* is used for quantifying effects in aquatic macrophytes. By comparison to these macrophytes, unicellular aquatic algae appear to be less sensitive to imazapyr and a concentration of 0.2 mg/L is taken as an EC_{50} for sensitive species of algae and an NOEC of 100 mg/L is taken as an NOEC for tolerant species of algae.

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 250 mg/kg/day. This estimate is based on a one-year dog NOAEL of 250 mg/kg/day (Shellenberger 1987) and is supported by higher chronic/lifetime NOAELs in rats and mice (Appendix 1). 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.

No acute RfD has been developed for imazapyr and the available data do not support the development of an acute RfD. As discussed in Section 3.3.3, the shorter term studies that might serve as the basis for an acute RfD or an acute NOAEL for mammals are essentially identical to the chronic NOAEL of 250 mg/kg/day. In other words, there is no substantial relationship between the duration of exposure and toxicity. Thus, analogous to the approach taken in the human health risk assessment (Section 3.4), the chronic NOAEL of 250 mg/kg/day is applied to both acute and chronic exposures.

The use of a NOAEL in dogs to characterize risks for all terrestrial mammals may be overly conservative. As detailed in Appendix 1, higher chronic NOAEL values are available in mice (e.g., over 1000 mg/kg/day from the study by Auletta 1988) and rats (e.g., over 500 mg/kg/day from the study by Daly 1988). Because of the low toxicity of imazapyr to mammals relative to plausible levels of exposure, the use of the lower NOAEL in dogs has no impact on the characterization of risk (Section 4.4).

4.3.2.2. Birds – As discussed in Section 4.1.2.2 and detailed in Appendix 2, imazapyr has a low order of acute toxicity in birds. After five day dietary exposures, no mortality or signs of toxicity are apparent at doses of up to 674 mg/kg/day (5000 ppm dietary concentration) in bobwhite quail (Fletcher 1983a) and 1419 mg/kg (5000 ppm dietary concentration) in mallard ducks (Fletcher 1983b). These NOAEL values are supported by single dose gavage NOAEL values of 2150 mg Arsenal/kg in both quail (Fletcher et al. 1984a) and mallards (Fletcher et al. 1984b). As noted in Appendix 2, this NOAEL value for Arsenal corresponds to a dose of about 600 mg imazapyr/kg.

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 674 mg/kg/day in bobwhite quail (Fletcher 1983a) 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 674 mg/kg/day, the highest dose used in the 5-day feeding study. Because of the very low hazard quotients for acute exposures of birds (Worksheet G02), the use of the lower acute NOAEL of 674 mg/kg/day for birds has no impact on the risk characterization.

For chronic toxicity, the18-week dietary NOAEL of 200 mg/kg/day is based on reproductive endpoints (i.e., egg production, hatchability, survival of hatchlings) in both bobwhite quail (Fletcher et al. 1995a) and mallard ducks (Fletcher et al. 1995b). While this NOAEL is somewhat lower than the chronic NOAEL used for mammals (i.e., 250 mg/kg/day), this does not imply that birds are more sensitive than mammals. Quite simply, 200 mg/kg/day is the highest subchronic (18 week) dose tested in birds, just as 250 mg/kg/day is the highest chronic dose tested in mammals.

4.3.2.3. Terrestrial Invertebrates – As discussed in Section 4.1.2.3, all that is known is that the acute LD_{50} in the honey bee is greater than 1000 mg/kg bw (Atkins 1984; Atkins and Kellum 1983). This apparently low acute toxicity is consistent with the data on mammals and birds. No quantitative consideration can be given to other potential subchronic or non-lethal effects and no information is available on other invertebrate species. Given the large number of species of terrestrial invertebrates, the use of this single acute toxicity value on a single species obviously leads to uncertainty in the risk assessment.

4.3.2.4. Terrestrial Plants (Macrophytes) – As detailed in Appendix 3, several toxicity studies are available on imazapyr in which exposure is characterized either as an application rate or a concentration in soil. The studies by American Cyanamid (1980) and Christensen et al. (1995), in which exposure is characterized as an application rate, were conducted as part of the registration requirements for herbicides and can be used directly to assess the potential effects from unintentional spraying or off-site drift. The studies in which imazapyr exposure is characterized as a concentration in soil (Rahman et al. 1993; Vizantinopoulos and Lolos 1994) were conducted essentially as classical bioassays. In other words, the response of plants at various concentrations of imazapyr in soil was determined so that plant responses rather than direct chemical analysis could be used to assess the movement and concentrations of imazapyr in soil. Thus, these types of studies are appropriate for assessing the effects of residual imazapyr concentrations in soil.

A detailed summary of the studies by American Cyanamid (1980) and Christensen et al. (1995) are given in Appendix 3. As indicated in this appendix, these studies are referred to as a Tier II assay and is actually a series of bioassays on seed germination, seed emergence, and effects on postemergent plant growth and viability.

The post-emergent bioassays are used to characterize risks to sensitive and tolerant plant species from drift (Worksheets G05a,b). In the study by American Cyanamid (1980), imazapyr was tested in all three types of assays at application rates ranging from 0.000068 kg/ha to1.12 kg/ha, corresponding to about 0.00006 to 1.0 lb a.e./acre. As indicated in Appendix 3, the greatest toxicity was observed in postemergence assays, with reported EC_{50} values of 0.00219 to 0.0175 kg/ha in a number of different species (green peas, soybeans, onions, corn, wheat, oats, sugar beets, sunflowers, tomatoes and cucumbers). In terms of an NOEC, sugar beets were the most sensitive species with an NOEC of 0.000548 kg/ha, equivalent to about 0.00049 lb/acre. In the more recent study by Christensen et al. (1995), sugar beet was also the most sensitive species

with an NOEC or 0.0010 lb/acre for shoot dry weight. For this risk assessment, the approximately two fold lower NOEC of 0.00049 lb/acre from the American Cyanamid (1980) is used to characterize risks associated with direct spray or spray drift and is included in Worksheet G05a (drift from ground application) and Worksheet G05b (drift from aerial application). The most tolerant species in the post-emergence assays appears to be onions, with an NOEC of 0.091 lb/acre based on survival and 0.018 lb/acre based on shoot length and weight in the study by Christensen et al. (1995). The lower NOEC of 0.018 lb/acre is included in Worksheet G05a (drift from ground application) and Worksheet G05b (drift from aerial application) and is used to assess potential effects on tolerant plant species.

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 assays (Appendix 3) are used to characterize risks associated with runoff. As in the post-emergence, the sugar beet is the most sensitive species and an NOEC for this species is not identified. The lowest application used in the study by American Cyanamid (1988b) was 0.00219 kg/ha, equivalent to about 0.002 lb/acre, and this application rate is identified as an EC_{25}. The most tolerant species, also identified in the study by American Cyanamid (1988b), appears to be wheat, sunflower, tomato, cucumber, oats, soybeans, and green peas, all with no significant effect on seedling emergence at an application rate of 1.12 kg/ha, equivalent to about 1 lb/acre. Thus, for characterizing risks from runoff, the EC_{25} of 0.002 lb/acre in sugar beet is used for the most sensitive species and the NOEC of 1 lb/acre is used for tolerant species in Worksheets G04.

Two studies (Rahman et al. 1993; Vizantinopoulos and Lolos 1994) could be used to characterize the dose/response relationships for toxicity to plants in terms of concentrations of imazapyr in soil. Vizantinopoulos and Lolos (1994) assayed the effects of varying concentrations of imazapyr in soil on the growth of wheat (*Triticum vulgare*) in clay and clay loam soils (see Figure 1, p. 406 in Vizantinopoulos and Lolos 1994). Rahman et al. (1993) assayed the effects of varying concentrations of imazapyr in soil on the growth of four plant species in sandy loam soil: white mustard (*Sinapis alba*), radish, oats, and corn (*Zea mays*). For this risk assessment, the study by Rahman et al. (1993) is used because of the greater number of species tested and because the results noted by Vizantinopoulos and Lolos (1994) for wheat are encompassed by the responses in the different species tested by Rahman et al. (1993). In the study by Rahman et al. (1993), white mustard is the most sensitive species, with an EC_{50} of about 0.006 mg/kg soil and an NOEC of 0.001 mg/kg soil. Corn was the least sensitive species, with an EC_{50} of about 0.1 mg/kg soil and an NOEC of 0.02 ppm.

4.3.2.5. Soil Microorganisms – No data have been encountered that permit the quantitative assessment of the effects of imazapyr in soil on soil microorganisms. As summarized in Section 4.1.2.5, liquid culture solutions of imazapyr were toxic to various soil bacteria, with LC_{50} values ranging from about 10 to 1000 µM (see Forlani et al. 1995, Figure 1, p. 248). These concentrations correspond to about 2.61 to 261 mg/L (ppm) [1 µM = 1 µM/L, MW of acid = 261 g/mole]. Because these concentrations involve liquid cultures and because bioavailability of

imazapyr is likely to be substantially less in a soil matrix, these values are not appropriate for direct use analogous to other NOAEL and NOEC values discussed in this risk assessment. This supposition is supported by the study of Ismail and Wong (1994) in which imazapyr had only a slight effect on the breakdown of cellulose at a soil concentration of 20 mg/kg and a substantial impact of cellulose decomposition only at a concentration of 150 mg/kg. These values are more relevant to the functional effect of imazapyr on soil microorganisms and are discussed further in the risk characterization (Section 4.4).

4.3.3. Aquatic Organisms.

4.3.3.1. Fish – As discussed in Section 4.1.3.1 and detailed in Appendix 4, standard bioassays submitted to U.S. EPA in support of the registration of imazapyr suggest a very low order of toxicity to fish with LC_{50} values greater than 100 mg/L in most bioassays (Cohle and McAllister 1984b; Drotter et al. 1995; Kintner and Forbis 1983a; Manning 1989a) and greater than 1000 mg/L in some bioassays (Cohle and McAllister 1984a). The study by Supamataya et al. (1981), however, reports much lower LC_{50} values in two species, silver barb (*Barbus gonionotus*) with a reported LC_{50} of 2.71 mg/L and the Nile Tilapia (*Sarotherodon niloticus*) with a reported LC_{50} of 4.36 mg/L. This study is published in Thai with an English abstract and a full text copy of this study was not obtained and translated for the current risk assessment. In addition, the species tested by Supamataya et al. (1981) are not native to the United States and may not be relevant to assessing risks associated with applications of imazapyr in the United States. Notwithstanding these reservations, the lowest LC_{50} value of 2.71 mg/L reported by Supamataya et al. (1981) is used in this risk assessment and included in Worksheet G03 to characterize risks in sensitive species of fish. This approach is taken because this risk assessment is intended to be protective of a large number of species of fish, most of which have not been tested in aquatic toxicity studies. Thus, while the report by Supamataya et al. (1981) is not well documented and the species are not native to the United States, the assumption will be made that these apparently sensitive species may encompass other sensitive species that are native to the United States. For tolerant species of fish, the NOEC of 100 mg/L, discussed above and supported by a large number of studies is used for acute exposures in Worksheet G03.

Three studies can be used to assess the potential effects of longer term exposures to imazapyr, one full-life cycle study in fathead minnow with an NOEC of 118 mg/L (Drotter et al. 1999), an early life-stage study in the fathead minnow with an NOEC of 120 mg/L, and an early life-stage study in the rainbow trout with an NOEC of 43.1 mg/L. The NOEC values in fathead minnows are about the same as the acute NOEC of 100 mg/L. The somewhat higher chronic NOEC of 120 mg/L does not suggest that imazapyr is simply an artifact of the concentrations selected for the different studies. One approach to assessing longer term risks to fish would be to designate the minnows as tolerant species and the trout as sensitive species. This approach, however, would not consider the very low LC_{50} values reported by Supamataya et al. (1981) and used to characterize acute risks. As an alternative, the NOEC of 120 mg/L is used for tolerant species. For sensitive species, however, the acute value of 2.71 mg/L is maintained to characterize risks. As discussed further in Section 4.4. this highly protective approach has no substantial impact on the risk characterization for fish.

4.3.3.2. Aquatic Invertebrates – Aquatic invertebrates do not appear to be any more sensitive to imazapyr than fish. Based on the studies by Forbis et al. (1984) and Kintner and Forbis (1983b) in *Daphnia magna*, summarized in Appendix 4, the acute NOEC of 100 mg/L will be adopted for aquatic invertebrates. Unlike the case with fish, there is no basis for identifying sensitive or tolerant species. The NOEC of 100 mg/L in *Daphnia* is virtually identical to the NOEC of 109 mg/L identified by Ward (1989) in oysters. As noted in Appendix 4, the Effect seen at 173 mg/L in the study by Ward (1989) may have been a response of the lower pH of the test water, caused by adding imazapyr, rather than a toxic response to imazapyr. This supposition is supported by the later study of Drotter et al. (1997). Thus, the concentration of 100 mg/L is used in Worksheet G03 to characterize acute risks to all aquatic invertebrates. Also as with fish, the chronic toxicity of imazapyr appears to be no greater than its acute toxicity, with a daphnid cycle NOEC of 97.1 mg/L (Manning 1989c), essentially equal to the acute NOEC of 100 mg/L. Thus, the NOEC from Manning (1989c) is used directly for assessing hazards with longer term exposures in aquatic invertebrates and no distinction is made between sensitive and tolerant species.

4.3.3.3. Aquatic Plants – As would be expected of a herbicide, some aquatic plants are much more sensitive to imazapyr than aquatic animals. The most sensitive species appears to be the aquatic macrophyte *Lemna gibba*, with a reported EC_{25} for growth of 0.013 (0.009–0.019) mg/L (Hughes 1987) and these estimated levels for growth inhibition will be used for the characterization of risk to sensitive aquatic plants. Other species of aquatic plants, particularly the unicellular algae, may be much less sensitive, with EC_{50} values of about 0.2 mg/L to 2 mg/L for *Chlorella* (Landstein et al. 1993). Some aquatic plants are relatively tolerant to imazapyr, with NOECs on the order of 10 to 100 mg/L, similar to aquatic animals (Hughes 1987). Further details of these studies are presented in Appendix 4. For assessing risks to aquatic macrophytes in Worksheets G03, the 0.013 mg/L EC_{25} in *Lemna gibba* is used. For aquatic algae, the NOEC of 100 mg/L is used for tolerant species and the EC_{50} of 0.2 mg/L is use for sensitive species.

4.4. RISK CHARACTERIZATION

4.4.1. Overview. Imazapyr is an effective herbicide and even tolerant plants that are directly sprayed with imazapyr at normal application rates are likely to be damaged. Some sensitive plant species could be affected by the off-site drift or by off-site movement in runoff of imazapyr depending on site-specific conditions. When applied to areas in which runoff is favored, damage from runoff appears to pose a greater hazard than drift. Residual soil contamination with imazapyr could be prolonged in some areas. In relatively arid areas in which microbial degradation may be predominant factor in the decline of imazapyr residues in soil, residual toxicity to sensitive plant species could last for several months to several years. In areas of relatively high rainfall rates, residual toxicity to sensitive plant species would be much shorter. This characterization of risk for residual soil contamination is general rather than site-specific. The persistence and movement of imazapyr in soil is highly complex and substantially different estimates of persistence and transport could be made if different site-specific factors were considered. Thus, these estimates of risk should be considered only as crude approximations of environmentally plausible consequences.

Some effects are also plausible in aquatic plants. Aquatic macrophytes appear to be more sensitive to imazapyr than unicellular algae. Peak concentrations of imazapyr in surface water could be associated with adverse effects in some aquatic macrophytes. Longer term concentrations of imazapyr, however, are substantially below the level of concern.

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 0.45 lb/acre or the maximum application rate of 1.25 lb/acre.

As in any ecological risk assessment, the risk characterization must be qualified. Imazapyr has been tested in only a limited number of species and under conditions that may not well-represent populations of free-ranging non-target organisms. 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). As in the risk characterization for the human health risk assessment (Section 4.4), all exposure assessments in Worksheet G01 are based on the typical application rate of 0.45 lb/acre. Thus, the level of concern for the hazard quotient is one (1) at the typical application rate. Because the maximum application rate is 1.25 lb/acre, the level of concern at the

maximum application rate is 0.36 – i.e., 0.45 lb/acre ÷ 1.25 lb/acre. When the hazard quotients are below the level of concern, there is no basis for asserting that adverse effects are plausible.

As indicated in Worksheet G02, the highest hazard quotient for any acute exposure is 0.1 [1e-01], 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 0.08, the upper range of the hazard quotient for the consumption of contaminated vegetation on site by a large bird. This hazard quotient of 0.08 is below the level of concern by a factor of 12.5 at the typical application rate [1÷0.08] and below the level of concern by a factor of 4.5 at the highest application rate [0.36÷0.08]. Thus, there is no basis for asserting that adverse effects are likely from acute or longer term exposures from the application of imazapyr 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 0.45 lb/acre or the maximum application rate of 1.25 lb/acre. As with the human health risk assessment, this characterization of risk must be qualified. Imazapyr has been tested in only a limited number of species and under conditions that may not well-represent populations of free-ranging non-target 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.

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 imazapyr to terrestrial invertebrates. For the honey bee, the hazard quotient is based on the non-lethal acute dose level of 1000 mg/kg (Atkins 1984; Atkins and Kellum 1983). At the exposure associated with a direct spray, the hazard quotient of 0.07 is below the level of concern by a factor of about 14 [1 ÷ 0.07 = 14.29] at the typical application rate and a factor of about 5 [0.36 ÷ 0.07 = 5.14] at the maximum application rate. Thus, there is not basis for expecting mortality in bees directly sprayed with imazapyr.

This risk characterization for terrestrial invertebrates must be more strongly qualified than that of vertebrates because the risk characterization is based only on a study in which mortality was assayed as the endpoint and data are available only a single invertebrate species.

4.4.2.3. Soil Microorganisms – As summarized in Table 4.1, peak concentrations of imazapyr in soil may reach up to about 6 mg/kg. This is in the range of reported LC_{50} values for microorganisms in liquid culture – i.e., 2.61 to 261 mg/L from the study by Forlani et al. 1995. While this could suggest a potential hazard to some sensitive soil microorganisms, the liquid culture assays are only marginally relevant to the assessment of effects in soil because of likely

differences in bioavailability (Section 4.3.2.5). The the study by Ismail and Wong (1994) on effects of imazapyr on the microbial breakdown of cellulose in soil suggest that soil concentrations of about 20 mg/kg will have only a slight impact on microbial function. This concentration is about a factor of 4 above peak soil concentrations and substantially higher than any longer term concentrations (Table 4-1). Thus, there does not appear to be any basis for asserting that imazapyr is likely to adversely effect microorganisms in soil. This conclusion appears to be consistent with the use of imazapyr as an effective herbicide. If imazapyr were extremely toxic to terrestrial microorganisms that are important for the maintenance of soil suitable for plant growth, it seems reasonable to assume that secondary signs of injury to microbial populations would have been reported.

4.4.2.4. 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 drift (Worksheets G05a and G05b), the benchmark exposures are NOEC values, as derived in Section 4.3.2.2, for both sensitive and tolerant species. For drift (Worksheet G04), an NOEC is available for tolerant species but the benchmark exposure used for sensitive species is an EC_{25} for seedling emergence.

Imazapyr is an effective herbicide and even tolerant plants that are directly sprayed with imazapyr at normal application rates are likely to be damaged. As indicated in Worksheets G05a and G05b, off-site drift of imazapyr may cause damage to sensitive plant species at distances of up to about 500 feet from the application site after both ground broadcast and aerial applications. For both ground and aerial drift, the closer that the non-target 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 imazapyr 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 imazapyr in ground broadcast applications (Worksheet G05a) but might show some damage close to the application site (i.e., about 50 feet or less) after aerial applications.

As summarized in Worksheet G04, runoff could pose a risk to sensitive non-target plant species (i.e., hazard quotients of up to 130) under conditions in which runoff is favored – i.e., clay soil over a wide range of rainfall rates or loam at annual rainfall rates of 100 inches or more.

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 or by off-site movement in runoff of imazapyr depending on site-specific conditions. When applied to areas in which runoff is favored, damage from runoff appears to pose a greater hazard than drift.

Residual soil contamination with imazapyr could be a longer-term problem in some areas. As indicated in Table 4-1, peak concentrations of imazapyr in soil at an application rate of 1 lb a.e./acre is about 6 mg/kg. Thus, at the typical application rate of 0.45 lb/acre, the expected peak concentration of imazapyr in soil shortly after treatment would be about 2.7 ppm.

Based on the dose/response data from Rahman et al. (1993), this concentration in soil would be associated with substantial growth inhibition in the four plant species for which data are available.

A central issue for the characterization of risk is how long these effects might last. As summarized in Table 2-2, reported field dissipation halftimes in soil range from about 25 days to 180 days, corresponding to dissipation or degradation rate coefficients of 0.0039 to 0.028 $days^{-1}$ [$k = \log_e(2) \div t_{1/2}$]. In any first order dissipation model, the fraction, *f*, remaining after time *t* is:

$$f = e^{-kt}.$$

By rearrangement, the time required to reach a certain fraction is:

$$t = \log_e(f) \div -k.$$

As discussed in Section 4.3.2.4, the approximate concentration of imazapyr in soil associated with a NOEC for the most sensitive plant species is about 0.001 mg/kg and the NOEC for the most tolerant plant species is about 0.02 mg/kg. Thus, taking the range of degradation rate coefficients of 0.0039 to 0.028 $days^{-1}$, time required to go from a concentration of 2.7 ppm (i.e., after the application of 0.45 lb./acre) to 0.001 ppm would be:

$$t = \log_e(0.001 \text{ mg/kg} \div 2.7 \text{ mg/kg}) \div - 0.0039 \text{ to } 0.028 \text{ days}^{-1} = 287 \text{ to } 2025 \text{ days},$$

corresponding to about 10 months to 5.5 years. Thus, at the typical application rate, some residual effects on plant species could be expected for several years if microbial degradation were the only significant mechanism in the reduction of imazapyr in the soil.

Based on the GLEAMS modeling, microbial degradation will be the controlling factor only in very arid environments. At annual rainfall rates of 10 inches/year or more, imazapyr will be removed from the soil by runoff or percolation. Runoff is likely to be the dominant mechanism in clay soils and percolation the dominant mechanism in sandy soils. Intermediate soil types such as loam evidence a mix of runoff and percolation depending on specific soil and site characteristics. The quantitative impact of losses from runoff and percolation are illustrated in Figure 4-1, which gives the concentration of imazapyr in clay soil at annual rainfall rates of 5, 25, 50, 100, and 200 inches based on the GLEAMS modeling discussed in Section 3.2.3.4. At an annual rate of 5 inches per year, the loss from soil is attributable completely to microbial degradation, which is characterized using a halftime of 25 days for the GLEAMS modeling in clay soil (Table 3.3). Under these conditions, the concentration of imazapyr in soil does not reach the NOEC of 0.001 mg/kg until about day 340 after application. As an annual rainfall rate of 200 inches per year, about 50% of the applied compound is lost from the application site by runoff and the estimated concentration in soil reaches the NOEC of 0.001 mg/kg in about 60 days.

This characterization of risk for residual soil contamination is general rather than site-specific. The persistence and movement of imazapyr in soil is highly complex and substantially different estimates of persistence and transport could be made if different site-specific factors were considered. Thus, these estimates of risk should be considered only as crude approximations of environmentally plausible consequences.

4.4.3. Aquatic Organisms.

4.4.3.1. Aquatic Animals – The risk characterization for aquatic animals is relatively simple and unambiguous. Imazapyr 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 imazapyr in ambient water over prolonged periods of time are estimated to be no greater than 0.00045 mg/L and peak concentration of imazapyr associated with runoff or percolation are estimated to be no more than 0.036 mg/L. As discussed in Section 3.2.3.4.1, the GLEAMS modeling appeared to somewhat underestimate peak exposures in streams compared to monitoring data and the monitoring data from a field application similar to those that may be used in Forest Service programs was used as the basis for the peak concentrations that might be expected. As summarized in Worksheet G03, all of the hazard quotients for aquatic animals are extremely low, ranging from 0.00000004 (the lower range for longer term exposures in tolerant species of fish) to 0.01 (the upper range for acute exposures for sensitive species of fish). Thus, there is no basis for asserting that effects on nontarget aquatic species are plausible. The highest hazard quotient of 0.01 is below the level of concern at the typical application rate (LOC=1.0) by

a factor of 100 and below the level of concern at the highest application rate (LOC=0.36) by a factor of 36.

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 about 2 mg/L to 8 mg/L with a central estimate of about 4 mg/L (Worksheet D05). These concentrations are in the range of the reported LC_{50} values for sensitive species of fish (i.e., about 3 to 4 mg/L as discussed in Section 4.3.3.1). Thus, in the case of an accidental spill of a large amount of imazapyr into a relatively small body of water, mortality in sensitive species of fish is plausible. The accidental spill scenario is an extremely arbitrary scenario and 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.

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 imazapyr exposure. For aquatic macrophytes, the upper range of the hazard quotient for peak concentrations (HQ=3) is above the level of concern by a factor of 3 at the typical application rate (LOC=1) and a factor of about 8 at the highest application rate (LOC=0.36, 3÷0.36=8.3). Thus, under foreseeable worst case conditions, acute effects could be seen in aquatic macrophytes. Longer term concentrations of imazapyr, however, result in hazard quotients for macrophytes that are well below a level of concern – i.e, HQs of 0.0003 to 0.03.

As indicated in Worksheet G03, hazard quotients for sensitive species of unicellular algae are below a level of concern based either on peak concentration of imazapyr in water (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 0.003 at the upper range of exposure). Thus, at both the typical application rate (LOC=1) and the maximum application rate (LOC=0.36), the upper ranges of the hazard quotients for sensitive species of algae are substantially below the LOC.

As noted above, accidental spills of large quantities of imazapyr into relatively small bodies of water could lead to much higher concentrations – i.e., 3 mg/L to 4 mg/L. After spills of this magnitude, adverse effects on aquatic plants could be anticipated from imazapyr in both macrophytes and sensitive species of algae.

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Table 2-1: Identification and Physical/Chemical Properties of Imazapyr and the Monethanolamine salt of Imazapyr.

Property	Value	Reference
Synonyms	Formulations: Arsenal, Arsenal AC, Chopper, Chopper RTU, Truce, AC252 925	BASF 2000a,b,c BASF 2001 Peoples 1984
CAS Number	81334-34-1 81510-83-0 (isopropylamine salt)	ARS 1995 ARS 1995; BASF 2003a (MSDS)
EPA Registration Number	241-346 (Arsenal) 241-299 (Arsenal AC) 241-296 (Chopper) 241-398 (Stalker)	BASF 2000a BASF 2000b BASF 2001 BASF 2000c
MW	261.3 (acid) 320.4 (isopropylamine salt)	USDA/ARS 1995 USDA/ARS 1995; BASF 2000a
Salt to acid conversion factor	0.8155	[261.3 ÷ 320.4]
pK_a	1.9 and 3.6 1.81 and 3.64 1.9 (pyridine) and 3.6 (carboxylate)	ARS 1995; American Cyanamide 1983b Chambarlain et al. 1995 Pusino et al. 1997
Water solubility	11,000 mg/L (acid) 13,100 mg/L(acid @ 25°C) 1%-1.5% (acid @ 25°C) 110,000 to 150,000 mg/L (acid) 6,500,000 mg/L (salt)	Knisel et al. 1992 Cortes 1990 Peoples 1984 USDA/ARS 1995 USDA/ARS 1995
pH of formulation	6.6 to 7.2 (Arsenal) 5.5 to 7.5 (Arsenal AC) 6 to 7.5 (Chopper and Stalker)	BASF 2003a [MSDS] BASF 2003b [MSDS] BASF 2002a,b [MSDS]
$K_{o/w}$	1.3 (acid, 22°C, neutral) 1.3 (acid, reported as log, 0.114) 1.3 (0.7-1.6)	Chambarlain et al. 1995; ASDA/ARS 1995 Reichert and Stanley-Millner 1983
$K_{o/c}$ (ml/g)	100 46 30.6(sand) 99.8 (silt loam)	Knisel and Davis 2000 Michael et al. 1996 Holman 2000 Holman 2000
Soil $t_{1/2}$	210 days (aerobic) 5.9 years (aerobic) 313 days (aerobic)	American Cyanamid 1983b Tollackson 1988 Ta 1999a
Water/ sediment, aerobic $t_{1/2}$	17 months No degradation	American Cyanamid 1986b American Cyanamid 1988c
Water/sediment, anaerobic $t_{1/2}$	Not metabolized	Sanders 1986
Field Dissipation $t_{1/2}$ in days	90 138 30 34-65 77-155 150 (Oregon) 180 (North Carolina) 94 25 to 58	Knisel et al. 1992 American Cyanamid 1983b Michael et al. 1996 Michael and Neary 1993 McDowell et al. 1996 York 1992a York 1992b Garrett 2000 El Azzouzi et al. 1998

Property	Value	Reference

Table 2-1: Identification and Physical/Chemical Properties of Imazapyr and the Monethanolamine salt of Imazapyr *(Continued)*.

Property	Value	Reference
Photolysis $t_{1/2}$	3.7 days at pH 7 in water 149 days, soil surface	American Cyanamid 1986b Mangels 1986
Hydrolysis $t_{1/2}$ (days)	325 at pH 7 Stable	American Cyanamid 1986b Mangels 1990a
Plant $t_{1/2}$	15-37 days (composite of different types of vegetation) 30 days	Neary and Michael 1993 Knisel et al. 1992

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

Use	Pounds	Acres	Lbs/Acre	Proportion of Use by lbs	Proportion of Use by Acres
Conifer and Hardwood Release	**68**	**1941**	**0.035**	0.308	0.450
Conifer Release	**55**	**1711**	**0.032**	0.249	0.397
Hardwood Release	**10**	**235**	**0.043**	0.045	0.054
Housekeeping/Facilities Maintenance	**3.57**	**0.34**	**10.5**	0.016	0.000
Noxious Weed Control Total	**11.06**	**24.5**	**0.451**	0.050	0.006
Right-of-Way Vegetation Management Total	**31.14**	**189.98**	**0.164**	0.141	0.044
Wildlife Habitat Improvement	**42**	**212**	**0.198**	0.190	0.049
Grand Total	**220.77**	**4313.82**	**0.051**		

Table 2-3: Use of Imazapyr by the Forest Service in 2001 Sorted by Region (USDA/FS 2002).

Region	Pounds	Acres		Proportion of Use by lbs	Proportion of Use by Acres
Region 2	**5.63**	**6.84**	**0.823**	0.026	0.002
Region 4	**9**	**18**	**0.500**	0.041	0.004
Region 8	**177**	**4107.75**	**0.043**	0.802	0.952
Region 9	**23.14**	**171.73**	**0.135**	0.105	0.040
	220.77	**4313.82**	**0.051**		

Table 3-1. Incidence of Proliferative Lesions Relative to Matched Controls (Daly 1988, 1991).

SEX	**MALES**			
Dietary level (ppm)	0	1000	5000	10,000
Thyroid gland (#examined)	65	65	63	65
C-cell hyperplasia	15 (23.10%)	8 (12.31%)	13 (20.63%)	6 (9.23%)
C-cell adenoma	2 (3.10%)	3 (4.62%)	9 (14.29%)	4 (6.15%)
C-cell carcinoma	1 (1.54%)	1 (1.54%)	1 (1.59%)	5 (7.69%)
C-cell adenoma and carcinoma	3 (4.62%)	4 (6.15%)	10 (15.87%)	9 (13.85%)
C-cell hyperplasia, adenoma and carcinoma combined	17 (26.15%)	12 (18.46%)	21 (33.33%)	15 (23.8%)

Table 3-2. Summary Incidence of Proliferative Thyroid Lesions in Male Rats and Historical Controls (Daly 1988).

Number examined/lesion/percentage	Low	High	Mean Incidence of Historical Data
# Examined	73	69	1413
C-cell hyperplasia percentage	0	1015	604.25
# Examined	131	70	1413
C-cell adenoma percentage	0	811	725.1
# Examined	129	131	1413
C-cell carcinoma percentage	0	1814	584.1
# Examined	54	70	1413
C-cell adenoma and carcinoma combined percentage	0	1217	1299.13
# Examined	54	70	1413
C-cell hyperplasia, adenoma and carcinoma combined percentage	0	1826	18312.95

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

Chemical Specific Parameters

Parameter	Clay	Loam	Sand	Comment/ Reference
Halftimes (days)				
Aquatic Sediment		N/A		Note 1
Foliar		26		Note 2
Soil	25	67	180	Note 3
Water		325		Note 4
Ko/c, mL/g		99.8		Note 5
K_d, mL/g	4.55	4.55	4.55	Note 6
Water Solubility, mg/L		13,100		Cortes 1990
Foliar wash-off fraction		0.9		Knisel and Davis 2000

Note 1 Imazapyr is not degraded under anaerobic conditions (American Cyanamid. 1986b). The sediment degradation rate is set to zero in the model runs.

Note 2 Central estimate from Michael and Neary (1993) and close to the reference value of 30 days given by Knisel and Davis(2000).

Note 3 The degradation halftime in soil is highly dependent on microbial population. The range of 25 to 180 days is based on a large number of soil degradation studies (Table 2-2). The central estimate of 67 days is taken as the geometric mean of the range.

Note 4 Based on hydrolysis halftime at pH 7 from American Cyanamid (1986b). More rapid degradation is plausible under conditions where photolysis may be the predominant mechanism of degradation.

Note 5 Value for silt loam from Holman (2000).

Note 6 Kd values vary substantially among soil types. The value of 4.55 is taken from Mangels (1994) and is the only Kd reported specifically for pond sediment.

Site Parameters
(see SERA 2003, SERA AT 2003-02d dated for details)

Pond	1 acre pond, 2 meters deep, with a 0.01 sediment fraction. 10 acre square field (660' by 660') with a root zone of 60 inches and four soil layers.
Stream	Base flow rate of 4,420,000 L/day with a flow velocity of 0.08 m/second or 6912 meters/day. Stream width of 2 meters (about 6.6 feet') and depth of about 1 foot. 10 acre square field (660' by 660') with a root zone of 60 inches and four soil layers.

Table 3-4: Summary of modeled concentrations of imazapyr 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	0.00052	0.05428	0.00000	0.00000	0.00003	0.00201
20	0.00105	0.12387	0.00000	0.00000	0.00130	0.03584
25	0.00160	0.20557	0.00000	0.00000	0.00352	0.06910
50	0.00379	0.62831	0.00008	0.00303	0.01028	0.15853
100	0.00588	1.28939	0.00109	0.08160	0.01268	0.31147
150	0.00648	1.72329	0.00166	0.10668	0.01172	0.38660
200	0.00651	2.02585	0.00188	0.10370	0.01034	0.42011
250	0.00621	2.04018	0.00192	0.09301	0.00914	0.43230

Table 3-5: Summary of modeled concentrations of Imazapyr 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	0.05302	0.08019	0.00000	0.00000	0.00067	0.00680
20	0.06714	0.14230	0.00000	0.00000	0.04062	0.09711
25	0.07795	0.21245	0.00000	0.00000	0.09448	0.16126
50	0.10288	0.50984	0.00080	0.00189	0.18822	0.27767
100	0.11113	0.92352	0.01236	0.04942	0.16624	0.39747
150	0.10758	1.29162	0.01587	0.06735	0.13768	0.43272
200	0.10179	1.62341	0.01624	0.06784	0.11701	0.44514
250	0.09347	1.72006	0.01563	0.06327	0.10169	0.44761

Table 4-1: Summary of modeled concentrations of Imazapyr 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	0.76079	6.62010	1.11501	5.98761	1.32710	5.16909
10	0.63146	6.15317	0.73722	5.25855	0.43507	3.67379
15	0.52475	5.82654	0.47153	4.59622	0.17919	3.53673
20	0.44498	5.50749	0.33411	4.02581	0.10247	3.52689
25	0.38989	5.23711	0.25183	3.52787	0.06782	3.52516
50	0.25047	4.26776	0.09879	3.52516	0.02347	3.52516
100	0.13332	3.99075	0.03455	3.52516	0.01482	3.52516
150	0.06940	3.99075	0.02004	3.52516	0.01332	3.52516
200	0.02588	3.99075	0.01479	3.52516	0.01263	3.52516
250	0.01261	3.99075	0.01315	3.52516	0.01224	3.52516

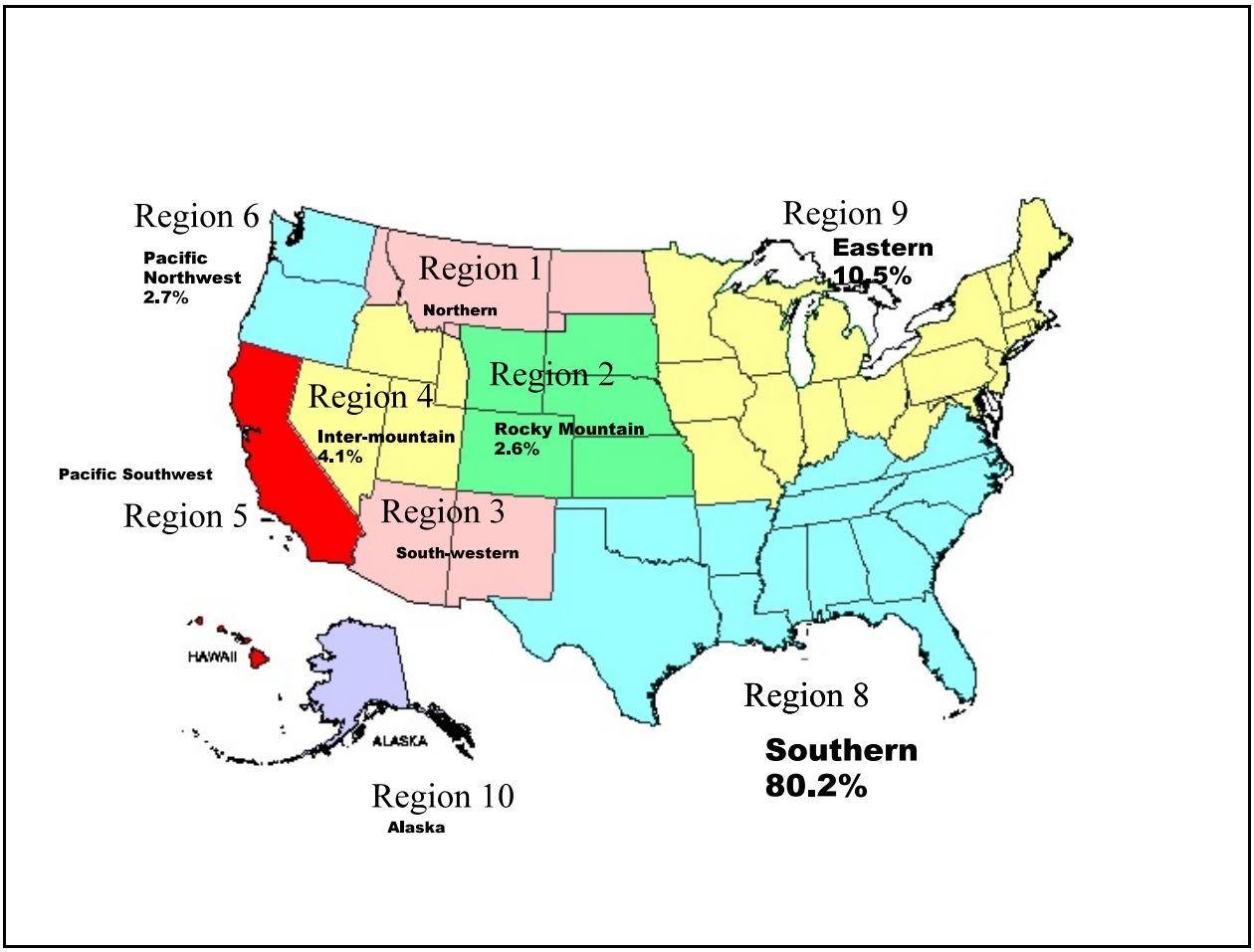

Figure 2-1. Use of imazapyr by the USDA Forest Service in various regions of the United States based on percentages of total use by the Forest Service.

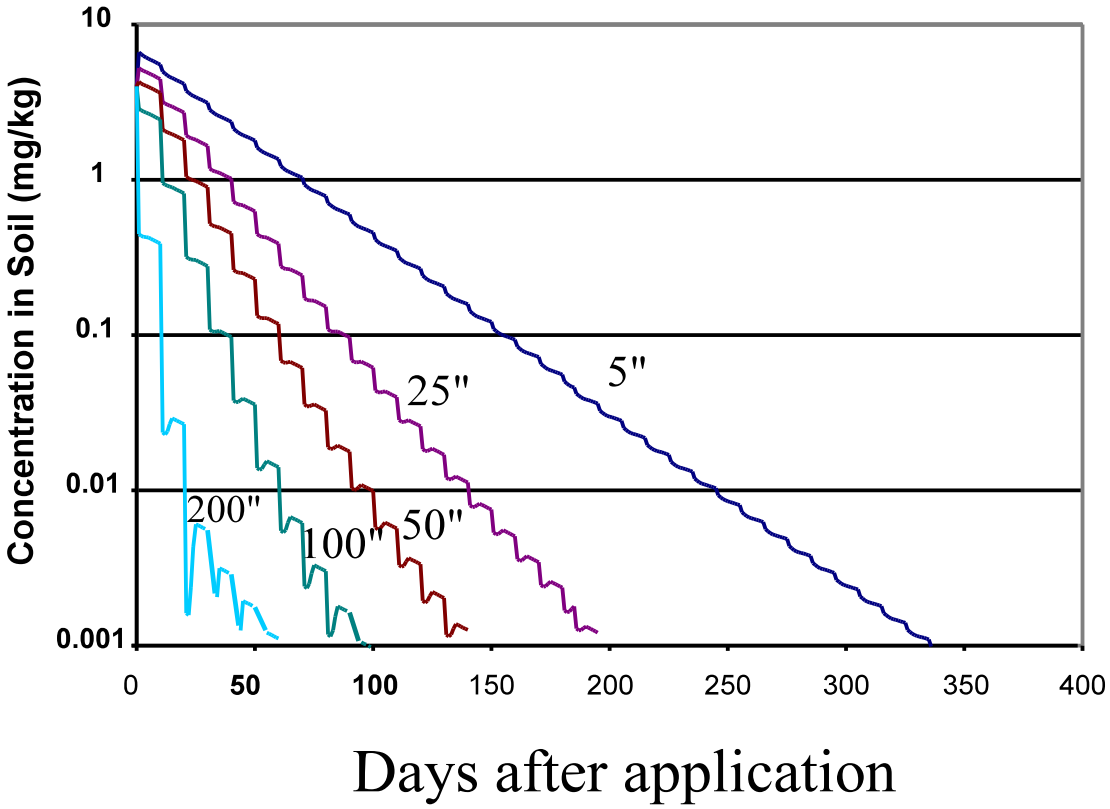

Figure 4-1: Concentration of imazapyr in clay soil after an application rate of 1 lb/acre at annual rainfall rates of 5, 25, 50, 100, and 200 inches.

LIST OF APPENDICES

Appendix 1: Toxicity of Imazapyr to Mammals

Animal	Dose	Response	Reference
ORAL			
	Acute Oral Toxicity Studies		
Rats, Charles River, albino, 6-weeks old, 5 males (bw=151–157 g) and 5 females (bw=120–124 g).	Single oral dose of 5000 mg/kg or 25 mL/kg. 14-day observation period. [Test material specified as AC 3532-149 or 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid; 2 lb/gallon formulation.] Fiche contains CBI data on ingredients not summarized in this appendix.	No mortality among females. One male rat died (necropsy revealed congestion of liver, kidney, and intestinal tract, and hemorrhagic lungs). Surviving test animals showed no visible lesions. LD_{50} = >5000 mg/kg	Fischer 1983 MRID No. 00132031
Rats, Charles River, albino, 7-weeks old, 5 males (bw=251–265 g) and 5 females (bw=171–190 g).	Single oral dose of 5000 mg/kg or 10 mL/kg. [Test material specified as Arsenal Herbicide 5% granular formulation or AC 243,977 Technical.] Fiche contains CBI data on ingredients not summarized in this appendix.	No toxic signs or mortality were observed in any of the test animals. No visible lesions were observed in any of the test animals. LD_{50} = >5000 mg/kg	Fishcer 1986a MRID No. 00162964
Rats, Charles River, albino, 6–7 weeks old, 5 males (bw=160–182 g) and 5 females (bw=142–164 g).	Single oral dose of 5000 mg/kg or 4.7 mL/kg. [Test material specified as Chopper C/S Formulation or AC 243,997 Technical, sample purity 22.6%.] Fiche contains CBI data on ingredients not summarized in this appendix.	Decreased activity (only sign of intoxication) but no mortality. Necropsies showed no visible lesions. 14-day observation period. LD_{50} = >5000 mg/kg	Fischer 1986b MRID No. 00163195

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
Rats, Crl: CD(SD)BR strain, albino, 5/sex.	Single oral dose of 5000 mg/kg bw administered via gavage. [Test substance specified as AC 243,997 6% RTU formulation.]	No mortality; signs of toxicity were limited to a bluish discoloration of the urine 2–8 hours after dosing. No other signs of toxicity were observed for the remainder of the 14-day observation period. Necropsy results included hydronephrosis of the kidney in 1/5 males and 3/5 females, but no other visible lesions were observed. LD_{50} = >5000 mg/kg	Fischer 1989c MRID No. 41353404
Rats, Charles River, albino, 7–10 weeks old, 5 males (bw=167–173 g) and 5 females (bw=193–199 g).	Single oral dose of 5000 mg/kg or 4.8 mL/kg. [Test material specified as AC 5329-101-C or Imazethapyr and Imazapyr 170/6.5 gallon/L AS formulation.]	No mortality; no signs of toxicity, no gross lesions at necropsy. LD_{50} = >5000 mg/kg	Lowe 1988 MRID No. 40763402
Rats, Sprague-Dawley, albino 8-weeks old, 5 males (bw=223–240 g) and 5 females (bw=161–179 g).	Single oral dose of 5000 mg/kg. [Test material specified as AC 243997, purity 98.8% w/w.]	Clinical signs of toxicity (salivation in 4/5, writhing in 1/5) and one death in males. Surviving males returned to normal appearance by 2 hours post-dosing. No signs of toxicity or mortality in females. No gross pathology in either sex. 14-day observation period. LD_{50} = >5000 mg/kg	Lowe 1999 MRID No. 44735301
	Subchronic Oral Toxicity Studies		
Rats, Charles River CD (Sprague-Dawley derived), 4.5-weeks old, 10 males (bw=100–130 g) and 10 females (bw=102–120g) per dose group.	0, 15,000, or 20,000 ppm in the diet for 13 weeks. The teported average daily test substance intake values, based on mean weekly body weight and food consumption data measured during the 13-week dosing period, correspond to 1248 and 1695 mg/kg/day for males and 1336 and 1740 mg/kg/day for females for 15,000 and 20,000 ppm concentrations, respectively. [Test material specified as AC	No exposure-related adverse effects at either dose level as shown by clinical signs, survival, body weight, food consumption, ophthalmo-logic condition, hematology, clinical chemistry, urinalysis, organ weights, gross pathology and histopath-ology. Absolute and relative kidney weights were increased in the high-dose females (≈12–15% higher than controls) but not	Hess 1992 MRID No. 42774401

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
	243,997, purity 99.3%.]	accompanied by any pathological or urinalysis changes. This study identified a subchronic dietary NOAEL of 20,000 ppm for imazapyr in rats (1695 mg/kg/day in males and 1740 mg/kg/day in females).	
Cows, Holstein, dairy, 3/group.	Dose levels of 0, 1.2 and 3.6 g for 28 days; 12 and 36 g for 29 days. The corresponding mg a.i./kg/day bw are 0, 2, 6, 20, and 60, respectively. [Test substance specified as CL 342997 (100% purity).]	Test substance residues in milk samples in the control group were ≤2.10 ppb. The pre-treatment milk samples from all cows were <10 ppb. The residues in the cows in the 1.2 g treatment group were<10 ppb. The average residue in the 3.6, 12, and 36 g treatment groups were 24.3–34.9, 75.3–108, and 222–313 ppb, respectively.	Khunachak 1999 MRID No. 45119721

Additional Notes on Khunachak 1999: The residues in muscle, fat, kidney, and liver samples from cows in the control group were <4.49, <4.71, <4.64, and <4.58 ppb, respectively. Residues in muscle samples in the 1.2, 3.6, 12, and 36 g treatment groups were <50.0, <50.0, 97.3, and 234 ppb, respectively. Residues in fat samples in the 1.2, 3.6, 12, and 36 g treatment groups were <50.0, <50.0, 66.7, and 92.1 ppb, respectively. Residues in kidney samples in the 1.2, 3.6, 12, and 36 g treatment groups were 246, 519, 4360, and 7510 ppb, respectively. Residues in liver samples in the 1.2, 3.6, 12, and 36 g treatment groups were <50.0, <50.0, 300, and 809 ppb, respectively.

Chronic Oral Toxicity Studies			
Mice, CD-1, approximately 42-days old, 65 males (mean bw=27 g) and 65 females (mean bw=21g) per dose level.	Dietary exposure to 0, 1000, 5000, or 10,000 ppm for 18 months. Test substance intake based on measured food consumption values ranged as follows: 126–254, 674–1194, and 1301–2409 mg/kg/day in males and 151–303, 776–1501, and 1639–3149 mg/kg/day in females.	No dose-related or statistically significant (Chi-square analysis) differences in mortality between controls and treated mice, but survival in treated males was slightly better than in control males and survival in mid- and high-dose females was slightly worse than in control females.	Auletta 1988 MRID No. 41039504; Hess 1992 MRID No. 42774401

Additional Notes on Auletta 1988: Although there were no treatment-related effects on body weight; increased food consumption was statistically significant among treated mice, but was not considered treatment related in the absence of a dose-response relationship.

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
		No statistically significant adverse effects on hematology were observed. Organ weight data indicate a "*few statistically significant differences*," which occurred sporadically and were not considered treatment related. Gross pathology revealed a slightly higher incidence of enlarged mesenteric lymph nodes in all treated mice, but no dose-response relationship; a slightly increased incidence of kidney cysts in high dose males [5/33 (15%)] compared with controls [2/28 (7%); and a dose-related, but not statistically significant increase in the number of enlarged seminal vesicles: [0 ppm 3/28 (11%); 1000 ppm 6/35 (17%); 5000 ppm 9/34 (27%); and 10,000 ppm 10/33 (30%)], which the investigators viewed as "*common findings in old mice*." Microscopic evaluation revealed changes that occurred with greater incidence in high-dose mice, compared with controls. These mild inflammatory changes, which were not statistically significant and not considered treatment related, included plasma cell hyperplasia in the mesenteric lymph nodes and erythrocytes in the sinus of the mediastinal lymph nodes in females. There was no difference in the incidence of pathological findings in gonads between treated and control mice and no dose-related differences in incidence or degree of hydronephrosis. Supplemental information on this study was requested by EPA for their carcinogenicity classification and chronic toxicity NOEL determination (Hess 1992). Additional histopathologic examination for brain tumors in the male rats and a statistical analysis of adrenal medullary neoplastic lesions in the female rats supported the conclusion that there was no carcinogenic potential for imazapyr. Additional evaluation of the female rats for extramedullary hematopoiesis in the spleen and bilateral squamous cysts in the thyroid supported determination of a 10,000 ppm NOAEL for chronic toxicity.	
Rats, Sprague-Dawley, 44-days old, 260 males (bw=158–221 g), and 260 females (bw=121–174 g), 65 males and 65 females per dose group, control plus 3-dose groups.	0, 1000, 5000, or 10,000 ppm for 2 years. Partial sacrifice (10 per group) after 12 months of treatment; all remaining survivors sacrificed after 24 months. Mean test substance intake values calculated over the 2-year study duration, based on individual body weight and food consumption, and the purity of the test material were 49.9, 252.6, and 503.0 mg/kg/day for males and 64.2, 317.6, and 638.6 mg/kg/day for females (cf: p. 13 of study).	No differences in the number of deaths among control and treated animals. In males, there was a slight but statistically insignificant relationship between dose level and time to death. Females (in all treatment groups) showed a slight (and in most cases statistically significant) increase in food consumption during the first year; however, the effect, which did not always exhibit a dose response, was not considered toxicologically significant.	Daly 1988 MRID No. 41039503; Hess 1992 MRID No. 42774401

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
Additional Notes on Daly 1988: In control and all treated groups there was a random distribution of gross lesions considered to be incidental changes unrelated to exposure to the test material. There were no treatment-related effects on hematology, clinical chemistry or urinalysis, mean organ weights, organ/body weight or organ/brain weight ratios; however, there was an increased incidence of C-cell carcinomas of the thyroid gland in high-dose males. [See Section 3.1.5 for a detailed discussion of the significance of these findings.] Supplemental information on this study was requested by EPA for their carcinogenicity classification and chronic toxicity NOEL determination (Hess 1992). Additional histopathologic examination for brain tumors in the male rats and a statistical analysis of adrenal medullary neoplastic lesions in the female rats supported the conclusion that there was no carcinogenic potential for imazapyr. Additional evaluation of the female rats for extramedullary hematopoiesis in the spleen and bilateral squamous cysts in the thyroid supported determination of a 10,000 ppm NOAEL for chronic toxicity.			
Dogs, Beagles, 5–6 months old, 6/sex/dose group, 4 dose groups.	0, 1000, 5000, or 10,000 ppm in the diet for 1 year. Positive dose levels correspond to 27.6, 129.18, or 262.88 mg/kg for males, and 29.71, 127.72, or 269.80 mg/kg for females (mg/kg doses calculated by USEPA (1997) based on midpoint food consumption and body weights reported in the study). [Test material specified as AC 243,997, purity = 99.5%.]	No mortality; no clinical signs of toxicity attributed to treatment, 10,000 ppm considered to be 'no-effect' level.	Shellenberger 1987 MRID No. 41039502
Reproduction/Teratogenicity Oral Toxicity Studies			
Rats, Sprague-Dawley, 25 males (bw=187–240 g) and 25 females (bw=128–166 g), forming F_0 generation in a 2-generation reproduction study.	0, 1000, 5000, or 10,000 ppm in the diet. Rats were treated for 64 days prior to mating, throughout the two mating periods and for approximately 3 weeks after the end of the second mating period. Ranges of achieved intake of AC 243,997 between weeks 1 to 10 and 18 to 19 were as follows: **males**: 48.3 to 142.8, 252.8 to 720.8, and 483.4 to 1471.8 mg/kg/day, corresponding to 1000, 5000, and 10,000 ppm, respectively; **females:** 80.2 to 149.9, 404.7 to 736.1, and 761.3 to 1537.1 mg/kg/day, corresponding to 1000, 5000,	**In the F_0 and F_{1b} adult generations**: There were no treatment-related effects on mortality or pathology, and no clinical signs of toxicity. There were no adverse effects on body weights or food consumption in any of the dose groups. There were no significant differences in fertility indices, day of mating, or other parameters of parental performance. The incidence of dead pups at birth varied markedly among groups and was occasionally statistically significant but did not show a clear dose-response relationship. Other parameters of reproductive toxicity (i.e., gestation index,	Robinson 1987 MRID No. 41039505

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
	and 10,000 ppm, respectively.	length of gestation, number of live pups at birth, and sex ratio) were similar to control values. **In the F_{1a}, F_{1b}, F_{2a}, F_{2b} pups**: There were no adverse effects on viability, survival, or lactation indices, or on the clinical condition of the pups. Except for one occasion, the body weights of pups in the treated group were not significantly different from controls. There were no pathology findings related to treatment.	
Rabbits, New Zealand white, albino, females, nominally 5/dose (only data for gravid females are summarized; VC=4; T-1=5; T-2=3; T-3=5; T-4=5).	0, 250, 1000, or 2000 mg/kg bw by gavage on days 6–18 of gestation. [Test material specified as AC 243,997.]	Mortality in does = 2/5 (250 mg/kg); 4/5 (1000 mg/kg); and 5/5 (2000 mg/kg). At 250 mg/kg, necropsy revealed fluid in the trachea and chronic non-suppurative pneumonia in one animal and pulmonary exudate and discoloration, gastric mucosal depressions and ulcers in the other. At 1000 mg/kg, necropsy revealed stomach lesions (discolorations/depressions) in all four animals. At 2000 mg/kg, necropsy revealed gastric mucosal changes (erosive lesions) in four animals and gastric and pyloric mucosal discolor-ations in the other animal. In animals that survived to final sacrifice, there were no treatment-related adverse effects on body weight, mean numbers of corpora lutea, implantation sites, resorption sites, viable fetuses, and gross pathology. Exposure levels of 1000 and	Salamon et al. 1983a MRID No. 00131614 This is a pilot study for Salamon et al. 1983b, MRID No. 00131613.

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
		2000 mg/kg resulted in maternal death; exposure levels of 250 and 500 mg/kg did not produce exaggerated pharmacological or embryo-cidal effects.	
Rabbits, New Zealand white, albino, females, nominally 18/dose (only data for gravid females are summarized; VC=17; T-1=18; T-2=16; T-3=17).	0, 25, 100, or 400 mg/kg bw by gavage on days 6–18 of gestation. [Test material specified as AC 243,997.]	Two rabbits in the control group and two rabbits in the 400 mg/kg died; gross pathology revealed only pulmonary changes. All other does survived to final sacrifice. A slightly increased incidence of common and expected pulmonary and hepatic changes was observed in the treated does but was not considered treatment related. There was no evidence of reproductive effects in the dams; there were no statistically significant differences in fetal body weight and crown-rump length compared with controls. **External anomalies:** There was one external anomaly observed in the 25 mg/kg group and four in the 400 mg/kg group. In the 25 mg/kg group (152 fetuses; 17 litters), one fetus had a short tail. [Another fetus had a left eye that appeared larger than normal, but appeared to be normal in size during internal examination.] In the 400 mg/kg group (144 fetuses; 16 litters), one fetus had a kink at the tip of the tail; there were two fetuses (from the same litter) with talipes; and one anurous fetus (from a different litter) with talipes and spina bifida.	Salamon et al. 1983b MRID No. 00131613

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
		Evaluations of fetal internal, skeletal, and internal head development indicated no consistent, adverse effects resulting from exposure to AC 243,997.	
Rats, Charles River, female, 25/dose group (only data for gravid females are summarized; VC=22; T-1=24; T-2=23; T-3=22).	0, 100, 300, or 1000 mg/kg bw by gavage on days 6–15 of gestation. [Test material specified as AC 243,997.]	No mortality; no teratogenicity; salivation was observed in 6/22 animals treated with 1000 mg/kg/day bw.	Salamon et al. 1983c MRID No. 00131611
Rats, Charles River, female, 5/dose group.	0, 250, 500, 1000, or 2000 mg/kg bw by gavage on days 6–15 of gestation. [Test material specified as AC 243,997.]	No mortality; no pharmacological or embryocidal effects; only recurring effect was salivation: 1/5 (250 mg/kg); 2/5 (500 mg/kg); 3/5 (1000 mg/kg); and 5/5 (2000 mg/kg)	Salamon et al. 1983d MRID No. 00131612 This is a pilot study for Salamon et al. 1983c, MRID No. 00131611.
		INHALATION	
Rats, Sprague-Dawley, 10/sex.	Whole body exposure of 4.62 ± 1.41 mg/L (analytical) for 4 hours. MMAD = 1.6 µm ± 0.06 (GSD). [Test material specified as Arsenal 4-AS (purity not reported).]	No mortality (LC_{50} >4.62 mg/L). All animals appeared normal during the 14-day observation period. Gross pathology findings included congested lungs (2/10 males, 4/10 females); slight lung congestion (3/10 males, 5/10 females); and hemorrhagic lungs (1/10 males).	Hershman and Moore 1986 MRID No. 00164539
Rats, Sprague-Dawley, 10/sex.	Whole body exposure of 1.3 mg/L aerosol (measured level) for 4 hours. MMAD = 3.3 µm ± 2.5 (GSD). 88% of particles were respirable (≤10 µm). [Test material specified as AC 243,997 (93% pure).]	Slight nasal discharge occurred in all rats subsequent to exposure on day 1, but animals returned to normal appearance on day 2; the finding was indicative of minor reversible irritation of the nares and/or upper respiratory tract. No mortality (LC_{50} >1.3 mg/L) or changes in body weight or absolute or relative organ weights (liver, kidneys,	Voss et al. 1983 MRID No. 00132032

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
		heart, lungs, testes, ovaries), or gross pathology in lungs or other tissues. 14-day post-exposure observation.	
Rats, Sprague-Dawley, 10/sex.	Whole body exposure of 3.34 ± 0.76 mg/L aerosol (measured level) for 4 hours. MMAD = 5.00 ± 2.94 µm, 6.15 ± 2.67 µm (two determinations). 65.7% of particles were respirable (≤10 µm). [Test material specified as Chopper RTU 6 (purity not reported).]	No mortality (LC_{50} >3.34 mg/L) and no clinical signs of intoxication including changes in body weight or absolute or relative organ weights (liver, kidneys, heart, lungs, testes, ovaries), and no changes in the gross pathology of the lungs or other tissues. 14-day post-exposure observation.	Werley 1987 MRID No. 41353408
DERMAL			
Rats, albino, 5 male and 5 female. 4 lb/gallon formulation (apparently Arsenal AC)	Single dermal dose of 5000 mg/kg bw.	Chromodacryorrhea and brown material around nose. No mortality, signs of toxicity or changes in body weight.	Lowe and Bradley 1996 MRID 44177001
Guinea Pigs, Hartley Albino, 10 males (bw not reported).	Dermal sensitization was assessed by 9 induction applications (thrice weekly for 3 weeks) followed by a challenge application 14 days after the last induction. Test material was applied beneath an occlusive covering and left in contact with the skin for 6 hours. 0.4 mL of test material was applied as a minimally irritating 75% dilution in saline for inductions and as a non-irritating 25% dilution for the challenge. [Test material specified as Chopper RTU 6 (purity not reported).]	No dermal sensitization as determined by erythema and edema reactions to the challenge dose as scored by the Draize method (scoring 24 and 48 hours after application). No Draize scores ≥1 (i.e., barely perceptible erythema or edema). No apparent effects on clinical signs, body weight, or survival.	American Cyanamid Co. 1988a MRID No. 41353409
Guinea Pigs, Hartley, 12 males (mean bw 0.419 kg initial, 0.665 kg final).	Dermal sensitization was assessed by thrice weekly induction applications for 3 weeks (9 total applications) followed by a challenge application 14 days after the last induction. The inductive	No erythema or edema reactions were observed after any application as scored by the Draize method, indicating that the test material was not irritating or sensitizing to the skin of the guinea pigs.	Costello 1986 MRID No. 00162965

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
	and challenge applications consisted of 0.4 g of test material applied to intact clipped skin for 6 hours via gauze pad moistened with 0.4 mL of saline and covered with an occlusive wrap. [Test material specified as Arsenal 5-G (purity not reported).]	There were no clinical signs of toxicity or significant changes in body weight gain. There was similarly no skin irritation in a naive control group (one challenge application), or in a preliminary screening test in which animals received a single application of unspecified amount of test material for 6 hours and evaluated 24 and 48 hours later.	
Rabbits, New Zealand, white, albino, males (mean bw 3.09) and females (mean bw 2.64), 12–14 weeks old, 5/sex/dose.	Single dermal dose of 2.0 mL/kg or 2148 mg/kg applied to shaved skin using an impervious plastic cuff that provided 24-hour contact. [Test material specified as AC 3532-149 or 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid; 2 lb/gallon formulation.] Fiche contains CBI data on ingredients not summarized in this appendix.	No mortality among females. One male died (necropsy revealed pneumonic areas of the lungs). Of survivors, 1/9 had mottled and pale liver; 1/9 had moderate congestion of the lungs; 7/9 had no visible lesions. LD_{50} = >2000 mg/kg or 2 mL/kg	Fischer 1983 MRID No. 00132031
Rabbits, New Zealand, white, albino, 6 males.	0.5 mL applied to shaved, abraded or intact skin (intact and abraded sites were on opposite side of the midline of the same animal) for 24 hours. [Test material specified as AC 3532-149 or 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid; 2 lb/gallon formulation.] Fiche contains CBI data on ingredients not summarized in this appendix.	Skin irritation was scored according to the Draize scoring system. At 24 hours, mean scores for erythema were 1.00 (intact skin) and 1.67 (abraded skin); mean scores for edema were 0.00 (intact skin) and 1.50 (abraded skin). At 72 hours, mean scores for erythema were 0.33 (intact skin) and 0.67 (abraded skin); mean scores for edema were 0.00 (intact skin) and 0.00 (abraded skin). The total mean score = 5.17; Primary Irritation Score (total score/4) = 1.29.	Fischer 1983 MRID No. 00132031

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
		The test material is considered to be mildly irritating to rabbit skin.	
Rabbits, New Zealand white, albino, 12–14 weeks old, 5 males (mean bw=2.7 kg) and 5 females (mean bw=3.4 kg).	Single dermal dose of 2000 mg/kg applied to the shaved intact dorsal skin (area equals approximately 10% of body surface) of nonfasted animals. Test material held under impervious plastic cuff for 24-hour continuous contact. After 24-hour exposure, cuff removed, treated site wiped with moistened gauze pad, and animals fitted with fiber collars to prevent further ingestion of remaining test material. 14-day observation period. [Test material specified as Arsenal Herbicide 5% granular formulation or AC 243,977 Technical.] Fiche contains CBI data on ingredients not summarized in this appendix.	No signs of toxicity were observed during the 14-day observation period. No visible gross lesions were observed in any of the test animals. LD_{50} = >2000 mg/kg	Fischer 1986a MRID No. 00162964
Rabbits, New Zealand white, albino, 6 males.	0.5 g applied to shaved, abraded or intact skin (intact and abraded sites were on opposite side of the midline of the same animal) for 24 hours. [Test material specified as Arsenal Herbicide 5% granular formulation or AC 243,977 Technical.] Fiche contains CBI data on ingredients not summarized in this appendix.	Skin irritation was scored according to the Draize scoring system. At 24 hours, mean scores for erythema were 0.50 (intact skin) and 0.83 (abraded skin); mean scores for edema were 0.00 for both intact and abraded skin. At 72 hours, mean scores for erythema and edema were 0.00 for both intact and abraded skin. The total mean score = 1.33; Primary Irritation Score (total score/4) = 0.33. The test material is considered to be mildly irritating to rabbit skin.	Fischer 1986a MRID No. 00162964

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
Rabbits, New Zealand white, albino, 12–14 weeks old, 5 males (mean bw=2.3 kg) and 5 females (mean bw=3.0 kg).	Single dermal dose of 2000 mg/kg or 1.9 mL/kg applied by application to shaved intact dorsal skin (area equals approximately 10% of body surface) of nonfasted animals. Test material held under impervious plastic cuff for 24-hour continuous contact. After 24-hour exposure, cuff removed, treated site wiped with moistened gauze pad, and animals fitted with fiber collars to prevent further ingestion of remaining test material. 14-day observation period. [Test material specified as Chopper C/S Formulation or AC 243,997 Technical, sample purity 22.6%.] Fiche contains CBI data on ingredients not summarized in this appendix.	Decreased activity (only sign of intoxication), but no mortality. Necropsies showed no visible lesions. LD_{50} = >2000 mg/kg	Fischer 1986b MRID No. 00163195
Rabbits, New Zealand white, albino, 6 males (age and bw not reported).	Test material (0.5 mL) was applied to shaved intact dorsal skin (1" square). An untreated site on the opposite side of the midline served as a control. The sites were covered with a gauze pad and occluded with a plastic wrap for a contact time of 4 hours. [Test material specified as Chopper C/S Formulation or AC 243,997 Technical, sample purity 22.6%.] Fiche contains CBI data on ingredients not summarized in this appendix.	Skin irritation was scored according to the Draize scoring system. The maximum possible score for a skin reaction is 4. Sites were scored for irritation at 4, 24, 48, and 72 hours. The test material was 'mildly irritating' to the intact skin of rabbits based on observations of erythema (total score of 0.67 and primary irritation score of 0.17); no edema was observed.	Fischer 1986b MRID No. 00163195
Rabbits, New Zealand, white, albino, males (mean bw 3.4 kg) and females (mean bw 3.3 kg), 5/sex.	Single dermal dose of 2000 mg test formulation/kg applied to clipped intact trunk skin (≈10% of total body surface area) using an impervious plastic wrap that provided 24-hour contact.	No signs of toxicity, mortality, changes in body weight gain, or significant gross pathology (1/10 rabbits had liver with granular texture but no visible lesions). 14-day post-	Fischer 1989a MRID No. 41353405c

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
	[Test material specified as AC 243,997 6% RTU formulation (6.0% a.i.).]	exposure observation period. LD_{50} = >2000 mg/kg [mg AC 243,997 6% RTU formulation/kg]	
Rabbits, New Zealand, white, albino, young adults, 10/sex/dose.	0, 100, 200, or 400 mg/kg/day to close-clipped, intact or abraded, occluded backs, 5 days/week for 3 weeks.	Two rabbits died with gross evidence (confirmed microscopically) of pneumonia; no systemic toxicity (i.e., no adverse effects on body weight, food consumption, hematology, serum chemistry, or organ weights). Microscopic evaluation of all tissues from control and high-dose group rabbits and all remarkable tissues from low- and middle-dose group rabbits did not indicate consistent or distinct treatment-related effects.	Larson and Kelly 1983 MRID No. 00131609
Guinea Pigs, American Shorthair (Hartley derived), 10 males (mean bw 0.54 kg initial, 0.59 kg final).	Dermal sensitization was assessed by once weekly induction applications for 3 weeks followed by a challenge application 14 days after the last induction. 0.3 g of test material moistened with 0.9% saline was used for the inductive and challenge applications. Test material was left in uncovered contact with clipped skin for 6 hours. [Test material specified as AC 243,997 (93% pure).]	No erythema or edema reactions were observed after any application, indicating that the test material was not sensitizing or irritating to the skin of the guinea pigs. There were no clinical signs of toxicity or significant changes in body weight. No skin irritation was observed in a naive control group (one challenge application) or in a preliminary dose range-finding study in which guinea pigs received a single application of 0.08–0.30 g of test material and evaluated for erythema and edema 24 and 48 hours later.	Ledoux 1983 MRID No. 00131607
Rabbits, New Zealand, white, albino, 5 males (mean bw=2.59 g), 5 females (mean bw=2.56 g).	Single dermal dose of 1.92 mL/kg or 2000 mg/kg applied by application to dorsal surface (area equals approximately 10% of body surface) to nonfasted, shaved	One male rabbit died on day 12 of the study due apparently to an incurrent respiratory infection. Necropsy revealed pale kidneys, consolidation and	Lowe 1988 MRID No. 40763402

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
	animals. Test material held under impervious plastic cuff for 24-hour continuous contact. After 24-hour exposure, cuff removed, treated site wiped with moistened gauze pad, and animals fitted with fiber collars to prevent further ingestion of remaining test material. [Test material specified as AC 5329-101-C or Imazethapyr/Imazapyr 170/6.5 gallon/L AS formulation.]	adhesions in the lungs, and fluid in the pleural cavity. No other deaths occurred and no other gross lesions were observed in the surviving animals. No overt signs of toxicity were observed during the study. LD_{50} = >2000 mg/kg or 1.92 mL/kg. Investigators indicate that the product is considered to be "*no more than slightly toxic by single skip applications*."	
Rabbits, New Zealand, white, albino, 6 males.	0.5 mL applied to shaved, 1" squares of intact skin on dorsal surface (opposite side of the midline of the same animal served as control). Test material was covered with gauze pad, occluded with plastic wrap, and left in contact with skin for 4 hours. [Test material specified as AC 5329-101-C or Imazethapyr/ Imazapyr 170/6.5 gallon/L AS formulation.]	Skin irritation was scored according to the Draize scoring system. The maximum possible score for skin irritation is 4. Sites were scored for irritation at 4, 24, 48, and 72 hours. The test material was not irritating to the skin of rabbits.	Lowe 1988 MRID No. 40763402
		EYES	
Rabbits, New Zealand, white, albino, males, 6 in group without rinsing, 3 in group with rinsing.	0.1 mL instilled into conjunctival sac of right eye (left eye served as control) with or without rinsing after 20 seconds. [Test material specified as AC 3532-149 or 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid; 2 lb/gallon formulation.] Fiche contains CBI data on ingredients not summarized in this appendix.	Eye irritation was scored according to the Draize scoring system. The maximum possible scores for eye irritation reactions are: cornea (80); iris (10), and conjunctiva (20). Observations of the cornea, iris, and conjunctiva at 24, 48, and 72 hours and 4 and 7 days indicated that the test material was irritating to the rabbit eye with complete recovery by 7 days. The group without rinsing had substantially higher mean irritation scores,	Fischer 1983 MRID No. 00132031

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
		compared with the group with rinsing.	
Rabbits, New Zealand, albino, 6 males.	100 mg instilled into conjunctival sac of the right eye (left eye served as control) without rinsing for 24 hours, after which time, treated eyes were rinsed with tap water. [Test material specified as Arsenal Herbicide 5% granular formulation or AC 243,997 Technical.] Fiche contains CBI data on ingredients not summarized in this appendix.	Examinations of the cornea, iris, and conjunctiva were performed at 1, 24, 48, 72 hours, and 4 and 7 days (with the aid of ultraviolet light and fluorescein). Eye irritation was scored according to the Draize scoring system. The maximum possible scores for eye irritation reactions are: cornea (80); iris (10), and conjunctiva (20). The test material was considered to be 'irritating' to the rabbit eye based on mean scores of 2.7 and 3.7 for conjunctiva at 1 hour and 24 hours, respectively; and 0.3 from 48 hours to 4 days; and mean scours of 5.8 and 2.5 for cornea at 24 and 48 hours, respectively. All animals recovered by 7 days.	Fischer 1986a MRID No. 00162964
Rabbits, New Zealand, albino, 6 males.	0.1 mL instilled into conjunctival sac of right eye (left eye served as control) without rinsing for 24 hours, after which time, treated eyes were rinsed with tap water. [Test material specified as Chopper C/S Formulation or AC 243,997 Technical, sample purity 22.6%.] Fiche contains CBI data on ingredients not summarized in this appendix.	Examinations of the cornea, iris, and conjunctiva were performed at 1, 24, 48, and 72 hours (with the aid of ultraviolet light and fluorescein). Eye irritation was scored according to the Draize scoring system. The maximum possible scores for eye irritation reactions are: cornea (80); iris (10), and conjunctiva (20). The test material was 'irritating' to the rabbit eye based on mean scores of 9.3 for conjunctiva (at 1 and 24 hours) and 8.3 for cornea. All animals recovered by 72 hours.	Fischer 1986b MRID No. 00163195

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
Rabbits, New Zealand, albino, 6 males.	0.1 mL of powdered test material was instilled into the conjunctival sac of the left eye (right eye served as untreated control) without rinsing for 24 hours, after which time, treated eyes were rinsed with tap water. [Test material specified as AC 243,997 6% RTU formulation (6.0% a.i.).]	Examinations of the cornea, iris, and conjunctiva were performed pretreatment and after 1, 24, 48, and 72 hours (with the aid of ultraviolet light and fluorescein). Eye irritation was scored according to the Draize scoring system. The maximum possible scores for eye irritation reactions are: cornea (80); iris (10), and conjunctiva (20). The test material was 'minimally irritating' to the rabbit eye based on slight injection of the conjunctival vessels, slight chemosis, and slight discharge in 6/6, 3/6 and 1/6 animals, respectively, at the 1-hour observation period. All animals recovered by 24 hours.	Fischer 1989b MRID No. 41353406c
Rabbits, New Zealand white, albino, 6 males (young adult, age 12–14 weeks, bw not reported).	Test material (0.5 mL) was applied to 1" square gauze patches and applied to clipped intact dorsal trunk skin. An untreated site on the opposite side of the midline served as a control. The sites were occluded with a plastic wrap for a contact time of 4 hours. [Test material specified as AC 243,997 6% RTU formulation (6.0% a.i.).]	Skin irritation was scored according to the Draize scoring system. The maximum possible score for a skin reaction is 4. Sites were scored for irritation at 1, 24, 48, and 72 hours. The test material was 'mildly irritating' to the intact skin based on observations of barely perceptible erythema in 2/6 rabbits at the 1-hour observation. No edema was observed and there were no overt signs of toxicity or mortality.	Fischer 1989d MRID No. 41353407c
Rabbits, New Zealand, white, albino, 6 males.	0.1 mL instilled into conjunctival sac of right eye (left eye served as control) without rinsing for 24 hours,	Eye irritation was scored according to the Draize scoring system. The maximum possible scores for	Lowe 1988 MRID No. 40763402

Appendix 1: Toxicity of Imazapyr to Mammals (listed alphabetically by author). *(continued)*

Animal	Dose	Response	Reference
	after which time, treated eyes were rinsed with tap water. [Test material specified as AC 5329-101-C or Imazethapyr/ Imazapyr 170/6.5 gallon/L AS formulation.]	eye irritation reactions are: cornea (80); iris (10), and conjunctiva (20). Examinations of the cornea, iris, and conjunctiva at 1 hour, 24, 48, and 72 hours (with the aid of ultraviolet light and fluorescein) indicated that the test material was 'nonirritating' to the rabbit eye.	

Appendix 2: Toxicity of Imazapyr to Birds after Oral Administration.

Animal	Dose	Response	Reference
Quail, Bobwhite, 11–17 days old at start, 10/dose, body weight of 20–35 g.	0, 312, 625, 1250, 2500, or 5000 ppm in the diet for 5 days. [0, 38, 72, 148, 322, and 674 mg/kg bw based on measured food consumption.] [Test material specified as AC 243,997.]	No mortality. Study included one control group for each test group.	Fletcher 1983a MRID No. 00131635
Ducks, Mallard, 4-days old at start, 10/dose.	0, 312, 625, 1250, 2500, or 5000 ppm in the diet for 5 days. [0, 64, 145, 273, 595, or 1149 mg/kg bw based on measured food consumption.]	No mortality. Study included one control group for each test group.	Fletcher 1983b MRID No. 00133553
Quail, Bobwhite, 19-weeks old, 5/sex/dose.	0, 1470, or 2150 mg/kg bw administered via gavage. [Test substance specified as Arsenal Herbicide. Based on 0.278 ratio of imazapyr in Arsenal (BASF 200a, the Arsenal doses correspond to imazapyr doses of about 410 and 600 mg/kg.]	No mortality and no abnormal behavioral reactions or systemic signs of toxicity were observed. Gross pathological examination (2/sex/dose) revealed no abnormal tissue alterations. 21-day observation period. LD_{50} = >2150 mg/kg bw	Fletcher et al. 1984a MRID No. 00153773
Ducks, Mallard, 27–30 weeks old, 5/sex/dose.	0, 1470, or 2150 mg/kg bw administered via gavage. [Test substance specified as Arsenal Herbicide. Based on 0.278 ratio of imazapyr in Arsenal (BASF 200a, the Arsenal doses correspond to imazapyr doses of about 410 and 600 mg/kg.]	No mortality and no abnormal behavioral reactions or systemic signs of toxicity were observed. Gross pathological examination (2/sex/dose) revealed no abnormal tissue alterations. 21-day observation period. LD_{50} = >2150 mg/kg bw	Fletcher et al. 1984b MRID No. 00153774
Quail, Bobwhite, 15-days old, 10/dose.	0, 312, 625, 1250, 2500, or 5000 ppm in the diet for 5 days and then a basal diet for the next 3 days. [Test substance specified as Arsenal Herbicide.]	No mortality and no abnormal behavioral reactions or systemic signs of toxicity were observed. Gross pathological examination (4 each from the 0, 2500, and 5000 ppm dose group) revealed no abnormal tissue alterations. LC_{50} = >5000 ppm	Fletcher et al. 1984c MRID No. 00153775

Appendix 3: Toxicity of Imazapyr to Birds after Oral Administration (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
Ducks, Mallard, 5-days old, 10/dose.	0, 312, 625, 1250, 2500, or 5000 ppm in the diet for 5 days and then a basal diet for the next 3 days. [Test substance specified as Arsenal Herbicide.]	No mortality and no abnormal behavioral reactions or systemic signs of toxicity were observed. Gross pathological examination (4 each from the 0, 2500, and 5000 ppm dose group) revealed no abnormal tissue alterations. LC_{50} = >5000 ppm	Fletcher et al. 1984d MRID No. 00133776
Quail, Northern Bobwhite, young adults, 12 males and 24 females per dose.	0, 500, 1000, or 2000 ppm in the diet for 18 weeks. [50, 100, or 200 mg/kg bw based on measured food consumption (i.e., the birds consumed approximately 10% body weight as specified in Table I of the study)]. [Test material specified as AC 243,997 Technical.]	No significant reductions for any of the reproductive endpoints examined (i.e., egg production, hatchability, survival of hatchlings). NOEC for reproductive effects = 2000 ppm. Mortality among the birds was as follows: 0 ppm = 2M, 5F 500 ppm = 1M, 4F 1000 ppm = 1M, 3F 2000 ppm = 0M, 5F.	Fletcher et al. 1995a MRID No. 43831401
Ducks, Mallard, approximately 23-weeks old, 16/sex/dose.	0, 500, 1000, or 2000 ppm in the diet for 18 weeks. [50, 100, or 200 mg/kg bw based on measured food consumption (birds consumed approximately 10% body weight as specified in Table II of fiche.)] [Test material specified as AC 243,997 Technical.]	No significant reductions for any of the reproductive endpoints examined (i.e., egg production, hatchability, survival of hatchlings). NOEC for reproductive effects = 2000 ppm.	Fletcher et al. 1995b MRID No. 43831402

Appendix 3: Toxicity of Imazapyr to Terrestrial Plants.

Organism	Exposure	Response	Reference
Tier II non-target terrestrial plants. Expresses data in units of a.i., but indicates that assays were conducted on the acid. ∴a.i. = a.e.	Seed germination: cucumber, soybean, wheat, onions, peas, tomato, corn, sugar beets, sunflower, and oats. Seeds on filter paper in petri dish. Chemical dissolved in acetone/water. Each dish sprayed at rates from 0.035 to 1.12 kg/ha.	**Tomatoes:** EC_{50} = 1.120 kg/ha **Sugar beet:** EC_{25} = 0.140 kg/ha	American Cyanamid 1988b MRID No. 40811801
	Seedling emergence: corn, wheat, sugar beets, sunflower, tomato, cucumber, oats, onions, soybeans, and green peas. Each crop planted in 4-inch dixie cups filled with sand. Ten seeds per cup. Spray applications of 0.00219 to 1.12 kg/ha in acetone water solution.	**Sugar beet:** EC_{25} = 0.00219 kg/ha **Corn and Onions:** EC_{25} = 1.12 kg/ha No significant effect on other species.	American Cyanamid 1988b MRID No. 40811801
	Post-emergence/foliar applications. Green peas, soybeans, onions, corn, wheat, oats, sugar beets, sunflowers, tomatoes, and cucumbers. [All on fiche 2 of 2]. Green house at 24° C. Technical grade acid in 1:1 (v/v) solution of acetone and water and sprayed at 400 L/ha with laboratory belt sprayer. Tween 20 surfactant added to spray solution at 0.25% (v/v). Five seedlings per pot, 3-replicate pots per application rate. Two series of studies. In first, seedlings grown 13 days prior to treatment with application rates of 0.00219 to 1.12 kg/ha. In second part of study, used only corn, wheat, oats, sugar beets, sunflowers, cucumbers, and tomatoes. Larger seedlings grown for 28 days with application rates of 0.000068 to 0.01750 kg/ha.	All crops tested EC_{25} = 0.00219–0.00875 kg/ha EC_{50} = 0.00219–0.0175 kg/ha **Most tolerant:** Green peas. 100% injury at 0.14 kg/ha and higher. No significant injury at 0.00438 kg/ha and lower. **Study 1:** Based on heights, no significant injury at <0.0085 kg/ha. Based on weights, no significant injury at <0.035 kg/ha. Height is most sensitive objective endpoint. All plants died at 0.28 kg/ha and above. **Most Sensitive:** Sugar beets affected at rates of >0.000548 kg/ha.	American Cyanamid 1988b MRID No. 40811801

Appendix 3: Toxicity of Imazapyr to Terrestrial Plants.

Organism	Exposure	Response	Reference
		Study 1: Table 19 shows visual injury (50%) at lowest concentration tested (0.00219 kg/ha). Table 20 shows about 80% inhibition based on fresh weight at 0.00219 kg/ha. Table 21 shows about 40% inhibition based on height at 0.00219. All plants died at 0.00875 kg/ha and above. **Study 2:** Table 40 shows visual injury (50%) at about 0.001 kg/ha, similar to Study 1. Table 41 shows about 50% inhibition based on height at 0.00219 kg/ha, again consistent with Study 1. Table 22 shows about 50% inhibition based on weight at 0.00219. All plants died at 0.00875 kg/ha and above. Large seedlings tolerated higher levels than smaller seedlings. Monocots could tolerate up to 0.00875 kg/ha without damage. Dicots were more variable.	American Cyanamid 1988b MRID No. 40811801
Tier II non-target terrestrial plants vegetative vigor phytotoxicity.	A single application was made using an overhead track sprayer applied to emerged seedlings. 28-day observation period. Nominal concentrations of 0.00025, 0.0005, 0.001, 0.002, 0.004, and 0.008 lb a.i./acre applied to sugar beets. And nominal concentrations of 0.008, 0.018, 0.0036 (soybean only), 0.041, 0.091, 0.21, and 0.46 lb a.i./acre applied to onions and soybeans. [Test substance specified as AC 252.925 in a 2 lb per gallon aquesous salt (2AS) formulation.]	**Plant Survival** **Onion:** EC_{25} = 0.095 lb a.i./acre; EC_{50} = 0.16 lb a.i./acre; NOEC = 0.091 lb a.i./acre. **Soybean:** EC_{25} = >0.46 lb a.i./acre; EC_{50} = >0.46 lb a.i./acre; NOEC = 0.46 lb a.i./acre. **Sugar beet:** EC_{25} = 0.0033 lb a.i./acre; EC_{50} = 0.0049 lb a.i./acre; NOEC = 0.002 lb a.i./acre.	Christensen et al. 1995 MRID No. 43889101

Appendix 3: Toxicity of Imazapyr to Terrestrial Plants.

Organism	Exposure	Response	Reference
		Shoot Lengths **Onion:** EC_{25} = 0.036 lb a.i./acre; EC_{50} = 0.075 lb a.i./acre; NOEC = 0.018 lb a.i./acre. **Soybean:** EC_{25} = 0.043 lb a.i./acre; EC_{50} = 0.34 lb a.i./acre; NOEC = 0.002 lb a.i./acre. **Sugar beet:** EC_{25} = 0.0025 lb a.i./acre; EC_{50} = 0.0036 lb a.i./acre; NOEC=0.002 lb a.i./acre. **Shoot Dry Weights** **Onion:** EC_{25} = 0.035 lb a.i./acre; EC_{50} = 0.063 lb a.i./acre; NOEC = 0.018 lb a.i./acre. **Soybean:** EC_{25} = 0.083 lb a.i./acre; EC_{50} = 0.26 lb a.i./acre; NOEC = 0.041 lb a.i./acre **Sugar beet:** EC_{25} = 0.0021 lb a.i./acre; EC_{50} = 0.0027 lb a.i./acre; NOEC = 0.001 lb a.i./acre. Sugar beet was the most sensitive crop tested and resulted in the lowest NOEC (0.0010 lb a.i./acre for shoot dry weight) and EC_{25} (0.0021 lb a.i./acre for shoot dry weight).	
Barley, corn, cotton, sorghum, sugar beets, sun-flower, and wheat.	Sprayed application of 400 L/ha to give rates up to 63 g/ha; 34-day observation period. [Test substance specified as Arsenal Herbicide (technical grade, purity NOS.]	The test substance at 63 g/ha or less has little to no effect on the seedling emergence of the crop species tested. Higher levels delayed or significantly reduced seedling emergence. The test substance is a potent inhibitor of plant growth, at 63 g/ha, severe growth inhibition and mortality of all species tested. Sugar beets were noted with being the most susceptible and soybeans being the most tolerant.	Malefyt 1986 MRID No. 40003711
Corn, cucumber, oats, onion, peas,	Test substance sprayed into petri dishes (10 seeds per dish)	The test substance has no statistically significant effect on	Malegyt 1990a MRID No. 93048029

Appendix 3: Toxicity of Imazapyr to Terrestrial Plants.

Organism	Exposure	Response	Reference
soybean, sugar beets, sunflowers, tomatoes, and wheat.	at a concentration of 35, 70, 140, 280, 560, and 1120 g/ha. [Test substance specified as AC 243,997 (99.1% purity).]	the germination of cucumber, soybean, wheat, onion, and peas. Tomatoes and corn showed a significant reduction in germination at the highest rate of 1.12 kg/ha. No significant reduction was observed at lower rates. Sugar beet, sunflower, and oats showed some reduction in germination at ceratin rates. A 25% detrimental effect level on seed germination was not obtained an any rate with cucumber, soybean, wheat, onions, peas, corn, or sunflower. A 25% detrimental effect level was observed at rates >14 kg/ha in sugar beets, and a 50% effect was observed at 1.12 kg/ha in tomatoes, and at various rates with oats.	
Corn, cucumber, oats, onions, peas, soybeans, sugar beets, sunglower, tomatoes, wheat (5/species/pot)	Test concentrations of 0.068, 0.137, 0.274, 0.548, 1.095, 2.19, 4.38, 8.75, and 17.5 g/ha for sugar beets, corn, and oats. For wheat, sunfloer, and cucumbers the lowest three rates were dropped and 35, 70, and 140 g/ha were added. [Test substance specified as AC 243,997 (99.1% purity).]	Green peas were the most tolerant crop species to post-emergence applications of the test substance. All other crop species tested shower higher sensitivity. Sugar beets were the most sensitive, they were affected at rates of 0.548 g/ah. Larger seedlings were able to tolerate higher levels than smaller seedlings. The monocot species could withstand up to 8.75 g/ha without noticeable crop injury. Dicot species were more variable in the amount of material they could tolerate. Larger seeded species were able to tolerate higher levels than smaller seeded species.	Malefyt 1990b MRID No. 93048030

Appendix 4: Toxicity of Imazapyr to Fish, Aquatic Invertebrates, and Aquatic Plants.

Organism	Exposure	Response	Reference
FISH			
Sunfish, Bluegill (*Lepomis macrochirus*), 10/concentration.	Nominal concentrations of the test substance were 0, 56, 100, 180, 320, 560, and 1000 mg/L. [Test substance specified as AC 252,925 (combination of AC 243,997 with isopropyl-amine in water).]	No mortality at any level tested. 96-hour LC_{50} = >1000 mg/L	Cohle and McAllister 1984a MRID No. 00147116
Sunfish, Bluegill (*Lepomis macrochirus*), 10/concentration.	Nominal concentrations of the test substance were 0, 56, 100, 180, 320, 560, and 1000 mg/L (81–93% nominal). [Test substance specified as Arsenal Herbicide (22.6% purity).]	Abnormal effects associated with mortality in responding fish included dark and light dicoloration and quiescence were observed at all concentrations during the 96-hour exposure period. Mortality data at 96 hours is as follows: 56 (1/10); 100 (2/10); 180 (6/10); 320 (7/10); 560 (9/10); and 1000 mg/L (10/10). 96-hour LC_{50} = 180 mg/L	Cohle and McAllister 1984b MRID No. 00153777
Trout, Rainbow (*Salmo gairdneri*), 10/concentration.	Nominal concentrations of the test substance were 0, 32, 56, 100, 180, and 320 mg/L. [Test substance specified as Arsenal Herbicide (22.6% purity).]	Abnormal effects of mortality included surfacing, loss of equilibrium, dark discolor-ation, fish on the bottom and quiescence were observed in the 32, 100, 180, and 320 mg/L test concentrations during the 96-hour exposure period. Mortality data at 96 hours is as follows: 32 (1/10); 100 (4/10); 180 (9/10); and 320 mg/L (9/10). 96-hour LC_{50} = 110 mg/L	Cohle and McAllister 1984c MRID No. 00153778
Trout, Rainbow (*Salmo gairdneri*), 20/concentration.	Mean measured concentrations of a.e. were 13, 29, 39, 68, and 110 mg a.e./L. [Test substance specified as Arsenal Herbicide (21.5% imazapyr).]	No test substance-related mortalities occurred. 96-hour LC_{50} = >110 mg a.e./L	Drotter et al. 1995 MRID No. 45119713

Appendix 4: Toxicity of Imazapyr to Fish, Aquatic Invertebrates, and Aquatic Plants (listed alphabetically by author) *(continued)*.

Organism	Exposure	Response	Reference
FISH *(continued)*			
Fathead minnow (*Pimephales promelas*).	Nominal concentrations of 7.5, 15, 30, 60, and 120 mg a.i./L. [Test substance specified as AC 342997 (purity NOS).]	There was no apparent treatment-related effects on time to hatch, hatching success, reproduction, or growth of fathead minnow for a life-cycle toxicity test. All biological parameters measured in the treatment groups were comparable and not statistically differ ($p>0.05$) to negative control fish. NOEC = 120 mg a.i./L LOEC = >120 mg a.i./L MATC = >120 mg a.i./L	Drotter et al. 1998 MRID No. 45119711
Fathead minnow (*Pimephales promelas*), 20 per replicates, 4 replicates.	Mean measured concentrations of 7.4, 15, 31, 62, and 118 mg a.i./L. [Test substance specified as AC 342997 (99.6% purity).]	No apparent treatment-related effects on time to hatch, hatching success, survival, or growth of fathead minnow for 28-days post-hatch. NOEC = >118 mg a.i./L LOEC = >118 mg a.i./L MATC = >118 mg a.i./L	Drotter et al. 1999 MRID No. 45119712
Sunfish, Bluegill (*Lepomis macrochirus*).	Nominal concentrations of the test substance were 0, 10, 18, 32, 53, and 100 mg/L (81–93% nominal). [Test substance specified as AC 243,997 (99.5% purity).]	96-hour LC_{50} = >100 mg/L	Kintner and Forbis 1983a MRID No. 00133549
Silversides, Atlantic (*Menidia menidia*).	Mean measured concentrations of the test substance were 0, 23.2, 39.5, 58.1, 112, and 184 mg/L (81–93% nominal). [Test substance specified as AC 243,997 (99.5% purity).]	The test substance was not acutely toxic at concentrations up to 184 mg/L. After 96 hours of exposure, mortality did not exceed 5% in any of the test concentrations. 96-hour LC_{50} = 184 mg/L	Manning 1989a MRID No. 41315801

Appendix 4: Toxicity of Imazapyr to Fish, Aquatic Invertebrates, and Aquatic Plants (listed alphabetically by author) *(continued)*.

Organism	Exposure	Response	Reference
FISH *(continued)*			
Trout, Rainbow, early life-stage (28-day post swim-up), 20 trout per concentration.	Measured concentrations of 0, 6.59, 12.1, 24.0, 43.1, or 92.4 mg/L for 62 days. Flow-through freshwater toxicity test. [Test material specified as AC 243,997.]	No statistical effects on hatching, survival, or growth. Investigators report a "*nearly significant effect on hatching in the 92.4 mg/L concentration and an observed reduction on survival at the same concentration*"; however, in the conclusion of the study, the investigators discount the significance of the effects due to a "*lack of a correlation to test concentration and lack of corresponding reductions in wet and dry weights*."	Manning 1989b MRID No. 41315804
Trout, Rainbow Sunfish, Bluegill Catfish, Channel	96-hours	LC_{50} >100 mg/L	Peoples 1984 Gagne et al. 1991
Nile tilapia (*Tilapia nilotica*).	Static acute toxicity testing in 2–3 cm fingerlings.	24-hour LC_{50} = 4670 µg/L (4442–4919 µg/L); 48-hour LC_{50} = 4630 µg/L (95% CI: not indicated); 72-hour LC_{50} = 4610 µg/L (95% CI: 4307–4878 µg/L); 96-hour LC_{50} = 4360 µg/L (95% CI: 4207–4529 µg/L).	Songklanakarin 1981
Silver barb (*Barbus gonionotus*).	Static acute toxicity testing in 2–3 cm fingerlings.	24-hour LC_{50} = 2706 µg/L (95% CI: 2664–2746 µg/L); 96-hour LC_{50} = 2706 µg/L (95% CI: 2664–2746 µg/L).	Songklanakarin 1981

Appendix 4: Toxicity of Imazapyr to Fish, Aquatic Invertebrates, and Aquatic Plants (listed alphabetically by author) *(continued)*.

Organism	Exposure	Response	Reference
AQUATIC INVERTEBRATES			
Daphnia magna	Nominal concentrations of the test substance were 0, 32, 56, 100, 180, 320, 560, and 1000 mg/L. [Test substance specified as Arsenal Herbicide (22.6% purity).]	The NOEC was 180 mg/L after 48 hours, based on the lack of mortality and abnormal effects. Mortality data at 48 hours is as follows: 320 (45%), 560 (90%), and 1000 mg/L (100%). 48-hour LC_{50} = 350 mg/L	Forbis et al. 1984 MRID No. 00153779
AQUATIC INVERTEBRATES *(continued)*			
Daphnia magna, <24-hours old, 5 replicates per concentration, 10 animals per replicate.	0, 10, 18, 32, 56, or 100 mg/L for 24 or 48 hours, static, no aeration. [Test material specified as AC 243,997 Technical.]	No mortality at 24 or 48 hours of exposure. 24-hour LC_{50} = >100 mg/L 48-hour LC_{50} = >100 mg/L	Kintner and Forbis, 1983b MRID No. 00133550
Daphnia magna, <26-hours old, 4 replicates per concentration, 10 animals per replicate.	Measured concentrations of <2.63 (control) 5.73, 11.7, 23.8, 45.6, or 97.1 mg/L in a 21-day flow-through test. [Test material specified as AC 243,997 (99.5% a.i.)]	No adverse effects on survival, reproduction, or growth of 1st generation. 7-, 14- and 21-day LC_{50} = >97.1 mg/L; NOEC = 97.1 mg/L; MATC = >97.1 mg/L.	Manning 1989c MRID No. 41315805
MOLLUSKS			
Clam, freshwater (*Corbicula fluminea*), 400 clams.	Single application of a nominal concentrations of 0 or 0.091 lb a.e./acre to a model freshwater pool system. 28-day observation period. [Test substance specified as Arsenal Herbicide (purity NOS).]	The concentrations of the test substance in clam tissue was less than the limit of quantitation (<50 ppb) during the conduct of the test.	Christensen et al. 1999 MRID No. 45119722
Oyster, Eastern (*Crassosstrea virginica*) and Grass shrimp (*Paleomonetes pugio*).	The bioconcentration test consisted of a 28-day uptake phase followed by a 14-day depuration phase. During the uptake phase, test concentrations consisted of a mixture of radio-labelled or non-radiolabelled test substance at a total nominal concentration of 0.25 mg a.i./L. [Test substance specified as AC 243,997 (purity NOS).]	The test substance was not found to bioconcentrate in the Eastern oyster. Tissue concentrations of the test substance did not exceed the exposure concentration. Steady-state BCF = <1 (not calculable) Uptake rate = not calculable Depuration rate = not calculable	Drotter et al. 1996 MRID No. 45119709

Appendix 4: Toxicity of Imazapyr to Fish, Aquatic Invertebrates, and Aquatic Plants (listed alphabetically by author) *(continued)*.

Organism	Exposure	Response	Reference
MOLLUSKS *(continued)*			
Oyster, Eastern (*Crassosstrea virginica*), 20/concentration.	Mean measure concentrations of 16, 27, 46, 80, and 132 mg a.i./L. 96-hour flow-through test. [Test substance specified as AC 243,997 (99.6% purity).]	Mean oyster new shell deposition (growth) in the negative control was 2.46 mm. Mean shell growth in the 16, 27, 46, 80, and 132 mg a.i./L treatment groups was 2.51, 2.72, 2.70, 2.05, and 2.03 mm, respectively. Oyster shell growth was not significantly reduced in any treatment group. When compared to negative control, percentage of shell growth inhibition ranged from -11% in the 27 mg a.i./L to 17% in the 80 and 132 mg a.i./L treatment groups.	Drotter et al. 1997 MRID No. 45119710
Oyster, Eastern (*Crassostrea virginica*).	Measured concentrations of the test substance were <10.5, 21.5, 42.4, 65.5, 109, and 173 mg/L. [Test substance specified as AC 243,997 (99.5%).]	Mean new shell growth ranged from 1.25 mm in the 21.5 mg/L to 0.69 mm in the 173 mg/L test concentration. No mortality occurred at any test concentrations. There was a concentration-response relationship; the percentage reduction in new shell growth ranged from 8% (21.5 mg/L) to 49% (173 mg/L). There was a statistical difference in new shell growth between the oysters exposed to 173 mg/L and the controls. NOEC is 109 mg/L. Authors state that "*there was no correlation with pH and test concentration; the higher the concentration the lower the pH. The effect observed at 173 mg/L may have been a response of the lower pH rather than directly to the test substance*." 96-hour EC_{50} = >173 mg/L	Ward 1989 MRID No. 41315802

Appendix 4: Toxicity of Imazapyr to Fish, Aquatic Invertebrates, and Aquatic Plants (listed alphabetically by author) *(continued)*.

Organism	Exposure	Response	Reference
AQUATIC MACROPHYTES			
Duckweed, water hyacinth, and water lettuce.	0.5 lb a.e./acre. [Test substance specified as AC 252,925 (purity NOS).]	At 0.5 lb a.e./acre provided 98–100% control 10 weeks after application.	Herrick 1986 MRID No. 40003710
Alligatorweed, lemon bacopa.	0.75 lb a.e./acre. [Test substance specified as AC 252,925 (purity NOS).]	85% control after 8 weeks of treatment for alligator weed and ineffective against lemon bacopa.	Herrick 1986 MRID No. 40003710
Egeriua, Elodea, hydrilla, southern naiad, fanwort, coontail, and Water-milfoil.	0.5 lb a.e./acre. [Test substance specified as AC 252,925 (purity NOS).]	Control achieved 10 weeks after treatment for Egeriua, Elodea, hydrilla, southern naiad, but less affective for fanwort, coontail, and Water-milfoil.	Herrick 1986 MRID No. 40003710
Lemna gibba	Nominal concentrations of 0, 0.01, 0.018, 0.032, 0.056, and 0.100 mg a.e./L for 14 days. Static. Measured concentrations not reported.	Frond counts EC_{25} = 0.013 (0.009–0.019) mg/L EC_{50} = 0.024 (0.016–0.033) mg/L An NOEC is not defined. At lowest concentration tested, 0.01 mg/L, 15.1 % inhibition.	Hughes 1987 MRID No. 40811802
Lemna gibba	Nominal concentrations of 0, 6.3, 12.6, 25.2, 50.4, and 100 µg a.i./L (ppb). [Test substance specified as AC 252,925 2 AS (purity NOS).]	The fronds in the 22.2, 46.3, and 96.5 µg a.i./L treatment concentrations were smaller than the controls at day 7. The fronds in the 46.3 µg a.i./L were also misshapen at test termination (day 14), with daughter fronds growing an atypically long and thin shoots. No visual phytotoxic effects were observed in concentrations >13.0 µg a.i./L. NOEC was 13.0 µg a.i./L. EC_{25} = 14.1 µg a.i./L EC_{50} = 22.8 µg a.i./L	Hughes et al. 1995 MRID No. 43889102

Appendix 4: Toxicity of Imazapyr to Fish, Aquatic Invertebrates, and Aquatic Plants (listed alphabetically by author) *(continued)*.

Organism	Exposure	Response	Reference
Myriophillum sibricium	14-day static exposure to nominal concentrations of imazapyr. Concentration range used NOS. [Test substance specified as Arsenal.]	Shoot growth EC_{25} = 0.013 mg a.i./L; EC_{50} = 0.032 mg a.i./L. Root number EC_{25} = 0.022 mg a.i./L; EC_{50} = 0.029 mg a.i./L. Root growth (dry mass) EC_{25} = 0.0079 mg a.i./L; EC_{50} = 0.0099 mg a.i./L.	Roshon et al. 1999
UNICELLULAR ALGAE			
Chara and Cladophora algae	[Test substance specified as AC 252,925 (purity NOS).]	Results 10 weeks after treatment showed algae were resistant to the test substance at all rates applied.	Herrick 1986 MRID No. 40003710
Selenastrum capriconutum, a green algae.	Nominal concentrations of 10–100 mg a.e./L. Mean measured concentrations of 9.4–101.2 mg/L. 7-day exposure.	Only the highest concentration caused inhibition (99.9%). Lower concentration (56 mg/L and less) caused stimulation. Based on cell density, EC_{25} of 48 mg/L and EC_{50} of 71 mg/L. Confidence intervals not provided.	Hughes 1987 MRID No. 40811802
Anabaen flosaquae, a blue-green algae.	Nominal concentrations of 0, 5.6, 10, 18, 32, 52, and 100 mg a.e./L for 7 days. Note: Study says a.i. but only identifies the material as AC 243,997. The water solubility that they give is that of the acid.	EC_{25} for cell count 7.3 (<0.0001–51.4) mg/L EC_{50} for cell count 11.7 (<0.0001–105.5) mg/L	Hughes 1987 MRID No. 40811802
Naviculla pelliculosa, a freshwater diatom.	Concentrations of 10 to 100 mg a.e./L for 7 days. Static.	All concentrations caused stimulation rather than inhibition of cell number. Extent of stimulation was 1.6 to 17% with no apparent dose/response relationship.	Hughes 1987 MRID No. 40811802
Skeletonema costatum, a marine diatom.	Nominal concentrations of 10–100 mg a.e./L. Mean measured concentrations of 8.9–90.5 mg/L. 7-day exposure.	Cell density EC_{25} = 42.2 mg/L EC_{50} = 85.5 mg/L Confidence limits could not be determined.	Hughes 1987 MRID No. 40811802

Appendix 4: Toxicity of Imazapyr to Fish, Aquatic Invertebrates, and Aquatic Plants (listed alphabetically by author) *(continued)*.

Organism	Exposure	Response	Reference
Chlorella emersonii, a green algae.	Concentrations ranging from 1 µM [0.261 mg/L] to about 100 µM [26.1 mg/L].	IC_{50} for growth of about 0.8 µM [≈0.2 mg/L] taken from Figure 1, p. 2. Resistant strains of *Chlorella* had about 10-fold higher IC_{50}s.	Landstein et al. 1993