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Metsulfuron Methyl - Human Health and Ecological Risk Assessment – Final Report

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TABLE OF CONTENTS

TABLE OF CONTENTS	ii
LIST OF APPENDICES	v
LIST OF TABLES	vi
ACRONYMS, ABBREVIATIONS, AND SYMBOLS	vii
COMMON UNIT CONVERSIONS AND ABBREVIATIONS	ix
CONVERSION OF SCIENTIFIC NOTATION	x
EXECUTIVE SUMMARY	xi
1. INTRODUCTION	1-1
2. PROGRAM DESCRIPTION	2-1
2.1. OVERVIEW	2-1
2.2. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS	2-1
2.3. APPLICATION METHODS	2-2
2.4. MIXING AND APPLICATION RATES	2-3
2.5. USE STATISTICS	2-4
3. HUMAN HEALTH RISK ASSESSMENT	3-1
3.1. HAZARD IDENTIFICATION	3-1
3.1.1. Overview.	3-1
3.1.2. Mechanism of Action.	3-2
3.1.3. Kinetics and Metabolism.	3-2
3.1.4. Acute Oral Toxicity.	3-3
3.1.5. Subchronic or Chronic Systemic Toxic Effects.	3-4
3.1.6. Effects on Nervous System.	3-5
3.1.7. Effects on Immune System.	3-5
3.1.8. Effects on Endocrine System.	3-5
3.1.9. Reproductive and Teratogenic Effects.	3-6
3.1.10. Carcinogenicity and Mutagenicity.	3-6
3.1.11. Irritation and Sensitization (Effects on the Skin and Eyes).	3-7
3.1.12. Systemic Toxic Effects from Dermal Exposure.	3-7
3.1.13. Inhalation Exposure.	3-8
3.1.14. Inerts and Adjuvants.	3-8
3.1.15. Impurities and Metabolites.	3-9
3.1.16. Toxicological Interactions	3-10

TABLE OF CONTENTS (continued)

3.2. EXPOSURE ASSESSMENT	3-11
3.2.1. Overview.	3-11
3.2.2. Workers.	3-11
3.2.2.1. General Exposures	3-12
3.2.2.2. Accidental Exposures	3-13
3.2.3. General Public.	3-15
3.2.3.1. General Considerations	3-15
3.2.3.2. Direct Spray	3-15
3.2.3.3. Dermal Exposure from Contaminated Vegetation	3-15
3.2.3.4. Contaminated Water	3-16
3.2.3.4.1. Acute Exposure	3-16
3.2.3.4.2. Longer-term Exposure	3-18
3.2.3.5. Oral Exposure from Contaminated Fish	3-18
3.2.3.6. Oral Exposure from Contaminated Vegetation	3-19
3.3. DOSE-RESPONSE ASSESSMENT	3-21
3.3.1. Overview	3-21
3.3.2. Existing Guidelines	3-21
3.3.2. Acute RfD	3-21
3.4. RISK CHARACTERIZATION	3-23
3.4.1. Overview	3-23
3.4.2. Workers	3-23
3.4.3. General Public.	3-24
3.4.4. Sensitive Subgroups.	3-24
3.4.5. Connected Actions.	3-25
3.4.6. Cumulative Effects.	3-25
4. ECOLOGICAL RISK ASSESSMENT	4-1
4.1. HAZARD IDENTIFICATION	4-1
4.1.1. Overview.	4-1
4.1.2. Toxicity to Terrestrial Organisms.	4-1
4.1.2.1. Mammals	4-1
4.1.2.2. Birds	4-2
4.1.2.3. Terrestrial Invertebrates	4-3
4.1.2.4. Terrestrial Plants (Macrophytes)	4-3
4.1.2.5. Terrestrial Microorganisms	4-5
4.1.3. Aquatic Organisms.	4-5
4.1.3.1. Fish	4-5
4.1.3.2. Amphibians	4-6
4.1.3.3. Aquatic Invertebrates	4-6
4.1.3.4. Aquatic Plants	4-6
4.1.3.5. Other Aquatic Microorganisms	4-7

TABLE OF CONTENTS (continued)

4.2. EXPOSURE ASSESSMENT	4-8
4.2.1. Overview.	4-8
4.2.2. Terrestrial Animals.	4-9
4.2.2.1. Direct Spray	4-10
4.2.2.2. Indirect Contact	4-11
4.2.2.3. Ingestion of Contaminated Vegetation or Prey	4-11
4.2.2.4. Ingestion of Contaminated Water	4-13
4.2.3. Terrestrial Plants.	4-13
4.2.3.1. Direct Spray	4-13
4.2.3.2. Off-Site Drift	4-13
4.2.3.3. Runoff	4-15
4.2.3.4. Contaminated Irrigation Water	4-15
4.2.3.5. Wind Erosion	4-16
4.2.4. Soil Organisms.	4-17
4.2.5. Aquatic Organisms.	4-17
4.3. DOSE-RESPONSE ASSESSMENT	4-18
4.3.1. Overview.	4-18
4.3.2. Toxicity to Terrestrial Organisms.	4-19
4.3.2.1. Mammals	4-19
4.3.2.2. Birds	4-19
4.3.2.3. Terrestrial Invertebrates	4-20
4.3.2.4. Terrestrial Plants (Macrophytes)	4-21
4.3.2.5. Terrestrial Microorganisms	4-21
4.3.3. Aquatic Organisms.	4-21
4.3.3.1. Fish	4-21
4.3.3.2. Aquatic Invertebrates	4-22
4.3.3.3. Aquatic Plants	4-22
4.3.3.4. Aquatic Microorganisms	4-22
4.4. RISK CHARACTERIZATION	4-23
4.4.1. Overview.	4-23
4.4.2. Terrestrial Organisms.	4-24
4.4.2.1. Terrestrial Vertebrates	4-24
4.4.2.2. Terrestrial Invertebrates	4-25
4.4.2.3. Soil Microorganisms	4-25
4.4.2.2. Terrestrial Plants	4-27
4.4.3. Aquatic Organisms.	4-27
4.4.3.1. Aquatic Animals	4-27
4.4.3.2. Aquatic Plants	4-27
4.4.3.3. Aquatic Microorganisms	4-28
5. REFERENCES	5-1

LIST OF APPENDICES

- Appendix 1:** Acute toxicity of metsulfuron methyl to experimental mammals
- Appendix 2:** Toxicity of metsulfuron methyl to birds
- Appendix 3:** Toxicity of metsulfuron methyl to terrestrial invertebrates
- Appendix 4:** Toxicity of metsulfuron methyl to terrestrial plants
- Appendix 5:** Toxicity of metsulfuron methyl to fish
- Appendix 6:** Toxicity of metsulfuron methyl to aquatic invertebrates
- Appendix 7:** Toxicity of metsulfuron methyl to aquatic plants
- Appendix 8:** Laboratory and simulation studies on the environmental fate of metsulfuron methyl

LIST OF TABLES

Table 2-1: Identification and physical/chemical properties of metsulfuron methyl	Tables-1
Table 2-2: Use of Metsulfuron Methyl by USDA Forest Service in 2001	Tables-2
Table 2-3: Use of metsulfuron methyl by USDA Forest Service in 2001 by Region	Tables-3
Table 3-1: Summary of toxicity tests of triazine amine, a plant and animal metabolite of metsulfuron methyl	Tables-4
Table 3-2: Chemical and site parameters used in GLEAMS Modeling for metsulfuron methyl	Tables-5
Table 3-3: Summary of modeled concentrations of metsulfuron methyl in streams	Tables-6
Table 3-4: Summary of modeled concentrations of metsulfuron methyl in ponds	Tables-7
Table 4-1: Summary of modeled concentrations of metsulfuron methyl in soil	Tables-8

LIST OF FIGURES

Figure 2-1. Use of metsulfuron methyl by the USDA Forest Service in various regions of the United States based on percentages of total use by the Forest Service	Figures-1
Figure 2-2 Agricultural used of metsulfuron methyl in the United States for 1992	Figures-2

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

LIST OF WORKSHEETS

Supplement 1: Metsulfuron methyl – WordPerfect Worksheets for Human Health and Ecological Risk Assessments, SERA WPWS 04-43-17-01b, Version 2.04d, dated December 8, 2004.	
Supplement 2: Metsulfuron Methyl – EXCEL Worksheets for Human Health and Ecological Risk Assessments, SERA EXWS 04-43-17-01b, Version 2.04d, dated December 8, 2004.	

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
m	meter
M	male
MMAD	mass median aerodynamic diameter
MCS	multiple chemical sensitivity

ACRONYMS, ABBREVIATIONS, AND SYMBOLS (*continued*)

mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
MOS	margin of safety
MRID	Master Record Identification Number
MSDS	material safety data sheet
MW	molecular weight
NCI	National Cancer Institute
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOS	not otherwise specified
NRC	National Research Council
NTP	National Toxicology Program
OM	organic matter
OPP	Office of Pesticide Programs
OPPTS	Office of Pesticide Planning and Toxic Substances
OSHA	Occupational Safety and Health Administration
ppm	parts per million
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SRC	Syracuse Research Corporation
UF	uncertainty factor
U.S.	United States
USDA	U.S. Department of Agriculture
U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey
WHO	World Health Organization
μ	micron
\blacktriangleright	greater than
\geq	greater than or equal to
$<$	less than
\leq	less than or equal to
$=$	equal to
\approx	approximately equal to
\sim	approximately

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, (lb)	0.002205
hectares (ha)	acres	2.471
inches (in)	centimeters (cm)	2.540
kilograms (kg)	ounces, (oz)	35.274
kilograms (kg)	pounds, (lb)	2.2046
kilograms per hectare (kg/ha)	pounds per acre (lb/acre)	0.892
kilometers (km)	miles (mi)	0.6214
liters (L)	cubic centimeters (cm ³)	1,000
liters (L)	gallons (gal)	0.2642
liters (L)	ounces, fluid (oz)	33.814
miles (mi)	kilometers (km)	1.609
miles per hour (mi/hr)	cm/sec	44.70
milligrams (mg)	ounces (oz)	0.000035
meters (m)	feet	3.281
ounces (oz)	grams (g)	28.3495
ounces per acre (oz/acre)	grams per hectare (g/ha)	70.1
ounces per acre (oz/acre)	kilograms per hectare (kg/ha)	0.0701
ounces fluid	cubic centimeters (cm ³)	29.5735
pounds (lb)	grams (g)	453.6
pounds (lb)	kilograms (kg)	0.4536
pounds per acre (lb/acre)	kilograms per hectare (kg/ha)	1.121
pounds per acre (lb/acre)	mg/square meter (mg/m ²)	112.1
pounds per acre (lb/acre)	µg/square centimeter (µg/cm ²)	11.21
pounds per gallon (lb/gal)	grams per liter (g/L)	119.8
square centimeters (cm ²)	square inches (in ²)	0.155
square centimeters (cm ²)	square meters (m ²)	0.0001
square meters (m ²)	square centimeters (cm ²)	10,000
yards	meters	0.9144

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

CONVERSION OF SCIENTIFIC NOTATION

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

EXECUTIVE SUMMARY

OVERVIEW

Metsulfuron methyl is an effective and potent herbicide. Adverse effects on some nontarget terrestrial plant species and, to a lesser degree, some aquatic plant species are plausible unless measures are taken to limit exposure. For terrestrial plants, the dominant factor in the risk characterization is the potency of metsulfuron methyl relative to the application rate. The typical application rate considered in this risk assessment, 0.03 lb/acre, is over 800 times higher than the NOEC in the vegetative vigor (direct spray) assay of the most sensitive nontarget species – i.e., 0.000037 lb/acre – and approximately 8 times higher than the NOEC for the most tolerant species in the same assay – i.e., 0.0039 lb/acre. The highest application rate that may be considered in Forest Service programs – i.e., 0.15 lb/acre – is over 4000 times the NOEC in sensitive species and a factor of about 40 above the NOEC in tolerant species. Given these relationships, damage to sensitive nontarget species could be expected in ground broadcast applications at distances of about 500 feet from the application site in areas in which off-site drift is not reduced by foliar interception. This risk characterization applies only to ground broadcast applications. When used in directed foliar applications (i.e., backpack), offsite drift could be reduced substantially but the extent of this reduction cannot be quantified.

Damage to aquatic plants, particularly macrophytes, appears substantially less than for terrestrial plants. Except for the hazard quotient of 2 associated with acute exposures based on the peak concentrations of metsulfuron methyl, all hazard quotients are below the level of concern, with a range of 0.002 to 2 for acute exposures and 0.02 to 0.08 for chronic exposures. Thus, if metsulfuron methyl is applied in areas where transport to water containing aquatic macrophytes is likely, it would be plausible that detectable damage could be observed.

Aquatic algae do not appear to be as sensitive to metsulfuron methyl. The highest hazard quotient observed for acute exposure is 0.03 associated with the upper range for the most sensitive species. For chronic exposures, the highest hazard quotient is 0.001 associated with the upper range for the most sensitive species. Therefore, it is not anticipated that adverse effects in aquatic algae would result from exposure to metsulfuron methyl at application rates used by the Forest Service.

Just as there is little reason to doubt that adverse effects on some plant species are plausible, there is no clear basis for suggesting that effects on terrestrial or aquatic animals are likely or would be substantial.

PROGRAM DESCRIPTION

Metsulfuron methyl is a selective pre-emergence and post-emergence sulfonyl urea herbicide used primarily to control many annual and perennial weeds and woody plants. The Forest Service uses only one commercial formulation of metsulfuron methyl, Escort® XP. Escort is manufactured by Du Pont as a dry flowable granule. The composition of the product is 60% metsulfuron methyl and 40% inert ingredients.

Metsulfuron methyl is used in Forest Service programs primarily for the control of noxious weeds. Minor uses include conifer release and rights-of-way management. The most common

methods of ground application for Escort XP involve backpack (selective foliar) and boom spray (broadcast foliar) operations. The Forest Service does not use aerial applications for Escort XP. Nonetheless, Escort XP is registered for aerial applications and aerial applications are included in this risk assessment in the event the Forest Service may wish to consider this application method. For this risk assessment, the typical rate of 0.03 lbs/acre, with a range 0.0125 to 0.15 lbs/acre, is used to reflect Forest Service practice. This range is based on lowest and highest labeled application rates recommended on the manufacturer's label. The Forest Service used approximately 235 lbs of metsulfuron methyl in 2002, the most recent year for which use statistics are available. Much greater amounts of metsulfuron methyl are used in agriculture (e.g., about 35,543 lbs in 1992).

HUMAN HEALTH RISK ASSESSMENT

Hazard Identification –In experimental mammals, the acute oral LD₅₀ for metsulfuron methyl is greater than 5000 mg/kg, which indicates a low order of toxicity. In addition, non-lethal signs of toxicity were apparent after single oral doses as low as 50 mg/kg. The most common sign of acute, subchronic, and chronic toxicity is decreased body weight gain. The only other commonly noted effect involves changes in various hematological parameters as well as changes in absolute and relative organ weights. None of these changes, however, suggest a clear or specific target organ toxicity. There is speculation that the effects of metsulfuron methyl on the blood might be related to saccharin, which is a metabolite of metsulfuron methyl. At very high doses, saccharin caused hematological effects in mice. Appropriate tests have provided no evidence that metsulfuron methyl presents any reproductive risks or causes malformations or cancer. Metsulfuron methyl also is irritating to the skin and eyes, but does not produce sensitizing effects following repeated dermal exposure.

Limited information is available on the toxicokinetics of metsulfuron methyl. The kinetics of absorption of metsulfuron methyl following dermal, oral or inhalation exposure are not documented in the available literature. Metsulfuron methyl is eliminated from the body by a combination of excretion of the unchanged compound and metabolism. In all species, metsulfuron methyl is eliminated rapidly with a half-time of 1 day or less and exhibits first order elimination kinetics. Most of the material is excreted as the unchanged compound. The primary excretory compartment for metsulfuron methyl and its metabolites is the urine, with smaller amounts excreted in the feces. In rats, metabolism of metsulfuron methyl appears to follow two main pathways, either hydrolysis to the corresponding sulfonamide or cleavage of the heterocycle ring.

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

The inhalation toxicity of metsulfuron methyl is not well documented in the literature. Available studies indicate that metsulfuron methyl induces irritant effects at very high exposure levels. Regardless, the potential inhalation toxicity of metsulfuron methyl is not of substantial concern to this risk assessment because of the implausibility of inhalation exposure involving high concentrations of this compound.

Exposure Assessment – Exposure assessments are conducted for both workers and members of the general public for the typical application rate of 0.03 lb/acre. The consequences of using the maximum application rate that might be used by the Forest Service, 0.15 lb/acre, are discussed in the risk characterization.

For workers, three types of application methods are generally modeled in Forest Service risk assessments: directed ground, broadcast ground, and aerial. Although Escort is registered for aerial applications (helicopter and sometimes fixed wing), the Forest Service does not currently use this method. Nonetheless, the aerial application method is included in this risk assessment in the event that the Forest Service considers using aerial applications. Central estimates of exposure for ground workers are approximately 0.0004 mg/kg/day for directed ground spray and 0.0007 mg/kg/day for broadcast ground spray. Upper range of exposures are approximately 0.0024 mg/kg/day for directed ground spray and 0.0045 mg/kg/day for broadcast ground spray. All of the accidental exposure scenarios for workers involve dermal exposures and all of these accidental exposures lead to estimates of dose that are either in the range of or substantially below the general exposure estimates for workers.

For the general public, the range of acute exposures is from approximately 0.000000014 mg/kg associated with the lower range for consumption of contaminated stream water by a child to 0.034 mg/kg/day associated with the upper range for consumption of contaminated water by a child following an accidental spill of metsulfuron methyl into a small pond. For chronic or longer term exposures, the modeled exposures are much lower than for acute exposures, ranging from approximately 0.0000000026 mg/kg/day associated with the lower range for the normal consumption of fish to approximately 0.0024 mg/kg/day associated with the upper range for consumption of contaminated fruit.

Dose-Response Assessment – The Office of Pesticide Programs of the U.S. EPA has derived a chronic RfD of 0.25 mg/kg/day for metsulfuron methyl. This RfD is based on a chronic rat NOAEL of 25 mg/kg/day (500 ppm in the diet) (Burns 1994) and an uncertainty factor of 100. In the same study, the LOAEL was 250 mg/kg/day (5000 ppm in the diet) and the only effect noted was a decrease in body weight. No frank signs of toxicity were seen at this or higher dose levels. The U.S. EPA (2002) did not explicitly derive an acute/single dose RfD for metsulfuron methyl. However, the U.S. EPA Office of Pesticides (U.S. EPA 2002) reported a short- and intermediate term oral exposure NOAEL of 34 mg/kg/day (for decreased body weight), a LOAEL of 342 mg/kg/day and a margin of exposure of 100. Thus, a functional acute RfD could be calculated as 0.34 mg/kg/day [34 mg/kg/day ÷ 100]. However, since there is not a substantial difference between the functional acute RfD value of 0.34 mg/kg/day value and the chronic RfD value of 0.25 mg/kg/day, this risk assessment will take the more conservative approach and use the chronic RfD of 0.25 mg/kg/day to characterize all risks of acute or short-term exposures.

Risk Characterization – Typical exposures to metsulfuron methyl do not lead to estimated doses that exceed a level of concern. For workers, no exposure scenarios, acute or chronic, exceeds the RfD even at the upper ranges of estimated dose. For members of the general public, all upper limits for hazard quotients are below a level of concern. Thus, based on the available information and under the foreseeable conditions of application, there is no route of exposure or scenario suggesting that workers or members of the general public will be at any substantial risk from longer-term exposure to metsulfuron methyl.

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

ECOLOGICAL RISK ASSESSMENT

Hazard Identification – The mammalian toxicity of metsulfuron methyl is relatively well characterized in experimental mammals; however, there is relatively little information regarding nontarget wildlife species. It seems reasonable to assume the most sensitive effects in wildlife mammalian species will be the same as those in experimental mammals (i.e., decreased body weight gain). Several acute toxicity studies and two reproduction studies are available on the toxicity of metsulfuron methyl to birds. These studies indicate that birds appear to be no more sensitive than experimental mammals to the toxic effects of metsulfuron methyl, with the major effect again being decrease body weight gain. There are also several acute assays on the honey bee that indicate that bees are no more sensitive than either mammals or birds to metsulfuron methyl. At exposure rates that exceed the highest recommended application rate by about a factor of 3, metsulfuron methyl appears to be somewhat toxic to the Rove beetle, *Aleochara bilineata*, causing a 15% decrease in egg hatching.

The toxicity of metsulfuron methyl to terrestrial plants was studied extensively and is well characterized. Metsulfuron methyl inhibits acetolactate synthase (ALS), an enzyme that catalyzes the biosynthesis of three branched-chain amino acids, all of which are essential for plant growth. Terrestrial microorganisms also have an enzyme that is involved in the synthesis of branched chain amino acids, which is functionally equivalent to the target enzyme in terrestrial macrophytes. There are laboratory and field studies on the effects of metsulfuron methyl to soil microorganisms. These studies suggest that transient effects on soil bacteria are plausible.

The available data suggest that metsulfuron methyl, like other herbicides, is much more toxic to aquatic plants than to aquatic animals. Frank toxic effects in fish are not likely to be observed at concentrations less than or equal to 1000 mg/L. Aquatic plants are far more sensitive than aquatic animals to the effects of metsulfuron methyl, with macrophytes appearing more sensitive than algae. Similar EC₅₀ values were observed in studies in duckweed and Northern watermilfoil. *Selenastrum capricornutum* appear to be the most sensitive species of algae and *Anabaena flosaquae* and *Navicula pelliculosa* appear to be the most tolerant species.

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 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 0.7 mg/kg under typical exposure conditions assuming 100% absorption. There is a wide range of exposures anticipated from the consumption of contaminated vegetation by terrestrial animals: central estimates range from 0.04 mg/kg for a small mammal to 0.8 mg/kg for a large bird under typical exposure conditions, with upper ranges of about 0.08 mg/kg for a small mammal and 2.3 mg/kg for a large bird. The consumption of contaminated water will generally lead to much lower levels of exposure. A similar pattern is seen for chronic exposures. The central estimated for daily doses for a small mammal from the consumption of contaminated vegetation at the application site is about 0.002 mg/kg/day, with an upper estimate of about 0.007 mg/kg/day. Exposures from contaminated vegetation far exceed doses that are anticipated from the consumption of contaminated water, which has a central estimate of about 0.0000009 mg/kg/day and an upper range of about 0.000002 for a small mammal. Based on general relationships of body size to body volume, larger vertebrates will be exposed to lower doses and smaller animals, such as insects, to much higher doses than small vertebrates under comparable exposure conditions. Because of the apparently low toxicity of metsulfuron methyl 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, 0.03 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 estimates are based on AgDRIFT modeling. The proportion of the applied amount transported off-site from runoff is based on GLEAMS modeling of clay, loam, and sand. The amount of metsulfuron methyl 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 estimated using 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. The peak estimated rate of contamination of ambient water associated with the normal application of metsulfuron methyl is 0.002 (0.00001 to 0.01) mg a.e./L at an application rate of 1 lb a.e./acre. For longer-term exposures, average estimated rate of contamination of ambient water associated with the normal application of metsulfuron methyl is 0.0002 (0.0001 to 0.0004) 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 for metsulfuron methyl is based on the same data as the human health risk assessment (i.e., the

chronic NOAEL of 25 mg/kg/day from a 2-year feeding study in rats is used to assess both acute and chronic risk). None of the exposure scenarios, acute or longer term, result in exposure estimates that exceed this NOAEL. Birds appear to be substantially less sensitive to metsulfuron methyl than mammals with an acute NOAEL of 1043 mg/kg/day from a 5-day feeding study and a longer-term NOAEL from a reproduction study of 120 mg/kg/day. For terrestrial invertebrates, based on direct spray studies in honey bees, no mortality would be expected following acute exposure to doses up to 270 mg/kg. Soil microorganisms are sensitive to metsulfuron methyl at concentrations of 5 ppm (or 5 µg/g soil), but most effects appear to be transient.

The toxicity of metsulfuron methyl to terrestrial plants is relatively well characterized. Metsulfuron methyl is a potent herbicide that causes adverse effects in a variety of target and nontarget plant species. Results of pre-emergent and post-emergent application studies in a variety of plant species yield LOELs ranging from 0.00022 to 0.0036 lbs/acre. For assessing the potential consequences of exposure to nontarget plants via runoff, an LOEC for seedling emergence of 0.00022 lb/acre is used for sensitive species and the corresponding value for tolerant species is 0.00089 lb/acre. For assessing the impact of drift, an LOEC for vegetative vigor of 0.00022 lb/acre is used for sensitive species and the corresponding value for tolerant species is 0.0036 lb/acre.

The data on toxicity to fish and aquatic invertebrates were obtained in only a few species – rainbow trout, bluegill sunfish and *Daphnia magna*. Metsulfuron methyl has a low order of toxicity to fish. Mortality is not likely to occur in fish exposed to metsulfuron methyl concentrations less than or equal to 1000 mg/L. For acute exposures in fish, the NOEC of 10 mg/L in rainbow trout is used for the most sensitive species and the NOEC of 1000 mg/L in bluegill sunfish is used for the most tolerant species. Toxicity values for chronic toxicity may be based on the available egg-and-fry/early life stage studies; only one study of chronic exposure in fish, a 90-day exposure of rainbow trout, yielding and NOEC of 4.5 mg/L. This value is used directly as a longer term NOEC in sensitive species because the rainbow trout appears to be a relatively sensitive species in acute toxicity assays. Using the relative potency for acute exposures of 100 (rainbow trout 100-times more sensitive than bluegill sunfish), an NOEC for tolerant species is estimated at 450 mg/L. Similarly, aquatic invertebrates do not appear to be sensitive to metsulfuron methyl. Since the only studies identified in aquatic invertebrates were in a single species, data obtained in *Daphnia magna* are used for both the sensitive and tolerant species. For acute exposure, a 48-hour NOEC for immobility of 420 mg/L is used. For chronic exposures, the NOEC of 17 mg/L for growth inhibition is used, although higher chronic NOECs, ranging from 100 to 150 mg/L, have been reported for survival, reproduction and immobility.

Aquatic plants appear to be much more sensitive to metsulfuron methyl than aquatic animals. An NOEC for plant damage of 0.00016 mg/L in duckweed is used to quantify effects for both acute and chronic exposure in aquatic macrophytes. This value is comparable to other studies in aquatic macrophytes and this is no basis for differentiating sensitive and tolerant species of aquatic macrophytes. For algae, the same data are used to quantify risk for both acute and chronic exposures. The most sensitive algal species appears to be *Selenastrum capricornutum*, with a 120-hour NOEC of 0.01 mg/L and the most tolerant species appear to be *Anabaena flosaquae* and *Navicula pelliculosa*, both with a 120-hour NOEC of 0.09 mg/L.

Risk Characterization – Metsulfuron methyl is an effective and potent herbicide. Adverse effects on some nontarget terrestrial plant species and, to a lesser degree, some aquatic plant species are plausible under some conditions. For terrestrial plants, the dominant factor in the risk characterization is the potency of metsulfuron methyl relative to the application rate. The typical application rate considered in this risk assessment, 0.03 lb/acre, is over 800 times higher than the NOEC in the vegetative vigor (direct spray) assay of the most sensitive nontarget species – i.e., 0.000037 lb/acre – and approximately 8 times higher than the NOEC for the most tolerant species in the same assay – i.e., 0.0039 lb/acre. The highest application rate that may be considered in Forest Service programs – i.e., 0.15 lb/acre – is over 4000 times the NOEC in sensitive species and a factor of about 40 above the NOEC in tolerant species. Given these relationships, damage to sensitive nontarget species could be expected in ground broadcast applications at distances of about 500 feet from the application site in areas in which off-site drift is not reduced by foliar interception. This risk characterization applies only to ground broadcast applications. When used in directed foliar applications (i.e., backpack), offsite drift could be reduced substantially but the extent of this reduction cannot be quantified.

The NOEC values for soil exposures (assayed in the seedling emergence test) are 0.000037 lb/acre for sensitive species and 0.0056 lb/acre for tolerant species. The offsite movement of metsulfuron methyl via runoff could be substantial under conditions that favor runoff – i.e., clay soils – and hazard quotients in the range of about 40 to nearly 500 are estimated for sensitive species over a wide range of rainfall rates – i.e., 15 inches to 250 inches per year. In very arid regions in which runoff might not be substantial, wind erosion could result in damage to nontarget plant species. The plausibility of observing such damage would, however, be highly dependent on local conditions. This risk characterization for the potential effects of runoff would be applicable to either broadcast ground or directed foliar applications.

Damage to aquatic plants, particularly macrophytes, appears substantially less than for terrestrial plants. All hazard quotients for aquatic macrophytes were based on an NOEC of 0.000016 mg/L in duckweed for both acute and chronic exposures. No sensitive or tolerant species were identified. Except for the hazard quotient of 2 associated with acute exposures based on the peak concentrations of metsulfuron methyl, all hazard quotients are below the level of concern, with a range of 0.002 to 2 for acute exposures and 0.02 to 0.08 for chronic exposures. Thus, if metsulfuron methyl is applied in areas where transport to water containing aquatic macrophytes is likely, it would be plausible that detectable damage could be observed.

Aquatic algae do not appear to be as sensitive to metsulfuron methyl. The highest hazard quotient observed for acute exposure is 0.03 associated with the upper range for the most sensitive species, based on an NOEC for growth inhibition. For chronic exposures, the highest hazard quotient is 0.001 associated with the upper range for the most sensitive species. Both values were based on an acute NOEC. Therefore, it is not anticipated that adverse effects in aquatic algae would result from exposure to metsulfuron methyl at application rates used by the Forest Service.

Just as there is little reason to doubt that adverse effects on some plant species are plausible, there is no clear basis for suggesting that effects on terrestrial or aquatic animals are likely or would be substantial. Adverse effects in mammals, birds, terrestrial insects, and microorganisms

are not likely using typical or worst-case exposure assumptions at the typical application rate of 0.03 lb a.e./acre or the maximum application rate of 0.15 lb a.e./acre. This characterization of risk, however, must be qualified. Metsulfuron methyl has been tested in only a limited number of species and under conditions that may not well-represent populations of free-ranging nontarget species. Notwithstanding this limitation, the available data are sufficient to assert that no adverse effects are anticipated in terrestrial animals.

Similarly, the risk characterization for aquatic animals is relatively simple and unambiguous. Metsulfuron methyl appears to have a very low potential to cause any adverse effects in aquatic animals. All of the hazard quotients for aquatic animals are extremely low, with a range in fish from 0.0000000003 (acute exposures in tolerant fish) to 0.00003 (longer-term exposures to sensitive fish). It should be noted that confidence in this risk characterization is reduced by the lack of chronic toxicity studies in potentially tolerant fish – i.e., bluegill sunfish trout. At the maximum application rate of 0.15 lbs/acre, all of the hazard quotients would be increased by a factor of about 5. However, this difference has no impact on the risk characterization for fish. Hazard quotients in aquatic invertebrates range from 0.0000000007 (acute exposure in *Daphnia*) to 0.0000007 (acute exposure in *Daphnia*). Thus, there is no basis for asserting that adverse effects on aquatic animals are likely.

1. INTRODUCTION

The USDA Forest Service uses metsulfuron methyl in its vegetation management programs. This document is an update to a risk assessment prepared in 2000 (SERA 2000) and provides risk assessments for human-health effects and ecological effects to support an assessment of the environmental consequences of these uses.

Although this is a technical support document and addresses some specialized technical areas, an effort was made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts, methods, and terms common to all parts of the risk assessment are described in plain language in a separate document (SERA 2001).

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. No published reviews regarding human health or ecological effects of metsulfuron methyl have been encountered. Moreover, almost all of the mammalian toxicology studies and most of the ecotoxicology studies are unpublished reports submitted to the U.S. EPA as part of the registration process for metsulfuron methyl.

Because of the lack of a detailed, recent review concerning metsulfuron methyl and the preponderance of unpublished relevant data in U.S. EPA files, a complete search of the U.S. EPA FIFRA/CBI 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 to this document.

While this document discusses the studies required to support the risk assessments, it makes no attempt to summarize all of the information. The Forest Service will update this and other similar risk assessments on a periodic basis and welcomes input from the general public on the selection of studies included in the risk assessment. This input is helpful, however, only if recommendations for including additional studies specify why and/or how the new or not previously included information would be likely to alter the conclusions reached in the risk assessments.

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). 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 metsulfuron methyl and its commercial formulation, an assessment of potential exposure to the product, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure. 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.

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 metsulfuron methyl 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.

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 and 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

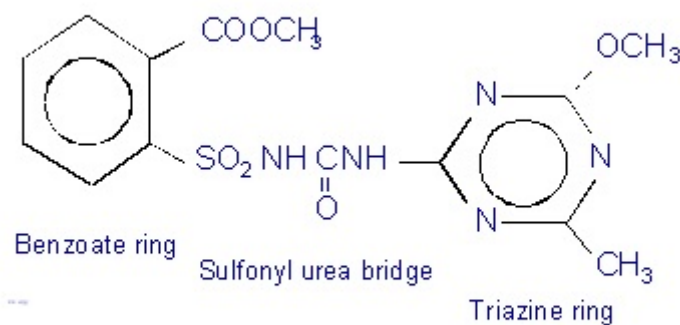
2.1. OVERVIEW

Metsulfuron methyl is a selective pre-emergence and post-emergence sulfonyl urea herbicide used primarily to control many annual and perennial weeds and woody plants. Only one commercial formulation of metsulfuron methyl, Escort® XP, is in Forest Service programs. Escort XP is manufactured by Du Pont as a dry flowable granule. The composition of the product is 60% metsulfuron methyl and 40% inert ingredients.

Metsulfuron methyl is used in Forest Service programs primarily for the control of noxious weeds. Minor uses include conifer release and rights-of-way management. The most common methods of ground application for Escort XP involve backpack (selective foliar) and boom spray (broadcast foliar) operations. The Forest Service does not use aerial applications for Escort XP. Nonetheless, Escort XP is registered for aerial applications and aerial applications are included in this risk assessment in the event the Forest Service may wish to consider this application method. For this risk assessment, the typical rate of 0.03 lbs/acre, with a range 0.0125 to 0.15 lbs/acre, is used to reflect Forest Service practice. This range is based on lowest and highest labeled application rates recommended on the manufacturer's label. The Forest Service used approximately 235 lbs of metsulfuron methyl in 2002, the most recent year for which use statistics are available. Much greater amounts of metsulfuron methyl are used in agriculture (e.g., about 35,543 lbs in 1992).

2.2. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS

Metsulfuron methyl is the common name for Methyl-2-[[[(4-methoxy-6-methyl-1,3,4-triazin-2-yl)amino]-carbonyl]amino]sulfonyl]benzoate and is essentially a methyl benzoate ring linked to a methyl (-CH₃) and methoxy (-OCH₃) substituted triazine ring by a sulfonyl urea bridge:



Selected chemical and physical properties of metsulfuron methyl are summarized in Table 2-1. Additional information is presented in worksheet B03. Detailed information regarding the environmental fate of metsulfuron methyl is provided in Appendix 8.

There are several formulations of metsulfuron methyl available in the United States, but only one, Escort XP, is registered specifically for forestry use (C&P Press 2003). All formulations of metsulfuron methyl contain 60% (w/w) metsulfuron methyl and 40% (w/w) inerts (C&P Press 2003). Except for differences in targeted crops specified on the product labels, it is not clear

how these formulations differ from one another. Escort XP is produced by Du Pont as a dry flowable granule, which is mixed with water and a surfactant and then applied as a spray (section 2.4). Escort, the commercial formulation of metsulfuron methyl used by the Forest Service, contains materials other than metsulfuron methyl that are included as adjuvants to improve either efficacy or ease of handling and storage. The Northwest Coalition for Alternatives to Pesticides (NCAP) has obtained information on the identity of the inerts in Escort 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/clopyralid.html>). The inerts are identified as sodium naphthalene sulfonate-formaldehyde condensate, a mixture of a sulfate of alkyl carboxylate and sulfonated alkyl naphthalene (sodium salt), polyvinyl pyrrolidone, trisodium phosphate, and sucrose. However, the quantity of these inerts compounds in the formulation is confidential and cannot be disclosed, although amounts in Escort were disclosed to the U.S. EPA (Du Pont 1985b,c) and reviewed in the preparation of this risk assessment. The potential risks associated with the inerts compounds in the Escort formulation are discussed in Section 3.1.14.

Information about the impurities in technical grade metsulfuron methyl was submitted to the U.S. EPA (Brennan 1990, Brennan 1995) and reviewed during the preparation of this risk assessment. Since the identities of the impurities are considered proprietary by Du Pont, this information cannot be addressed specifically in this document. The potential impact of impurities on this risk assessment is discussed in section 3.1.

2.3. APPLICATION METHODS

The most common methods of ground application for Escort XP 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. Usually, a worker treats approximately 0.5 acres/hour with a plausible range of 0.25-1.0 acre/hour (USDA 1989a,b,c).

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 1989a, p. 2-9 to 2-10).

Escort XP is registered for aerial applications (Du Pont 2001-2002). Although this is not an application method that the Forest Service will typically employ for Escort XP, this method is covered by this risk assessment in the event that the Forest Service may need to consider aerial applications. Aerial applications may be made using helicopters. Escort XP 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 (USDA 1989a,b,c).

2.4. MIXING AND APPLICATION RATES

The specific application rates used in a ground application vary according to local conditions and the nature of the target vegetation. Application rates of Escort XP are expressed in ounces or pounds per acre. An application rate of 1/3 to 4 ounces of Escort XP per acre are recommended on the product label (Du Pont 2001-2002). Given that Escort XP contains 60% metsulfuron methyl by weight, these rates correspond to 0.20 to 2.4 ounces or to 0.0125 to 0.15 pounds of metsulfuron methyl per acre. The upper range of 3 to 4 ounces Escort XP per acre is only recommended for the control of kudzu. For other applications the maximum recommended application rate is 2 ounce Escort XP per acre or 0.074 pounds metsulfuron methyl per acre. No more than 4 ounces Escort XP per acre should be applied per year (Du Pont 2001-2002).

The use of metsulfuron methyl in Forest Service Programs for fiscal year 2001, the most recent year for which data are available, is summarized in Table 2-2. Metsulfuron methyl is used currently in Forest Service Programs primarily in noxious weed control (approximately 88% of total use). Other minor uses include conifer release (approximately 7% of total use) and rights-of-way management (approximately 5% of total use). Based on the total amount used and number of acres treated, the application rates are approximately 0.03 lb/acre for noxious weed control, 0.03 lb/acre for conifer release, and 0.018 lb/acre for rights-of-way management.

For this risk assessment, the typical application rate for metsulfuron methyl will be taken as 0.03 lbs/acre. This is the average value of applications conducted by the Forest Service in 2001 for the predominant uses. The range of application rates will be taken as 0.0125 lbs/acre to 0.15 lbs/acre to reflect plausible ranges that the Forest Service may use, as well as the lower and upper limits of the labeled rates. As indicated in Table 2-3, some Forest Service regions use much lower application rates – i.e., an average application rate of 0.008 in Region 2. These lower application rates do not have a substantial impact on this risk assessment relative to the lowest labeled rate. This is discussed further in the risk characterization sections for Human Health (Section 3.4) and Ecological Effects (Section 4.4). The worksheets that accompany this risk assessment are based on the typical application rate of 0.03 lbs/acre rather than the full range of application rates. The consequences of varying application rates within the range of 0.0125 to 0.15 lb/acre is considered in the risk characterization for human health (Section 3.4) and ecological effects (Section 4.4).

For forestry applications, mixing volumes of 10 to 400 gallons of water per acre are recommended, depending upon the application method. Recommended mixing volumes for ground applications range from 100 to 400 gallons of water per acre for high volume applications, from 20 to 50 gallons of water per acre for low volume ground applications, and from 10 to 20 gallons of water per acre for ultra-low volume applications. For aerial applications, 15-25 gallons of water per acre are recommended (Du Pont 2001-2002 Label, p. 4).

For this risk assessment, the extent to which the Escort XP formulation is 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 metsulfuron methyl in the applied spray). The higher the concentration of metsulfuron methyl, the greater the risk. For this risk assessment, the lowest dilution will be taken at 10 gallons/acre, the minimum recommended for ground broadcast applications. The highest dilution (i.e., that which results in the lowest risk) will be based on 400

gallons of water per acre, the highest application volume recommended for ground broadcast. For this risk assessment the central value for dilution will be taken as 50 gallons/acre, the upper range for low volume ground applications.

In some regions, 100 gallons per acre might better reflect the maximum dilution volume. Nonetheless, the selection of application rates and dilution volumes in this risk assessment is intended to simply reflect typical or central estimates as well as plausible lower and upper ranges. In the assessment of specific program activities, the Forest Service will use program specific application rates in the worksheets that are included with this report to assess any potential risks for a proposed application.

2.5. USE STATISTICS

The USDA Forest Service (USDA/FS 2002) tracks and reports use 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 in Table 2-3, the heaviest use of metsulfuron methyl (expressed as the total in pounds used in each region) occurs in Region 2 (Rocky Mountain), followed by Region 4 (Intermountain) and Region 3 (Southwestern). Small quantities of metsulfuron methyl are used in the Region 1 (Northern), Region 8 (Southeastern), and Region 9 (Eastern). Metsulfuron methyl is not used at all in Region 5 (Pacific Southwest) or Region 6 (Pacific Northwest).

Metsulfuron methyl is used extensively in agriculture. A summary of the agricultural use of metsulfuron methyl is presented in Figure 2-2 (USGS 1998). These use statistics are for 1992, the most recent year for which data are available. As illustrated in Figure 2-2, all agricultural use of the metsulfuron methyl was in states east of the Mississippi, excluding California, Nevada, Arizona, and New Mexico (USGS 1998). The annual use of metsulfuron methyl in agricultural applications in 1992 amounted to 35,534 lbs, 97.34% of which was used on wheat and grains. As shown in Table 2-3, the annual use of metsulfuron methyl by the Forest Service in 2002 was 235.64 lbs. Thus, the amount of metsulfuron methyl by the Forest Service is less than 1% of, or approximately 150-fold less than, the amount used in agriculture. Thus, there is no basis for asserting that Forest Service programs will substantially contribute to general concentrations of metsulfuron methyl nationally. The potential for local contamination of environmental media by the use of metsulfuron methyl in Forest Service programs is discussed in detail in the human health risk assessment (Section 3) and the ecological risk assessment (Section 4).

3. HUMAN HEALTH RISK ASSESSMENT

3.1 HAZARD IDENTIFICATION

3.1.1 Overview.

The mechanism of action of sulfonylurea herbicides, including metsulfuron methyl, is fairly well characterized in plants; however, the mechanism by which metsulfuron methyl is toxic to mammals and other animals is less clear. A variety of sulfonylureas reduce blood glucose by stimulating the release of insulin from pancreatic B cells, and some sulfonylureas reduce the hepatic extraction of insulin. Secondly, sulfonylureas may affect levels of blood cholesterol and serum triglycerides. There is some evidence that metsulfuron methyl may cause both of these effects, at least at high doses.

In experimental mammals, the acute oral LD₅₀ for metsulfuron methyl is greater than 5000 mg/kg, which indicates a low order of toxicity. In addition, non-lethal signs of toxicity were apparent after single oral doses as low as 50 mg/kg. The most common sign of acute, subchronic, and chronic toxicity is decreased body weight gain. The only other commonly noted effect involves changes in various hematological parameters as well as changes in absolute and relative organ weights. None of these changes, however, suggest a clear or specific target organ toxicity. There is speculation that the effects of metsulfuron methyl on the blood might be related to saccharin, which is a metabolite of metsulfuron methyl. At very high doses, saccharin caused hematological effects in mice. Appropriate tests have provided no evidence that metsulfuron methyl presents any reproductive risks or causes malformations or cancer. Metsulfuron methyl also is irritating to the skin and eyes, but does not produce sensitizing effects following repeated dermal exposure.

Limited information is available on the toxicokinetics of metsulfuron methyl. The kinetics of absorption of metsulfuron methyl following dermal, oral or inhalation exposure are not documented in the available literature. Metsulfuron methyl is eliminated from the body by a combination of excretion of the unchanged compound and metabolites. In all species, metsulfuron methyl is eliminated rapidly with a half-time of 1 day or less and exhibits first order elimination kinetics. Most of the material is excreted as the unchanged compound. The primary excretory compartment for metsulfuron methyl and its metabolites is the urine, with smaller amounts excreted in the feces. In rats, metabolism of metsulfuron methyl appears to follow two main pathways, either hydrolysis to the corresponding sulfonamide or cleavage of the heterocycle ring.

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

The inhalation toxicity of metsulfuron methyl is not well documented in the literature. Available studies indicate that metsulfuron methyl induces irritant effects at very high exposure levels. Regardless, the potential inhalation toxicity of metsulfuron methyl is not of substantial concern to this risk assessment because of the implausibility of inhalation exposure involving high concentrations of this compound.

3.1.2 Mechanism of Action

Although the mechanism of phytotoxic action of sulfonylurea herbicides including metsulfuron methyl is characterized in some detail (Section 4.1.2.5), the mechanism of toxic action in mammals or other animal species is not well characterized.

As noted in the recent review on a closely related herbicide, sulfometuron methyl (Cox 1993), and described in detail by Melander et al. (1989), several of the sulfonylureas are biologically active in humans and are used or were considered for use in the treatment of non-insulin-dependent diabetes mellitus (NIDDM or type 2 diabetes). A variety of sulfonylureas reduce blood glucose, stimulating the release of insulin from pancreatic B cells, and some sulfonylureas may reduce the hepatic extraction of insulin. Secondly, some sulfonylureas may affect levels of blood cholesterol and serum triglycerides. As noted above, decreased blood glucose levels and increased cholesterol were observed in rats after subchronic exposure to metsulfuron methyl (Brock 1985).

Hematological changes were observed in some of the mammalian toxicity studies. Exposure to some sulfonamides are associated ($p=0.004$) with the development of hemolytic anemia in humans (Issaragrisil et al. 1997). This finding is supported by an earlier, more qualitative association of sulfonamide with anemia in humans (Dickerman 1981). Moreover, saccharin, which is a metabolite of metsulfuron methyl, was shown to cause hematological effects in mice (Prasad and Rai 1987). The doses of saccharin associated with hematological effects in mice—500, 1000, and 1500 mg/kg/day—are much higher than the doses of metsulfuron methyl that caused similar effects in rats and dogs (i.e., 20-30 mg/kg/day) (Section 3.1.5).

3.1.3 Kinetics and Metabolism

Limited information is available on the toxicokinetics of metsulfuron methyl. The kinetics of absorption of metsulfuron methyl following dermal, oral or inhalation exposure are not documented in the available literature. The lack of experimental data regarding the dermal absorption of metsulfuron methyl adds substantial uncertainties to this risk assessment. Nonetheless, the available data, albeit relatively sparse, do not suggest that metsulfuron methyl is likely to be absorbed through the skin in amounts that may cause systemic toxic effects. Uncertainties in the rates of dermal absorption, although they are substantial, can be estimated quantitatively and are incorporated in the human health exposure assessment (section 3.2).

As discussed in Durkin et al. (1995), dermal exposure scenarios involving immersion or prolonged contact with chemical solutions use Fick's first law and require an estimate of the permeability coefficient, K_p , expressed in cm/hour. Using the method recommended by U.S. EPA (1992), the estimated dermal permeability coefficient for metsulfuron methyl is 0.0000005 cm/hour with a 95% confidence interval of 0.0000001-0.000002 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 B04.

For exposure scenarios like direct sprays or accidental spills, which involve deposition of the compound on the skin's surface, dermal absorption rates (proportion of the deposited dose per unit time) rather than dermal permeability rates are used in the exposure assessment. Using the methods detailed in SERA (2001), the estimated first-order dermal absorption coefficient is $0.000087 \text{ hour}^{-1}$ with 95% confidence intervals of 0.000012 - $0.00063 \text{ hour}^{-1}$. The calculations for these estimates are presented in worksheet B03.

The elimination of metsulfuron methyl has been studied in rats (Hundley 1985, Hunt 1984), hens (Charlton and Bookhart 1996), cows (Hershberger and Moore, 1985), and, as summarized by U.S. EPA (1998b), in goats. Metsulfuron methyl is eliminated from the body by a combination of excretion of the unchanged compound and metabolism. In all species, metsulfuron methyl is eliminated rapidly with a half-time of 1 day or less and exhibits first order elimination kinetics. Most of the material is excreted as the unchanged compound. The primary excretory compartment for metsulfuron methyl and its metabolites is the urine, with smaller amounts excreted in the feces. In cows, very small amounts (< 1% of the total daily dose) are excreted in milk. In rats, metabolism of metsulfuron methyl appears to follow two main pathways, either hydrolysis to the corresponding sulfonamide or cleavage of the heterocycle ring (Hunt 1984). The primary metabolites (approximately 5-15% of the administered dose) formed by hydrolysis are saccharin, 2-[(amino)sulfonyl]benzoic acid, and methyl 2-[(amino)sulfonyl]benzoate and the major metabolite formed by cleavage of the heterocycle ring is methyl 2-[[[(amino)carbonyl]amino]sulfonyl]benzoate.

3.1.4 Acute Oral Toxicity

Other than standard bioassays for acute toxicity that were conducted as part of the registration process, there is not much information regarding the acute toxicity of metsulfuron methyl. The most common measure of acute oral toxicity is the LD_{50} , the estimate of a dose that is most likely to cause 50% mortality in the test species after a single oral dose. As summarized in Appendix 1, there are four acute oral studies involving exposure to technical grade metsulfuron methyl in rats (Dashiell and Hall 1982a, Sarver 1990, Sarver 1991, Ullman 1985a), one acute oral exposure study of a 60% metsulfuron methyl formulation in rats (Redgate 1984), and one acute oral exposure study of technical grade metsulfuron methyl in mice (Ullman 1985b). These studies demonstrate that a single oral dose of technical grade metsulfuron methyl up to 5000 mg/kg or single doses of a 60% metsulfuron methyl formulation up to 5000 mg/kg (equivalent to 3000 mg/kg a.i.) did not cause 50% mortality in any of the treated animal groups. Thus, the acute oral LD_{50} for metsulfuron methyl is correctly referenced as >5,000 mg/kg by ExToxNet (1996), USDA/FS (1998), and the U.S. EPA (1998b), and the compound is classified as *practically non-toxic*. As summarized in Appendix 1, a mortality rate of 20% was observed in male rats after doses of 1000 mg/kg and 2000 mg/kg and a mortality rate of 40% was observed in female rats after a dose of 4000 mg/kg (Sarver 1991). However, no clear dose-response relationship for mortality was observed for both sexes in this study. Furthermore, no mortalities were reported in other acute exposure studies using doses up to 5000 g/kg (Dashiell and Hall 1982a, Redgate 1984,). No mortalities were observed in rats exposed to single doses of 5000 mg/kg of a 60% metsulfuron methyl formulation (equivalent to 3000 mg/kg a.i.) (Redgate 1985).

Clinical signs of toxicity, including discharges (not otherwise specified) from eyes, nose, or mouth were observed after single oral doses as low as 50 mg/kg technical grade metsulfuron methyl (Ullman 1985a). Other signs of toxicity after single oral doses of 500 mg/kg or greater include lethargy, weight loss, and sensitivity to touch. So, although metsulfuron methyl is not regarded as highly toxic, the compound is reported to have caused adverse effects at doses that are 100 times lower than the acute oral LD₅₀. Clinical signs of toxicity observed for both technical grade metsulfuron methyl and the 60% formulation of metsulfuron methyl are comparable and the 60% formulation of metsulfuron methyl does not appear to differ in toxicity from technical grade metsulfuron methyl.

3.1.5 Subchronic and Chronic Systemic Toxic Effects

Systemic toxicity encompasses virtually any effects that a chemical has after the chemical has been absorbed. Certain types of effects, however, are of particular concern and involve a specific subset of tests. Such special effects are considered in following subsections and include effects on the nervous system (Section 3.1.6) and immune system (Section 3.1.7), development or reproduction (Section 3.1.8), and carcinogenicity or mutagenicity (Section 3.1.9). This section encompasses the remaining signs of general and non-specific toxicity.

The subchronic or chronic toxicity of metsulfuron methyl to humans or mammals is not documented in the published literature, and all of the available toxicological data comes from unpublished studies that were conducted to support the registration of metsulfuron methyl as a herbicide. As summarized in Appendix 1, there are several subchronic studies in rats (Brock 1985; Burdock et al. 1982; Daly 1985; Pastoor 1985; Wiechman et al. 1982), one subchronic study in dogs (Daly 1985), and one subchronic study in rabbits (Feussner et al. 1982b). Two rat studies (Brock 1985; Wiechman et al. 1982) also involved assays for reproductive performance and are discussed further in section 3.1.9. All subchronic and chronic exposure studies were conducted using technical grade metsulfuron methyl.

All of the subchronic rat studies report a decrease in body weight and/or growth rate (Brock 1985; Burdock et al. 1982; Daly 1985; Pastoor 1985; Wiechman et al. 1982). Brock (1985) noted that the decrease in body weight was accompanied by a decreased food conversion efficiency, which suggests that the effect could be associated with an underlying change in metabolism rather than a simple decrease in food intake. In the same study, a significantly lower serum glucose and higher serum cholesterol was observed in females at 1 and 3 months. The other effects commonly reported in the available subchronic studies involve changes in various hematological parameters and changes in absolute and relative organ weights. None of these changes, however, suggest a clear or specific target organ toxicity.

The chronic toxicity of metsulfuron methyl was investigated in rats (Burns 1984; Burdock and Hamada 1985), mice (Stadler 1984), and dogs (Burdock 1984). Like the subchronic studies, the chronic studies report decreased body weight as the most consistently observed adverse effect. Similarly, with respect to the subchronic studies, other signs of chronic toxicity included various changes in organ weights and changes in some hematological parameters that do not suggest any specific target organ toxicity.

As discussed in Section 3.3., an RfD of 0.25 mg/kg/day has been derived by the U.S. EPA's RfD workgroup (U.S. EPA 1988) and is currently listed on the U.S. EPA's Integrated Risk Information System (<http://www.epa.gov/iriswebp/iris/index.html>). This RfD has been adopted by the U.S. EPA Office of Pesticides (U.S. EPA 2002). The RfD for metsulfuron methyl is based on the results of the 52-week dietary exposure study in rats (Burns 1994) using decreased body weight gain as the most sensitive effect. Detail of this study are provided in Appendix 1 and in Section 3.3.2. Based on a review of the studies considered by the U.S. EPA, the selection of this study seems reasonable and appropriate.

3.1.6 Effects on Nervous System

As discussed in Durkin and Diamond (2002), a *neurotoxicant* is 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* is critical because it 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.

By this definition, metsulfuron methyl may be classified as an indirect neurotoxicant. At high doses that produce a broad spectrum of toxicologic effects (5000 mg/kg body), lethargy, tremors and hypersensitivity were observed in rats (Sarver 1991, Ullman 1985a, 1985b). These reports, however, do not implicate metsulfuron methyl as a direct neurotoxicant. No studies designed specifically to detect impairments in motor, sensory, or cognitive functions in animals or humans exposed to metsulfuron methyl were identified. No evidence for metsulfuron methyl producing direct effects on the nervous system was found.

3.1.7 Effects on Immune System

There is very little information on which to assess the immunotoxic potential of metsulfuron methyl. Studies designed specifically to assess the effects of metsulfuron methyl on immune system function were not identified. The only studies specifically related to the effects of metsulfuron methyl on immune function are skin sensitization studies (Section 3.1.11) in which metsulfuron methyl did not cause skin sensitization. No other information suggesting that metsulfuron methyl produces direct effects on the immune system was found.

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). Metsulfuron methyl, however, has not been tested for activity as an agonist or antagonist of the major hormone systems (e.g., estrogen, androgen, thyroid hormone). Thus, all inferences concerning the potential effect of metsulfuron methyl on endocrine function must be based on inferences from standard toxicity studies.

As noted in Section 3.1.2., a variety of sulfonylureas reduce blood glucose by stimulating the release of insulin from pancreatic B cells, and some sulfonylureas reduce the hepatic extraction

of insulin. No studies specifically designed to investigate the effects of metsulfuron methyl on insulin release or metabolism were identified. However, dietary exposure of male and female rats to 1750 and 5000 ppm for up to 90 days resulted in significantly lower serum glucose compared to control rats (Brock 1985). Also, as noted in Appendix 1, both weight loss and weight gain are observed in animals treated with metsulfuron methyl, implying a change in metabolic status. However, there is no evidence to suggest that changes in weight are due to effects of metsulfuron methyl on the endocrine system. No evidence for metsulfuron methyl producing direct effects on the endocrine system was found.

3.1.9. Reproductive and Teratogenic Effects

Metsulfuron methyl was tested for its ability to cause birth defects (i.e., teratogenicity) as well as its ability to cause reproductive impairment. All of these studies are detailed in Appendix 1.

Teratogenicity studies typically entail gavage administration to pregnant rats or rabbits on specific days of gestation. Two such studies (each of which is detailed in Appendix 1) were conducted on metsulfuron methyl: one in rats (Feussner et al. 1982a) and one in rabbits (Feussner et al. 1982b). No signs of teratogenicity or fetal toxicity were noted in either study. Decreased weight gain was the only effect noted in the dams.

Another type of reproduction study involves exposing more than one generation of the test animal to the compound. One such study (Shriram Institute for Industrial Research, 1995) was conducted on metsulfuron methyl. In this study, the only effect noted was a decrease in growth rate at doses of 50 mg/kg/day or greater. As noted in section 3.1.3, this effect is also commonly seen in standard subchronic toxicity studies.

As discussed above, some test animals were allowed to mate in two of the subchronic oral toxicity studies in order to assay for potential reproductive effects. In the dietary study (Wiechman et al. 1982), no adverse effects were noted. In a gavage study (Christian and Doll 1985), there were no significant dose-related incidences of specific fetal malformations observed by external, soft tissue, or skeletal examination although various non-specific effects were noted in the offspring at maternally toxic doses.

In a recent review of these studies, the U.S. EPA (1998b) concluded that:

The results of a series of studies indicated that there were no reproductive, developmental or teratogenic hazards associated with the use of metsulfuron methyl. ... In studies conducted to evaluate developmental toxicity potential, metsulfuron methyl was neither teratogenic nor uniquely toxic to the conceptus (i.e., not considered a developmental toxin).

The current review of these studies supports this assessment.

3.1.10. Carcinogenicity and Mutagenicity

As summarized in section 3.1.3, no evidence of carcinogenic activity was found in any of the chronic toxicity studies conducted on metsulfuron methyl. In addition, *in vivo* and *in vitro*

studies conducted in rats and mice indicate that metsulfuron methyl is not mutagenic. Single exposure to ≤ 5000 mg/kg bw by gavage did not induce chromosome aberrations in the bone marrow cells of male or female Sprague-Dawley rats (Ullman 1985a,) or CD-1 mice (Ullman 1985b). *In vitro* studies indicate that concentrations ≤ 3000 $\mu\text{g/mL}$ metsulfuron methyl failed to induce unscheduled DNA synthesis in primary rat hepatocyte cultures (Vincent 1985, Bentley 1993,). Conflicting evidence has been obtained in mutagenicity studies using CHO cells. Metsulfuron methyl was negative in a CHO/HPRT gene mutation assay with and without S-9 activation (Rickard 1985). However, in one study in CHO cells, metsulfuron tested positive for clastogenic activity both with and without S-9 activation. The concentrations of metsulfuron methyl tested in this study ranged from 0.13 to 7.9 mM, with positive results observed only at the highest concentration (Vlachos et al. 1983). Mutagenicity studies in *Salmonella typhimurium* were negative with and without S-9 activation (Krahn and Donovan 1980, Haskell Lab 1983). Based on a review of these studies, the U.S. EPA (1998b) concluded that: “*the weight-of-evidence indicates that metsulfuron methyl is neither genotoxic nor mutagenic and that “Metsulfuron methyl was not oncogenic in the chronic rat and mouse bioassays”*”. Thus, there is no basis for contending that exposure to metsulfuron methyl will pose an increased risk of cancer.

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

Metsulfuron methyl was tested for irritant effects on the skin and eyes of rabbits and the skin of guinea pigs (Appendix 1). Application of 0.5 g technical grade metsulfuron methyl to the skin of rabbits did not produce any dermal irritation (Brock 1987a). However, 2000 mg/kg (assuming 100% a.i.) applied directly to the skin, technical grade metsulfuron methyl caused slight to moderate edema, erythema, and thickening of the skin (associated with adherence of the compound to the skin) (Gargus 1985a,b). Technical grade metsulfuron methyl produced slight patchy erythema when applied to the skin of guinea pigs, but no sensitization was observed upon challenge (Brock 1987a). Application of 0.5 g/animal of a 70% formulation to the skin of rabbits produced only mild irritation (Dashiell and Hall 1982b). Finlay (1996) reported that a dermal application of 0.5 g/animal of the commercial formulation, Escort, caused edema and erythema in rabbits. In guinea pigs, a 35% solution of a 70% commercial formulation produced mild to moderate erythema, but no sensitization was observed upon challenge (Dashiell and Hall 1982b).

When applied directly into the eyes of rabbits, metsulfuron methyl caused mild conjunctival redness in all six animals tested and slight corneal opacity and slight chemosis in one rabbit (Brock 1987). Application of metsulfuron methyl (0.03 mg a.i.) to the conjunctival sac of rabbits caused slight conjunctival redness, which cleared within 24 hours (Kuhn 2002). Application of a 70% formulation of metsulfuron methyl (corresponding to 20 mg a.i.) caused slight corneal clouding, mild conjunctivitis, and mild discharge (Dashiell and Hinckle 1982c). Accordingly, the MSDS for Escort warns that exposure to this formulation may cause skin irritation (C&P Press 2003).

3.1.12. Systemic Toxic Effects from Dermal Exposure

Most of the occupational exposure scenarios and many of the exposure scenarios for the general public involve the dermal route of exposure. For these exposure scenarios, dermal absorption is estimated and compared to an estimated acceptable level of oral exposure based on subchronic or chronic toxicity studies. Thus, it is necessary to assess the consequences of dermal exposure

relative to oral exposure and the extent to which metsulfuron methyl is likely to be absorbed from the surface of the skin.

Systemic effects resulting from dermal exposure of rabbits to both technical grade metsulfuron methyl and formulations of metsulfuron methyl containing are summarized in Appendix 1. Results of these studies do not reveal any differences between metsulfuron methyl or formulations of metsulfuron methyl for systemic toxicity resulting from dermal exposure. Dermal exposure to single doses of up to 2000 mg/kg of technical grade metsulfuron methyl did not cause any mortality, yielding an LD₅₀ > 2000 mg/kg (Dashiell and Hinckle 1982a, Gargus 1984b, Gargus 1985a,b). Dermal exposure to single doses of up to 2000 mg/kg of a 60% formulation of metsulfuron methyl did not cause any mortality, yielding an LD₅₀ > 2000 mg/kg (Gargus 1984a). The only significant clinical finding reported in these studies following dermal exposure to metsulfuron methyl is changes in body weight. Conflicting results have been observed regarding changes in body weight. Following acute dermal exposure of doses up to 2000 mg/kg technical grade metsulfuron methyl anorexia and weight loss were observed (Gargus 1985b, Dashielle and Hinckle 1982a), similar to that observed in experimental mammals after subchronic and chronic oral exposure (Sections 3.1.4 and 3.1.5). However, weight gain was observed in rabbits exposed to single doses of 2000 mg/kg technical grade metsulfuron methyl and to single doses of 2000 mg/kg of a 60% formulation of metsulfuron methyl (equivalent to 1200 mg/kg a.i.) (Gargus 1984a,b). In one study of subchronic dermal exposure to doses up to 2000 mg/kg of technical grade metsulfuron methyl for 21 consecutive day, no clinical or gross pathology finding was attributable to exposure (Wylie 1983).

3.1.13. Inhalation Exposure

As summarized in Appendix 1, there are two inhalation toxicity studies on metsulfuron methyl (Burgess et al. 1983; Hutt 1985). Both studies follow a relatively standard protocol involving acute (4-hour) exposure to relatively high concentrations (>1.3 mg/L or >13,000 mg/m³). No mortality or gross tissue pathology was observed in either study. A transient decrease in body weight was observed, consistent with both oral and dermal routes of administration. The only other signs of toxicity were hair loss, nasal discharges (probably attributable to irritation), and, in one rat, abnormal lung sounds (Hutt 1985).

These extremely limited data suggest only that metsulfuron methyl can induce irritant effects and perhaps systemic toxic effects at very high exposure levels. As discussed in section 3.3, this finding is not directly relevant to this risk assessment because of the implausibility of exposure to such high concentrations of the compound.

3.1.14. Inerts and Adjuvants

Escort, the commercial formulation of metsulfuron methyl used by the Forest Service, contains materials other than metsulfuron methyl that are included as adjuvants to improve either efficacy or ease of handling and storage. The Northwest Coalition for Alternatives to Pesticides (NCAP) has obtained information on the identity of the inerts in Escort 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/clopyralid.html>). The inerts listed on this web site are sodium naphthalene sulfonate-formaldehyde condensate, mixture of a sulfate of alkyl carboxylate and sulfonated alkyl naphthalene (sodium salt), polyvinyl pyrrolidone, trisodium phosphate, and

sucrose. Both trisodium phosphate (CAS No. 7601-54-9) and sucrose (CAS No. 57-50-1) are classified by the U.S. EPA as List 4 inerts and therefore, are generally recognized as safe compounds and are approved as food additives (U.S. EPA 2003, Clydesdale 1997). There is no evidence to assert that these compounds will materially impact the risks associated with the use of metsulfuron methyl. Polyvinyl pyrrolidone (CAS No. 88-12-0) is classified as a List 3 inert (U.S. EPA 2003). In other words, there is insufficient information to categorize this compound as either hazardous (Lists 1 or 2) or non-toxic (List 4). Sodium naphthalene sulfonate-formaldehyde condensate and the mixture of a sulfate of alkyl carboxylate and sulfonated alkyl naphthalene (sodium salt) were not identified in the EPA Inert List (U.S. EPA 2003). Other naphthalene derivatives identified on the EPA Inert List are classified as List 3 or List 4; no naphthalene derivatives are classified as List 1 or List 2 inerts (U.S. EPA 2003). Thus, there is insufficient information available to assess the impact of either polyvinyl pyrrolidone or the naphthalene derivatives on the risks associated with the use of metsulfuron methyl. However, as noted above, the toxicity of a formulated product that is comparable to Escort appears to be comparable to that of technical grade metsulfuron methyl (Sections 3.1.4, 3.1.11, and 3.1.13). Therefore, there is no plausible basis for asserting that these inerts are present in Escort in toxicological amounts. Although the identity of inerts has been disclosed, the quantity of the inert agents in Escort is confidential and cannot be disclosed. The amount of each inert agent in Escort was disclosed to the U.S. EPA (Du Pont 1985b,c) and reviewed in the preparation of this risk assessment.

As noted in Section 2.2, the manufacturer recommends that Escort be mixed with a surfactant for application. There is no published literature or information in the FIFRA files that would permit an assessment of toxicological effects of metsulfuron methyl mixed with surfactant.

3.1.15. Impurities and Metabolites

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

There is no published information regarding the impurities in technical grade metsulfuron methyl or any of its commercial formulations. Information on all of the impurities in technical grade metsulfuron methyl were disclosed to the U.S. EPA (Brennan 1995), and the information was obtained and reviewed as part of this risk assessment. Because this information is classified as confidential business information, details about the impurities cannot be disclosed. Nonetheless, all of the toxicology studies on metsulfuron methyl involve technical metsulfuron methyl, which is presumed to be the same as or comparable to the active ingredient in the formulation used by the Forest Service.

3.1.15.2. Metabolites –The metabolism of metsulfuron methyl is discussed in Section 3.1.3. Although information on the toxicity of each metabolite identified is not available, a single study evaluated the effects of a plant and animal metabolite of metsulfuron methyl, triazine amine (1,3,5-triazine-2-amine, 4-methoxy-6-methyl-), following acute and 10-day oral exposures, acute

dermal and inhalation exposures and in the Ames test for point mutations (O'Neal 1987). Results are summarized in Table 3-1. The acute LD₅₀ for triazine amine is 1680 mg/kg, which is less than the LD₅₀ of > 5000 mg/kg reported for metsulfuron methyl (see section 3.1.4). The clinical signs of toxicity resulting from acute oral, dermal and inhalation exposures to triazine amine do not appear to differ from those for metsulfuron methyl. Following subacute oral exposure to triazine amine, cardiotoxicity was observed; this effect was not reported in subacute oral exposure studies of metsulfuron methyl.

Regarding the toxicity of the other metabolites of metsulfuron methyl, toxicity is likely to be encompassed by the available mammalian toxicity studies. An exception to this would be metabolites that are formed in the environment but not in mammals. As discussed by the U.S. EPA (1998b):

There were two major plant specific metabolites identified, that were not detected in the rat. However, in residue studies, no detectable residues of parent or major plant unique metabolites, were found in the feed and food items of cereal crops treated at the maximum seasonal use rate. Hence, toxicity testing of other degradation products of metsulfuron methyl was not needed.

3.1.16. Toxicological Interactions. The Forest Service may apply Escort in combination with other herbicides, particularly 2,4-D. There is no published literature or information in the FIFRA files that would permit an assessment of potential toxicological interactions between metsulfuron methyl and 2,4-D or any other compounds.

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 0.03 lb/acre. The consequences of using the maximum application rate that might be used by the Forest Service, 0.15 lb/acre, are discussed in the risk characterization.

There are no occupational exposure studies in the available literature that are associated with the application of metsulfuron methyl. Consequently, worker exposure rates are estimated from an empirical relationship between absorbed dose per kilogram of body weight and the amount of chemical handled in worker exposure studies on nine different pesticides. For workers, three types of application methods are generally modeled in Forest Service risk assessments: directed ground, broadcast ground, and aerial. Although Escort is registered for aerial applications (helicopter and sometimes fixed wing), the Forest Service does not currently use this method. Nonetheless, the aerial application method is included in this risk assessment in the event that the Forest Service considers aerial applications in the future. Central estimates of exposure for ground workers are approximately 0.0004 mg/kg/day for directed ground spray and 0.0007 mg/kg/day for broadcast ground spray. Upper range of exposures are approximately 0.0024 mg/kg/day for directed ground spray and 0.0045 mg/kg/day for broadcast ground spray. All of the accidental exposure scenarios for workers involve dermal exposures and all of these accidental exposures lead to estimates of dose that are either in the range of or substantially below the general exposure estimates for workers.

For the general public, the range of acute exposures is from approximately 0.000000014 mg/kg associated with the lower range for consumption of contaminated stream water by a child to 0.034 mg/kg/day associated with the upper range for consumption of contaminated water by a child following an accidental spill of metsulfuron methyl into a small pond. For chronic or longer term exposures, the modeled exposures are much lower than for acute exposures, ranging from approximately 0.0000000026 mg/kg/day associated with the lower range for the normal consumption of fish to approximately 0.0024 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 metsulfuron methyl that accompany this risk assessment (Supplement 1). A copy of this documentation is available at www.sera-inc.com. This section on workers and the following section on the general public provides a plain verbal description of the worksheets and discuss metsulfuron methyl 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 metsulfuron methyl 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 untoward 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 0.03 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). Although Escort is registered for aerial applications (Section 2), this is not an application method that the Forest Service will typically employ for Escort. However, aerial application is covered by this risk assessment in the event that the Forest Service may need to consider aerial applications. 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. The typical application rate is taken directly from the program description (see section 2.4). The central estimate of the amount handled per day (0.03 lbs metsulfuron methyl/acre) is calculated as the product of the central estimate of the acres treated per day and the application rate.

No worker exposure studies with metsulfuron methyl 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 $\log K_{o/w}$ 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 metsulfuron methyl is 391.4 and the $\log K_{o/w}$ at pH 7 is approximately -1.7. Because the $K_{o/w}$ for metsulfuron methyl is slightly below the range of $K_{o/w}$ values used in formulating the regression model, confidence in these assessments are diminished. This uncertainty is compounded by the uncertainties inherent in the available data on worker exposure. 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.

Metsulfuron methyl can cause irritant effects to the skin and eyes (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/ORD 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/ORD (1992), Fick's first law is used to estimate dermal exposure. As discussed in Section 3.1.3, an experimental dermal permeability coefficient (K_p) for metsulfuron methyl is not available. Thus, the K_p for metsulfuron methyl is estimated using the algorithm from U.S. EPA/ORD (1992), which is detailed in Worksheet A07b. The application of this algorithm to metsulfuron methyl, 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 metsulfuron methyl. Nonetheless, as summarized in Worksheet E01, there is a noteworthy similarity between the exposure scenario in which contaminated gloves are worn for 1 hour (Worksheet C02b) and the exposure scenario in which a chemical solution is spilled on to the skin surface of the hands and cleaned after 1 hour (Worksheet C03a). Confidence in these assessments is enhanced somewhat by the fact that two similar scenarios based on different empirical relationships yield similar estimates of exposure.

3.2.3. General Public

3.2.3.1. General Considerations – Under normal conditions, members of the general public should not be exposed to substantial levels of metsulfuron methyl. 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 D01–D09). The remainder of this section focuses on a qualitative description of the rationale for and quality of the data supporting each of the assessments.

3.2.3.2. Direct Spray – Direct sprays involving ground applications are modeled in a manner similar to accidental spills for workers (Section 3.2.2.2). In other words, it is assumed that the individual is sprayed with a solution containing the compound and that an amount of the compound remains on the skin and is absorbed by first-order kinetics. For these exposure scenarios, it is assumed that during a ground application, a naked child is sprayed directly with metsulfuron methyl. 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 metsulfuron methyl 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 metsulfuron methyl in ambient water are acute/accidental exposure from an accidental spill and longer-term exposure to metsulfuron methyl 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 metsulfuron methyl 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 metsulfuron methyl in a small pond is estimated to range from about 0.0076 mg/L to 0.30 mg/L with a central estimate of about 0.076 mg/L (Worksheet D05).

The other acute exposure scenario for the consumption of contaminated water involves runoff into a small stream. As summarized in Appendix 8, three studies report monitoring data on metsulfuron methyl. Metsulfuron methyl was not detected in any of the 130 random water samples collected from Midwestern streams and rivers (method reporting limit of 0.01 µg/L) (Bagglin et al. 1999). In this same study, no metsulfuron methyl was detected in 25 random samples of ground-water. Similarly, no metsulfuron methyl was detected in 300 random samples of Danish ground-water (limit of detection: 0.004 µg/L) (Spliid and Koppen 1998) or in 17 random ground-water samples from Oklahoma (limit of detection: 0.025 µg/L) (USGS, no date).

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. The available monitoring data (Bagglin et al. 1999, Spliid and Koppen 1998, USGS no date) is of limited use in the exposure assessment because sampling was random and the monitoring was not associated with a specific application of metsulfuron methyl. Consequently, for this component of the exposure assessment, modeled estimates are made 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).

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 3-2. The GLEAMS modeling yielded estimates runoff, sediment and percolation that were used to estimate concentrations in the stream adjacent to a treated plot, as detailed in Section 6.4 of SERA (2003b). The results of the GLEAMS modeling for the small stream are summarized in Table 3-3 and the corresponding values for the small pond are summarized in Table 3-4. 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 3-3, no stream contamination is estimated in very arid regions – i.e., annual rainfall of 10 to 15 inches or less depending on soil type. The modeled maximum concentrations in the stream range from about 0.1 µg/L or less (in loam or sand) to somewhat over 2 µg/L (clay) at annual rainfall rates from 15 to 250 inches per year, with the highest concentrations associated with clay at annual rainfall rates of 100 inches or more. While not detailed in Table 3-3, the losses from clay are associated almost exclusively with runoff (about 93%), with the remaining amount due to sediment loss. For loam, about 75% of the loss is associated with runoff and most of the remaining loss with percolation. For sand, the pesticide loss is associated almost exclusively with percolation. For clay, the maximum losses occur with the first rainfall after application. For loam and to a lesser extent for sand, time to maximum loss is delayed.

Modeled peak concentrations in ponds (Table 3-4) are generally similar to those in streams, ranging from about 0.2 to 1.6 µg/L in clay soil, up to about 0.7 µg/L in sand, and less than 0.2 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 0.4 µg/L – i.e., sandy soil at a rainfall rate of 50 inches per year. Over all soil types, typical concentrations are in the range of 0.1 to 0.2 µg/L. As with the stream modeling, virtually no contamination is modeled in very arid regions. Due to the lack of monitoring data obtained following a known application of metsulfuron methyl and since available monitoring studies did not detect metsulfuron methyl at concentrations above the methodological limit of detection (Bagglin et al. 1999, Spliid and Koppen 1998, USGS no date), no comparisons of the modeled maximum concentrations to monitoring data are possible.

The GLEAMS scenarios do not specifically consider the effects of accidental direct spray. For example, the stream 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 [$1 \text{ lb/acre} = 112,100 \text{ µg/m}^2$, $6' \times 660' = 3960 \text{ ft}^2 = 368 \text{ m}^2$, $112,100 \text{ µg/m}^2 \times 368 \text{ m}^2 = 41,252,800 \text{ µg}$]. This would result in a downstream concentration of about 10 µg/L [$41,252,800 \text{ µg/day} \div 4,420,000 \text{ L/day}$]. As indicated in Table 3-3, the expected peak concentrations from runoff or percolation are below this value by a factor of about 5 or more – i.e., a maximum modeled peak concentration of about 2 µg/L.

For the current risk assessment, the upper range for the short-term water contamination rate will be taken as 10 µg/L per lb/acre, the maximum that is estimated based on an accidental direct spray. This value, converted to 0.01 mg/L per lb/acre, 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. 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 15 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 discussed in Section 3.2.3.4.2, the results of three monitoring studies in random samples obtained from streams, rivers, and ground-water did not detect metsulfuron methyl at concentrations above the methodological limit of detection (Bagglin et al. 1999, Spliid and Koppen 1998, USGS no date). As with the acute exposure assessment, these studies are of little use in assessing the quality of the GLEAMS modeling. Nonetheless, the limit of detection in these studies was about 0.004 µg/L to 0.01 µg/L. The highest modeled longer-term concentration in streams is about 0.01 µg/L and many of the longer term modeled concentrations are below 0.004 µg/L (Table 3-3). Thus, for the type of applications considered in this risk assessment, the failure to detect concentrations of metsulfuron in water would be expected.

For this risk assessment, the typical longer term water contamination rate (WCR) is taken as 0.2 µg/L or 0.0002 mg/L per lb/acre. This is about the average concentration that is predicted to be in a pond using GLEAMS at a rainfall rate of 15 to about 100 inches per year in clay soil as well as average concentrations predicted in water after runoff from loam and sand at various rainfall rates (Table 3-4). The upper range of the WCR is taken as 0.4 µg/L or 0.0004 mg/L per lb/acre. This is the highest average concentration predicted from percolation through sandy soil at an rainfall rate of 50 inches per year. The lower range is taken as 0.1 µg/L or 0.0001 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 reported limit of detection of metsulfuron methyl ranges from 0.004 to 0.025 µg/L (Spliid and Koppen 1998, USGS no date). Thus, the range of longer term concentrations in standing water (modeled as a pond) that are used in this risk assessment are above the range for the limit of detection for measurement of metsulfuron methyl in water.

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

3.2.3.5. Oral Exposure from Contaminated Fish – Many chemicals may be concentrated or partitioned from water into the tissues of animals or plants in the water. This process is referred to as bioconcentration. Generally, bioconcentration is measured as the ratio of the concentration

in the organism to the concentration in the water. For example, if the concentration in the organism is 5 mg/kg and the concentration in the water is 1 mg/L, the bioconcentration factor (BCF) is 5 L/kg [5 mg/kg ÷ 1 mg/L]. As with most absorption processes, bioconcentration depends initially on the duration of exposure but eventually reaches steady state. Details regarding the relationship of bioconcentration factor to standard pharmacokinetic principles are provided in Calabrese and Baldwin (1993).

The potential for accumulation of metsulfuron methyl in fish was studied in bluegill fish exposed to 0.01 and 1.0 mg/L ¹⁴C-metsulfuron methyl (Han 1982). The bioconcentration of ¹⁴C-metsulfuron methyl in muscle (edible tissue), liver and viscera was examined during a 28-day exposure period. Details of these studies are provided in Appendix 8. Following 1 day of exposure, no bioconcentration of metsulfuron methyl in edible tissue occurred bluegill sunfish (BCF = 0.21). Over the 28-day exposure period, no bioconcentration metsulfuron methyl in edible tissue was observed, with the highest BCF of 0.61 on day 7 of exposure. For this risk assessment, a bioconcentration factor for edible tissue in fish will be taken as 0.21 L/kg for acute exposure and a BCF of 0.61 L/kg is used for chronic exposure.

For both the acute and longer-term exposure scenarios involving the consumption of contaminated fish, the water concentrations of metsulfuron methyl 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 m² or about one-quarter acre. No dissipation or degradation is considered. Because of the available and well-documented information and substantial differences in the amount of caught fish consumed by the general public and native American subsistence populations, separate exposure estimates are made for these two groups, as illustrated in worksheet D08. The chronic exposure scenario is constructed in a similar way, as detailed in worksheet D09, except that estimates of metsulfuron methyl concentrations in ambient water are based on GLEAMS modeling as discussed in Section 3.2.3.4.

3.2.3.6. Oral Exposure from Contaminated Vegetation – None of the Forest Service applications of metsulfuron methyl 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 metsulfuron methyl 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 metsulfuron methyl (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 metsulfuron methyl 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-time of 30 days reported by Knisel and Davis (2000). Although the duration of exposure of 90 days is somewhat arbitrarily chosen, this duration is intended to represent the consumption of contaminated fruit that might be available over one season. Longer durations could be used for certain kinds of vegetation but would lower the estimated dose (i.e., would reduce the estimate of risk).

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

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

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

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

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

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview. The Office of Pesticide Programs of the U.S. EPA has derived a chronic RfD of 0.25 mg/kg/day for metsulfuron methyl. This RfD is based on a chronic rat NOAEL of 25 mg/kg/day (500 ppm in the diet) (Burns 1994) and an uncertainty factor of 100. In the same study, the LOAEL was 250 mg/kg/day (5000 ppm in the diet) and the only effect noted was a decrease in body weight. No frank signs of toxicity were seen at this or higher dose levels. The U.S. EPA has not derived an acute RfD. The chronic RfD of 0.25 mg/kg/day is used in the current risk assessment for characterizing risks associated with both acute and chronic exposure to metsulfuron methyl.

3.3.2. Chronic RfD

The U.S. EPA derived an agency-wide chronic RfD for metsulfuron methyl of 0.25 mg/kg/day (U.S. EPA 1988), as currently listed at the U.S. EPA web site for RfDs <http://www.epa.gov/ngispgm3/iris/>. This RfD has been adopted by the U.S. EPA Office of Pesticides (U.S. EPA 2002). Although RfD derived by EPA has not changed since the previous risk assessment for metsulfuron methyl (SERA 2000), the previous risk assessment rounded the 0.25 mg/kg/day value to 0.3 mg/kg/day. For this risk assessment, the chronic RfD value of 0.25 mg/kg/day is used directly for consistency with the U.S. EPA.

The chronic RfD of 0.25 mg/kg/day is based on a NOAEL of 25 mg/kg/day from a 52-week feeding study in rats using decreased body weight gain as the most sensitive effect (Burns 1994). In this study, rats were exposed to dietary concentrations of metsulfuron methyl (ranging in purity from 93 to 95.8%) of 5, 25, 500, 2500, and 5000 ppm for 52-weeks. The investigators observed a statistically significant, treatment related decrease in mean body weight in males (2500 and 5000 ppm) at 13 weeks and in males and females (5000 ppm) at 52 weeks. A statistically significant decrease in body weight gain, compared with controls, in males and females (500, 2500, and 5000 ppm) at 13 weeks and in males and females (5000 ppm) at 52 weeks was also observed. No overt signs of toxicity were observed at any dose level. As summarized in Appendix 1, there were various changes in relative and absolute organ weights as well as in hematological parameters; however, these effects either were not statistically significant or did not suggest a coherent pattern of toxicity. Based on these results, the U.S. EPA (1990) classified 500 ppm as the NOAEL. Using a conversion factor of 1 ppm dietary equal to 0.05 mg/kg body weight/day, the U.S. EPA (1984) converted the dietary NOAEL of 500 ppm to a daily dose of 25mg/kg/day. The dose conversion factor used by U.S. EPA (1990) is not referenced but the conversion factor is consistent with the estimated daily doses reported by Burns (1984, Table 5, pp. 99-124). The RfD of 0.25 mg/kg/day was derived with an uncertainty factor of 100. This uncertainty factor consists of two components: a factor of 10 for extrapolating from animals to humans and a factor of 10 for extrapolating to sensitive individuals within the human population. Using the same conversion factor, the 2500 ppm LOAEL based on body weight would correspond to a dose of 125 mg/kg/day.

3.3.3. Acute RfD.

The U.S. EPA (2002) did not explicitly derive an acute/single dose RfD for metsulfuron methyl. However, the U.S. EPA Office of Pesticides (U.S. EPA 2002) reported a short- and intermediate term oral exposure NOAEL of 34 mg/kg/day (for decreased body weight) with a corresponding LOAEL of 342 mg/kg/day and a margin of exposure of 100. Thus, a functional acute RfD could

be calculated as 0.34 mg/kg/day [34 mg/kg/day ÷ 100]. The U.S. EPA (2002) does not explicitly identify this study, although the sensitive effect is identified as decreased body weight and the study is described as a 2-generation reproductive study in rats. This study does not appear to correspond to any of the studies summarized in Appendix 1 or in the U.S. EPA (1988) documentation for the RfD . Although a functional acute RfD of 0.34 mg/kg/day can be derived, there is not a substantial difference between this value and the chronic RfD value of 0.25 mg/kg/day. This risk assessment will use the chronic RfD of 0.25 mg/kg/day to characterize all risks of acute or short-term exposures. This somewhat more conservative approach has no impact on the characterization of risk.

3.4. RISK CHARACTERIZATION

3.4.1. Overview. Typical exposures to metsulfuron methyl do not lead to estimated doses that exceed a level of concern. For workers, no exposure scenarios, acute or chronic, exceeds the RfD even at the upper ranges of estimated dose. For members of the general public, all upper limits for hazard quotients are below a level of concern. Thus, based on the available information and under the foreseeable conditions of application, there is no route of exposure or scenario suggesting that workers or members of the general public will be at any substantial risk from acute or longer term exposures to metsulfuron methyl.

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

3.4.2. Workers. A quantitative summary of the risk characterization for workers associated with exposure to metsulfuron methyl 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 acute exposures – i.e., accidental or incidental exposures – the acute RfD of 0.25 mg/kg/day is used (Section 3.3.3). For general exposures – i.e., daily exposures that might occur over the course of an application season – the chronic RfD of 0.25 mg/kg/day is used (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 0.03 lb a.e./acre and the “level of concern” is one – i.e., if the hazard quotient is below 1.0, the exposure is less than the RfD. For all exposure scenarios, the estimated dose scales linearly with application rate. Thus, at an application rate of 0.15 lb a.e./acre, the highest application rate contemplated by the Forest Service, the level of concern would be 0.2 – i.e., $0.03 \text{ lb/acre} \div 0.15 \text{ lb/acre}$. The highest hazard quotient for workers (Worksheet E02) is 0.02 – the upper range for directed 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. It should be noted that confidence in these assessments is diminished by the lack of a worker exposure study and the lack of experimental data on the dermal absorption kinetics of metsulfuron methyl (Section 3.1). Nonetheless, the statistical uncertainties in the estimated dermal absorption rates, both zero-order and first-order, are incorporated into the exposure assessment and risk characterization.

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. None of these hazard quotients approach a level of concern at the upper ranges, even when considering the level of concern associated with an application rate of 0.15 lbs a.e./acre – i.e., a level of concern of 0.2. The simple verbal interpretation of this quantitative characterization of risk is that under the most protective set of exposure assumptions, workers would not be exposed to levels of metsulfuron methyl that are regarded as unacceptable so long as reasonable and prudent handling practices are followed.

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

3.4.3. General Public. The quantitative hazard characterization for the general public associated with exposure to metsulfuron methyl 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 acute RfD of 0.25 mg/kg/day for acute/short term exposure scenarios and the chronic RfD of 0.25 mg/kg/day chronic or 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 at an application rate of 0.03 lbs/acre are sufficiently below a level of concern. Thus, 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 metsulfuron methyl even if the level of concern is set to 0.2 – i.e., that associated with the maximum application rate of 0.15 lbs/acre that will be used in Forest Service programs.

For the acute/accidental scenarios, none of the central estimates representing typical exposures exceed the RfD. Exposure resulting from the consumption of contaminated water is of greatest concern. The estimate of the upper range of exposure resulting from the consumption by a child of contaminated water from a small pond immediately after an accidental spill (Section 3.2.3.4.1) is below the level of concern at the maximum application rate of 0.15 lbs/acre – i.e., a hazard quotient of 0.1 and a level of concern of 0.2. This is an extremely conservative scenario that typically results in an excursion above the RfD. This is not the case with metsulfuron methyl.

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 risk can be quantitatively characterized by simply adding the hazard quotients for each exposure scenario. For metsulfuron methyl, considerations of multiple exposure scenarios has little impact on the risk assessment. For example, based on the upper ranges for typical levels of acute/accidental exposure for being directly sprayed on the lower legs, staying in contact with contaminated vegetation, eating contaminated fruit, drinking contaminated water from a stream, and consuming contaminated fish at rates characteristic of subsistence populations leads to a combined hazard quotient of 0.0215 ($0.0004 + 0.0001 + 0.02 + 0.0001 + 0.0009$). Note that virtually all of the risk is associated with the consumption of contaminated vegetation (i.e., $0.02 \div 0.0215 = 0.93$ or 93% of the exposure). Similarly, for all of the chronic exposure scenarios, the addition of all possible pathways lead to hazard quotients that are below the level of concern of 0.2 – i.e., the level of concern at the maximum application rate.

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 metsulfuron methyl. Due to the

lack of data in humans, the likely critical effect of metsulfuron methyl in humans cannot be identified clearly. As indicated in Section 3.1.3, in animals the most sensitive effect of metsulfuron methyl appears to be weight loss. However, there is some suggestion that metsulfuron methyl may influence blood glucose levels and cholesterol regulation. If exposure levels were sufficient to induce decreases in serum glucose, individuals taking medication to lower serum glucose could be at increased risk. Nonetheless, this exposure scenario is highly implausible.

3.4.5. Connected Actions. As noted in section 2.2, the manufacturers recommend that metsulfuron methyl formulations be mixed with a surfactant. There is no published literature or information in the FIFRA files that would permit an assessment of toxicological effects or risk assessment of metsulfuron methyl mixed with a surfactant. According to the product label, Escort may be applied in combination with other herbicides. However, there are no animal data to suggest that metsulfuron methyl will interact, either synergistically or antagonistically with any other herbicide.

3.4.6. Cumulative Effects. As noted above, this risk assessment specifically considers the effect of both single and repeated exposures. Based on the hazard quotients summarized in Worksheet E04, as discussed above, there is no indication that repeated exposures will exceed the threshold for toxicity.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview. The mammalian toxicity of metsulfuron methyl is relatively well characterized in experimental mammals; however, there is relatively little information regarding nontarget wildlife species. It seems reasonable to assume the most sensitive effects in wildlife mammalian species will be the same as those in experimental mammals (i.e., decreased body weight gain). Several acute toxicity studies and two reproduction studies are available on the toxicity of metsulfuron methyl to birds. These studies indicate that birds appear to be no more sensitive than experimental mammals to the toxic effects of metsulfuron methyl, with the major effect again being decreased body weight gain. There are also several acute assays on the honey bee that indicate that bees are no more sensitive than either mammals or birds to metsulfuron methyl. At exposure rates that exceed the highest recommended application rate by about a factor of 3, metsulfuron methyl appears to be somewhat toxic to the Rove beetle, *Aleochara bilineata*, causing a 15% decrease in egg hatching.

The toxicity of metsulfuron methyl to terrestrial plants was studied extensively and is well characterized. Metsulfuron methyl inhibits acetolactate synthase (ALS), an enzyme that catalyzes the biosynthesis of three branched-chain amino acids, all of which are essential for plant growth. Terrestrial microorganisms also have an enzyme that is involved in the synthesis of branched chain amino acids, which is functionally equivalent to the target enzyme in terrestrial macrophytes. There are laboratory and field studies on the effects of metsulfuron methyl to soil microorganisms. These studies suggest that transient effects on soil bacteria are plausible.

The available data suggest that metsulfuron methyl, like other herbicides, is much more toxic to aquatic plants than to aquatic animals. Frank toxic effects in fish are not likely to be observed at concentrations less than or equal to 1000 mg/L. Aquatic plants are far more sensitive than aquatic animals to the effects of metsulfuron methyl. Macrophytes appear to be more sensitive than algae. Similar EC₅₀ values were observed in studies in duckweed and Northern watermilfoil, with an NOEC of 0.00016 mg/L reported in duckweed. *Selenastrum capricornutum* appears to be the most sensitive species of algae, with an NOEC value of 0.01 mg/L. *Anabaena flosaquae* and *Navicula pelliculosa* appear to be the most tolerant species, both with an NOEC value of 0.09 mg/L.

4.1.2. Toxicity to Terrestrial Organisms.

4.1.2.1. Mammals— As summarized in the human health risk assessment (see Section 3.1), the mode of action of metsulfuron methyl in mammals is not well understood. There are several standard toxicity studies in experimental mammals that were conducted as part of the registration process. The most consistent toxic effect observed in mammals after exposure to metsulfuron methyl is body weight loss; furthermore, there is some information suggesting that metsulfuron methyl may influence glucose and cholesterol metabolism. Other than these effects, metsulfuron methyl does not appear to cause specific target organ toxicity in mammals.

No field studies are available in which the impact of metsulfuron methyl applications were assessed on mammalian wildlife communities. In standard experimental toxicity studies, metsulfuron methyl has low acute oral toxicity. A common measure of acute oral toxicity is the

LD₅₀, the estimate of the dose that may be lethal to 50% of the exposed animals. As summarized in Section 3.1.4, in rats the acute oral LD₅₀ for technical grade metsulfuron methyl is greater than 5000 mg/kg (Dashiehl and Hall 1982a) and for a 60% formulation of metsulfuron methyl is greater than 5000 mg/kg (equivalent to 3000 mg a.i./kg/day) (Redgate 1984), indicating a low order of toxicity. The acute LD₅₀ values derived from experimental mammals are several orders of magnitude higher than any plausible exposures and have no practical impact on the risk assessment. Clinical signs of toxicity, including discharges (not otherwise specified) from eyes, nose, or mouth were observed after single oral doses as low as 50 mg/kg technical grade metsulfuron methyl (Ullman 1985a). Other signs of toxicity after single oral doses of 500 mg/kg or greater include lethargy, weight loss, and sensitivity to touch. As detailed in Appendix 1, however, these low dose effects were not clearly dose related – i.e., the effects were seen in 2/15 females at 50 mg/kg and 1/15 females at 500 mg/kg.

The subchronic and chronic toxicity studies on metsulfuron methyl were conducted in rats, mice, rabbits and dogs. As discussed in section 3.1.3., the most common and sensitive effect related to metsulfuron methyl exposure is decreased body weight. As discussed in Section 3.3., an RfD of 0.25 mg/kg/day has been derived by the U.S. EPA's RfD workgroup (U.S. EPA 1988). The chronic RfD of 0.25 mg/kg/day is based on a NOAEL of 25 mg/kg/day (corresponding to the dietary concentration of 500 ppm) from a 52-week feeding study in rats using decreased body weight gain as the most sensitive effect (Burns 1994). In this study, rats were exposed to dietary concentrations of metsulfuron methyl of 5, 25, 500, 2500, and 5000 ppm for 52-weeks. The investigators observed a statistically significant, treatment related decrease in mean body weight in males (2500 and 5000 ppm) at 13 weeks and in males and females (5000 ppm) at 52 weeks. A statistically significant decrease in body weight gain, compared with controls, in males and females (500, 2500, and 5000 ppm) at 13 weeks and in males and females (5000 ppm) at 52 weeks was also observed. No overt signs of toxicity were observed at any dose level. Based on these results, the U.S. EPA (1990) classified 500 ppm as the NOAEL. Using a conversion factor of 1 ppm dietary equal to 0.05 mg/kg body weight/day, the U.S. EPA (1984) converted the dietary NOAEL of 500 ppm to a daily dose of 25mg/kg/day.

4.1.2.2. Birds– As summarized in Appendix 2, acute and subchronic toxicity studies on metsulfuron methyl have been conducted in bobwhite quail (Beavers 1984b,c, Beavers et al. 1996a, Fink et al. 1981a) and mallard ducks (Beavers 1984a, Beavers et al. 1996b, Fink et al. 1981b). In adult bob white quail, 14-day oral LD₅₀ of technical grade metsulfuron methyl administered by gavage is >2250 mg/kg (Beavers 1984b), similar to the low order of toxicity of metsulfuron methyl in mammals. No acute oral gavage studies in birds using a 60% formulation of metsulfuron methyl were identified. Dietary exposure of juvenile ducks and quail to technical grade metsulfuron methyl at concentration ranging from 292 to 5620 ppm for up to 5 days did not result in a single mortality in any study (Beavers 1984a,c, Fink 1981a, b). The only sign of toxicity reported in these studies was weight loss following 5-day exposure of 10-day-old bobwhite quail (Beavers 1984c) and 8-day old mallard ducks (Beavers 1984a) to 3160 and 5620 ppm dietary metsulfuron methyl. In both of these studies, the NOAELs for weight loss ranged from 1780 to 3160 ppm.

The most relevant studies for assessing the longer-term toxicity of metsulfuron methyl are the two 23- week feeding studies on reproductive effects conducted by Beavers et al. (1996a,b) in

bobwhite quail and mallard ducks. In both of these studies, dietary levels of up to 1000 ppm had no effect on body weight, food consumption, or reproductive performance. Thus, for both bobwhite quail and mallard ducks, the NOAEL for chronic dietary exposure is 1000 ppm, the highest dose tested.

4.1.2.3. Terrestrial Invertebrates—As summarized in Appendix 3, several standard bioassays were conducted on the toxicity of metsulfuron methyl to bees (Meade 1984a,b). For the most part, the results are unremarkable indicating that the acute LD₅₀ of metsulfuron methyl to bees is greater than 25 µg/bee and possibly greater than 100 µg/bee. Using a body weight of 0.093 g for the honey bee (USDA/APHIS 1993), these values correspond to doses ranging from about 270 to 1075 mg/kg [0.025 mg/0.000093 kg to 0.1 mg/0.000093 kg].

The open literature includes three toxicity studies involving other terrestrial invertebrates exposed to metsulfuron methyl: Kjaer and Heimbach 2001, Oomen et al. (1991), and Samsøe-Petersen (1995). Following the protocols adopted by European community for testing toxicity to beneficial insects, Oomen et al. (1991) summarizes a series of bioassays on the toxicity of several pesticides, including metsulfuron methyl, to the predatory mite, *Phytoseiulus persimilis*. The study classifies the metsulfuron methyl formulation Ally as harmless; however, specific details about the assay and the endpoints measured are not provided in the publication. Samsøe-Petersen 1995 assayed the toxicity of metsulfuron methyl to the eggs of the Rove beetle, *Aleochara bilineata*. In this study, a 15% decrease in egg hatching but no mortality in adult beetles and no effects on egg production were noted after direct spray of 0.067% product (20% a.i.) at a level of 6 µL/cm². As detailed in Appendix 3, metsulfuron methyl had no adverse effects on survival or growth rate of larvae of three insect species (large white butterfly, beetle and grain aphid) placed on plants sprayed with metsulfuron applied at an application rate of 0.00004 to 0.003 lbs a.i./acre (Kjaer and Heimbach 2001).

4.1.2.4. Terrestrial Plants (Macrophytes)—The toxicity of metsulfuron methyl to terrestrial plants was studied extensively and is well characterized (e.g., Anderson et al. 1989; Badon et al. 1990; Brudenell et al. 1995; Drake 1988; Fayez et al. 1994; Kotoula-Syka et al. 1993; Pool and De Villiers 1993; Stork and Hannah 1996). Metsulfuron methyl inhibits acetolactate synthase (ALS), an enzyme that catalyzes the biosynthesis of three branched-chain amino acids (valine, leucine, and isoleucine), all of which are essential for plant growth. Other ALS inhibiting herbicides include other sulfonylureas such as sulfometuron methyl as well as imidazolinones, triazolopyrimidines, and pyrimidinylthiobenzoates.

The most relevant laboratory bioassays regarding the toxicity of metsulfuron methyl to terrestrial plants by direct spray are summarized in Appendix 4. Two sets of pre- and post-emergence bioassays have been conducted (Drake 1988; Heldreth and McKelvey 1996). In the earlier study by Drake (1988) 10 species of plants were tested by both pre-emergence and post-emergence applications: dicots—soybean, cocklebur, cotton, morningglory, wild buckwheat, and sugar beet—and monocots—corn, barnyardgrass, rice and nutsedge. The most sensitive species was the morningglory, which showed 70% growth inhibition at pre-emergence applications of 0.25 g/ha, or about 0.00022 lbs a.i./acre. At the same application rate, the cocklebur evidenced 20% growth inhibition and the sugar beet evidenced 40% growth inhibition. Rice was the only monocot to respond (20% inhibition) to the application rate of 0.25 g/ha. At 4 g/ha or about

0.0036 lbs a.i./acre, all of the dicots were sensitive to metsulfuron methyl with growth inhibition of 90% or greater while the monocots showed growth inhibition ranging from 30 to 70%. At 16 g/ha or about 0.014 lbs a.i./acre, about a factor of two below the typical application rate used by the Forest Service (0.03 lb/acre), all of the plants showed 60 to 100% growth inhibition.

In a more recent study submitted to the U.S. EPA (Heldreth and McKelvey 1996), bioassays were conducted on pre-emergence and post-emergence toxicity to corn, cucumber, onion, pea, rape, sugar beet, sorghum, soybean, tomato, wheat. In the pre-emergence assay, the most sensitive species based on the NOEC were cucumber and onion with an NOEC of 0.000037 lb/acre. The most tolerant species based on the NOEC was wheat with an NOEC of 0.0056 lb/acre). In the post-emergence assay, the cucumber was also the most sensitive species, with an NOEC of 0.000037 lb/acre, identical to that in the pre-emergence assay. The most tolerant species in the post-emergence assay was wheat with an NOEC of 0.0039 lb/acre.

The results of these laboratory bioassays (Drake 1988; Heldreth and McKelvey 1996) are consistent with field studies summarized by Obrigawitch et al. (1998). In these field studies, the lowest application rate associated with adverse effects is reported as 0.1 g/ha, an application rate associated with a decreased yield of both tomatoes and onions (Obrigawitch et al. 1998, Table 1, p. 207). This is similar to the LOEC of 0.25 g/ha reported for other dicots in the bioassay by Drake (1988, detailed in Appendix 4). The most tolerant species in the field studies summarized by Obrigawitch et al. (1998) consisted of various grasses for which NOEC values based on crop yield ranged up to 6 g/ha – i.e., the NOEC values for wheatgrass and brome grass. This NOEC value of 6 g/ha is equivalent to an application rate of about 0.0054 lb/acre, a value that is virtually identical to the NOEC value for wheat of 0.0056 lb/acre reported in the standard Tier 2 plant bioassay by Heldreth and McKelvey (1996, also detailed in Appendix 4).

Levels of metsulfuron methyl in soil (James et al. 1995; Kotoula-Syka et al. 1993; Stork and Hannah 1996) or soil leachate (Guenther et al. 1993) were examined in several bioassays involving various plant species. These studies calibrate the response of various plant species to metsulfuron methyl residues in soil and use the responses in plants to measure or estimate unknown concentrations of metsulfuron methyl in soil. As discussed in the dose-response assessment (section 4.3), these studies are used primarily to quantify the potential effects of soil residues on nontarget plant species. The use of bioassays to measure the amount of a chemical in a medium, like soil, is a long-standing and well-studied practice. The method of extending that use to assess the toxicity of a chemical to nontarget plant species is less direct because the bioassays may vary from laboratory to laboratory. For example, Streibig et al. (1995) examined variability in greenhouse bioassays of EC_{50} values in *Brassica rapa*. Although most of the laboratories reported EC_{50} values within a factor of 10, EC_{50} values among all of the laboratories varied between 0.05 and 3.9 g a.i./ha, a factor of 78 fold.

Some of this variability noted by Streibig et al. (1995) could be associated with different experimental conditions, specifically a negative correlation with soil pH and a positive correlation with organic matter in soil. The negative correlation of EC_{50} values with soil pH (i.e., lower EC_{50} values or greater toxicity in alkaline or high pH soils) is consistent with bioassays of root growth in corn, sunflowers, lentils, and sugar-beets (James et al. 1995; Pool and De Villiers 1993; Pool and Du Toit 1995). As discussed by Pool and De Villiers (1993), the

increase in toxicity may be associated with increased persistence of metsulfuron methyl in soil with a high pH (i.e., lower acid levels and thus lower rates of acid mediated hydrolysis).

The toxicity of metsulfuron methyl may also be influenced by the use of surfactants or other herbicides. Some surfactants, like Silwet L-77, Activator 90, and LI-700 enhance efficacy while others like Bond, appear to retard efficacy (Balneaves 1992a,b,c; Lawrie and Clay 1993; McDonald et al. 1994). A recent study by Holloway et al. (1995) suggests that the MCPA ester may have a synergistic effect with metsulfuron methyl but that the amine salt of MCPA may have an antagonistic action. It is not clear, however, how significant these effects might be in the field because synergism was apparent at the ED₉₀ but not the ED₅₀. There is additional evidence that metsulfuron methyl inhibits the phytotoxicity of tralkoxydim in *Avena fatua* (Devine and Rashid 1993) as well as the phytotoxicity of 1,8-naphthalic anhydride to corn roots (Milhomme and Bastide 1990). Moreover, the efficacy of metsulfuron methyl was enhanced somewhat by sequential but not concurrent applications with imazapyr (Lawrie and Clay 1993).

4.1.2.5. Terrestrial Microorganisms– Terrestrial microorganisms have an enzyme that is involved in the synthesis of branched chain amino acids, which is functionally equivalent to the target enzyme in terrestrial macrophytes. As detailed in Appendix 3, metsulfuron methyl at a concentration of 5 ppm in culture inhibited the growth of several strains of *Pseudomonas*. This effect was attributed to ALS inhibition because the bacteria grew normally with excess amounts of valine, leucine, and isoleucine (Boldt and Jacobson 1998). The same concentration in soil (i.e., 5 mg/kg) decreased levels of amylase, urease, and protease activity in loamy sand and clay loam soil (Ismail et al. 1998). The reduced amylase and urease levels were apparent for the 28-day observation period; protease activity was reduced on day 7 but recovered by day 14 (Ismail et al. 1998, Figure 1 p. 31). At surface application rates of 0.05-0.075 kg/ha, transient decreases in soil bacteria were apparent for 3 days but reversed completely after 9 days (Ismail et al. 1996).

4.1.3. Aquatic Organisms.

4.1.3.1. Fish – Standard toxicity bioassays to assess the effects of exposure of fish to metsulfuron methyl are summarized in Appendix 5. Acute toxicity studies have been conducted in rainbow trout (Hall 1984b, Muska and Hall 1982) and bluegill sunfish (Hall 1984a, Phillips and Hall 1982a) and chronic exposure was studied in rainbow trout (Kreamer 1996). No field studies on the effect of metsulfuron methyl in fish were identified published literature or the U.S. EPA files.

For acute toxicity studies in bluegill sunfish and rainbow trout, the range for 96-hour LC₅₀ values was >150 mg/L to > 1000 mg/L and was the same for both species. The lowest concentration at which mortality was observed in any species of fish is 100 mg/L (Hall 1984b). At this level, mortality was observed in 3/10 bluegill sunfish over a 96-hour exposure period. No mortality, however, was observed in 10 bluegills exposed to 1000 mg/L (Hall 1984a). Because of the lack of a dose-response relationship, Hall (1984a) asserts that the mortality in the 100 mg/L exposure group was probably incidental rather than treatment related. Given the lack of a dose-response relationship in the Hall (1984a) study as well as the results of all of the other bioassays summarized in Appendix 7, it appears that compound-related mortality after acute exposure is not likely to be observed in fish exposed to concentrations less than or equal to 1000 mg/L. In bluegill sunfish, no signs of toxicity were reported at concentrations up to 1000 mg/L (Hall

1984a, Phillips and Hall 1982a). In rainbow trout, signs of toxicity, including erratic swimming behavior, laying on the bottom, lethargy and color changes, were noted, with NOEC values of 10 mg/L (Hall 1984b) and 100 mg/L (Muska and Hall 1982).

Kreamer (1996) is the only study available regarding the toxicity of metsulfuron methyl to fish, eggs, or fry. These investigators observed no effects on rainbow trout hatching, larval survival, or larval growth over a 90-day exposure period at a concentration of up to 4.7 mg/L.

Concentrations greater than 8 mg/L resulted in small but significant decreases in hatching and survival of fry.

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

4.1.3.3. Aquatic Invertebrates– Standard toxicity bioassays to assess the effects of metsulfuron methyl on aquatic invertebrates are summarized in Appendix 6. No field studies are available on the toxicity of metsulfuron methyl to aquatic invertebrates. Metsulfuron methyl appears to be relatively non-toxic to aquatic invertebrates, based on acute bioassays in *Daphnia*, with an acute EC₅₀ value for immobility ranging from >150 mg/L to 720 mg/L and acute NOEC values for immobility ranging from >150 to 420 mg/L (Phillips and Hall 1982a; Wetzel 1984). For chronic exposures (21-days), the EC₅₀ values for survival, reproduction and immobility ranged from 100 to 150 mg/L (Drottar and Krueger 1998, Hutton 1989). A significantly lower NOEC was observed for growth (as measure by body length following chronic exposure (Hutton 1989), which was observed at concentrations as low as 5.1 mg/L. However, at concentrations less than 39 mg/L (measured concentration), the effect was not statistically significant. Thus, the NOEC for growth in this study is 17 mg/L. In aquatic invertebrates, as in birds and mammals, decreased growth appears to be the most sensitive endpoint. Wei et al. (1999) report that neither metsulfuron methyl nor its degradation products are acutely toxic to *Daphnia* at concentrations that approach the solubility of the compounds in water at pH 7. The specific exposure concentrations are not reported in this publication.

4.1.3.4. Aquatic Plants– The toxicity of metsulfuron methyl has been examined in both algae and aquatic macrophytes. Study results are summarized in Appendix 7. Studies on the mechanism of action of metsulfuron methyl in aquatic plants were not identified. However, metsulfuron methyl is assumed to have the same mechanism in aquatic plants as in terrestrial plants (i.e., the inhibition of ALS as described in Section 4.1.2.4). As might be expected for a herbicide, aquatic plants are far more sensitive than aquatic animals to the effects of metsulfuron methyl.

Only two studies were identified that demonstrate the toxicity of metsulfuron methyl to aquatic macrophytes – one 14-day exposure study in duckweed (Douglas and Handley 1988) and one 14-day exposure study in Northern Watermilfoil (Roshon et al. 1999). For both species, EC₅₀ values are comparable, although the specific endpoints examined in each study were different. In duckweed, the 14-day EC₅₀ value of 0.36 µg/L for toxicity (chlorosis of fronds) and NOEC value of 0.16 µg/L for toxicity were reported by Douglas and Handley (1988). In Northern watermilfoil, a 14-day EC₅₀ value of 0.22 µg/L for toxicity (decreased dry root mass) was

reported by Roshon et al. (1999); no NOEC value was reported. Growth stimulation was observed in duckweed exposed to a concentration of 0.003 mg/L (Peterson et al. 1994).

Several studies have investigated the effects of metsulfuron methyl on algae. Fahl et al. (1995) found that the EC₅₀ value of metsulfuron methyl to *Chlorella fusca*, a freshwater alga, is 1.2 mg/L for effects on cell volume growth and 0.85 mg/L for cell reproduction at pH of 6.5. Unlike the relationship for terrestrial plants, toxicity increases with lower or more acidic pH, most probably because of decreased ionization leading to more rapid uptake. Nystrom and Blanck (1998) report a similar EC₅₀, 1.6 mg/L, for growth inhibition in *Selenastrum capricornutum*, another freshwater algal species, with a 72-hour NOEL of 0.038 mg/L. As with terrestrial microorganisms, effects were attributed to ALS inhibition because the growth inhibition was antagonized by addition of branched chain amino acids. A lower NOEC of 0.01 mg a.i./L for growth inhibition following incubation of *Selenastrum capricornutum* with Ally (a 60% metsulfuron formulation) was reported by Forbis (1987). The lower NOEC observed for the formulation may reflect a slightly higher toxicity of the Ally formulation, although variations in experimental conditions, such as incubation time, could also be factors. A higher NOEC value of 95 µg a.i./L for growth inhibition in algae was reported for both *Anabaena flosaquae* (Hicks 1997a) and *Navicula pelliculosa* (Hicks 1997b). Both Hicks studies used the metsulfuron methyl formulation Ally. At a concentration of 0.003 mg/L, metsulfuron methyl was associated with a 6-16% inhibition (not statistically significant) in algal growth rates for three species but stimulation of growth was observed in *Selenastrum capricornutum* (Peterson et al. 1994, Table 5, p. 284). Wei et al. (1998; 1999) assayed the toxicity of metsulfuron methyl degradation products in *Chlorella pyrenoidosa*. Based on 96-hour algae growth inhibition assays, the acute toxicity of the degradation products was about 2-3 times less than that of metsulfuron methyl itself.

In addition to these laboratory studies, there is one field study on the effects of metsulfuron methyl in algal species indicating that concentrations of metsulfuron methyl as high as 1 mg/L are associated with only slight and transient effects on plankton communities in a forest lake (Thompson et al. 1993a,b,c).

4.1.3.5. Other Aquatic Microorganisms– The only information on toxicity to aquatic microorganisms comes from the study by Peterson et al. (1994) in which significant inhibition in growth was noted in three species of cyanobacteria at a concentration of 0.003 mg/L. By analogy to the effects on terrestrial bacteria and aquatic algae, it seems plausible that aquatic bacteria and fungi will be sensitive to the effects of metsulfuron methyl at low concentrations.

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 contact with contaminated vegetation. In acute exposure scenarios, the highest exposures for terrestrial vertebrate involves the consumption of contaminated insects by a small bird, which could reach up to about 3 mg/kg. There is a wide range of exposures anticipated from the consumption of contaminated vegetation by terrestrial animals: central estimates range from 0.04 mg/kg for a small mammal to 0.8 mg/kg for a large bird under typical exposure conditions, with upper ranges of about 0.08 mg/kg for a small mammal and 2.3 mg/kg for a large bird. The consumption of contaminated water will generally lead to much lower levels of exposure. A similar pattern is seen for chronic exposures. The central estimate for daily doses for a small mammal from the longer term consumption of contaminated vegetation at the application site is about 0.002 mg/kg/day, with an upper estimate of about 0.007 mg/kg/day. Longer term exposures from contaminated vegetation far exceed doses that are anticipated from the consumption of contaminated water, which has a central estimate of about 0.0000009 mg/kg/day and an upper range of about 0.000002 for a small mammal. Based on general relationships of body size to body volume, larger vertebrates will be exposed to lower doses than small vertebrates under comparable exposure conditions. Because of the apparently low toxicity of metsulfuron methyl 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, 0.03 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. Estimated levels of exposure for the other scenarios 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. The analysis of spray drift is based on estimates from 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 metsulfuron methyl 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 estimated using 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. The peak estimated rate of contamination of ambient water associated with the normal application of metsulfuron methyl is 0.002 (0.00001 to 0.01) mg a.e./L at an application rate of 1 lb a.e./acre. For longer-term exposures, average estimated rate of contamination of ambient water associated with the normal application of metsulfuron methyl is 0.0002 (0.0001 to 0.0004) 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 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 of surface area of the organism and abbreviated as mg/cm². In estimating dose, however, a distinction is made between the exposure dose and the absorbed dose. The *exposure dose* is the amount of material on the organism (i.e., the product of the residue level in mg/cm² and the amount of surface area exposed), which can be expressed either as mg/organism or mg/kg body weight. The *absorbed dose* is the proportion of the exposure dose that is actually taken in or absorbed by the animal.

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

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

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

4.2.2.1. Direct Spray – In the broadcast application of any herbicide, wildlife species may be sprayed directly. This scenario is similar to the accidental exposure scenarios for the general public discussed in Section 3.2.3.2. In a scenario involving exposure to direct spray, the amount absorbed depends on the application rate, the surface area of the organism, and the rate of absorption.

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

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 over-estimate 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 metsulfuron methyl 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 metsulfuron methyl by bees or other invertebrates, this exposure scenario, detailed in Worksheet F02b, also assumes complete absorption over the first day of exposure.

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

4.2.2.2. Indirect Dermal Contact – As in the human health risk assessment (see Section 3.2.3.3), the only approach for estimating the potential significance of indirect dermal contact is

to assume a relationship between the application rate and dislodgeable foliar residue. The study by Harris and Solomon (1992) (Worksheet A04) is used to estimate that the dislodgeable residue will be approximately 10 times less than the nominal application rate.

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

It is reasonable to assume that for prolonged exposures an equilibrium may be reached between levels on the skin, rates of absorption, and levels on contaminated vegetation, although there are no data regarding the kinetics of such a process. However, the high water solubility and low octanol/water partition coefficient for metsulfuron methyl suggest that metsulfuron methyl is not likely to partition from the surface of contaminated vegetation to the surface of skin, feathers, or fur. 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 exposure scenarios for contaminated vegetation are not further elaborated in this document.

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

For the consumption of contaminated vegetation, a small mammal is used because allometric relationships indicate that small mammals will ingest greater amounts of food per unit body weight, compared with large mammals. The amount of food consumed per day by a small mammal (i.e., an animal weighing approximately 20 g) is equal to about 15% of the mammal's total body weight (U.S. EPA/ORD 1989). When applied generally, this value may overestimate or underestimate exposure in some circumstances. For example, a 20 g herbivore has a caloric requirement of about 13.5 kcal/day. If the diet of the herbivore consists largely of seeds (4.92 kcal/g), the animal would have to consume a daily amount of food equivalent to approximately 14% of its body weight $[(13.5 \text{ kcal/day} \div 4.92 \text{ kcal/g}) \div 20\text{g} = 0.137]$. 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 $[(13.5 \text{ kcal/day} \div 2.46 \text{ kcal/g}) \div 20\text{g} = 0.274]$ (U.S. EPA/ORD 1993, pp.3-5 to 3-6). For this exposure assessment (Worksheet F03), the amount of food consumed per day by a small mammal weighing 20 g is estimated at about 3.6 g/day or about 18% of body weight per day from the general allometric relationship for food consumption in rodents (U.S. EPA/ORD 1993, p. 3-6).

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

For the acute exposures, the assumptions are made that the vegetation is sprayed directly, the animal grazes on site, and that 100% of the animal's 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 F11a. 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 (lowering 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 metsulfuron methyl in insects after applications of metsulfuron methyl. 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, metsulfuron methyl 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 metsulfuron methyl in water are identical to those used in the human health risk assessment (Worksheet B06). The only major differences involve the weight of the animal and the amount of water consumed. There are well-established relationships between body weight and water consumption across a wide range of mammalian species (e.g., U.S. EPA 1989). Mice, weighing about 0.02 kg, consume approximately 0.005 L of water/day (i.e., 0.25 L/kg body weight/day). These values are used in the exposure assessment for the small (20 g) mammal. Unlike the human health risk assessment, estimates of the variability of water consumption are not available. Thus, for the acute scenario, the only factors affecting the variability of the ingested dose estimates include the field dilution rates (i.e., the concentration of the chemical in the solution that is spilled) and the amount of solution that is spilled. As in the acute exposure scenario for the human health risk assessment, the amount of the spilled solution is taken as 200 gallons. In the exposure scenario involving contaminated ponds or streams due to contamination by runoff or percolation, the factors that affect the variability are the water contamination rate, (see Section 3.2.3.4.2) and the application rate. Details regarding these calculations are summarized in Worksheets F06 and Worksheet F07.

4.2.3. Terrestrial Plants. In general, the primary hazard to nontarget terrestrial plants associated with the application of most herbicides is unintended direct deposition or spray drift. In addition, herbicides may be transported off-site by percolation or runoff or by wind erosion of soil.

4.2.3.1. Direct Spray – Unintended direct spray will result in an exposure level equivalent to the application rate. For many types of herbicide applications – e.g., rights-of-way management – it is plausible that some nontarget plants immediately adjacent to the application site could be sprayed directly. This type of scenario is modeled in the human health risk assessment for the consumption of contaminated vegetation.

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

Drift Task Force, a coalition of pesticide registrants. AgDRIFT is based on the algorithms in FSCBG (Teske and Curbishley, 1990), a drift model previously used by USDA.

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

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

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

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

or

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

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

In typical backpack ground sprays, droplet sizes are greater than 100μ , 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 400μ , 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 100μ 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 \cdot 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 \cdot 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 \cdot 15 \cdot 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 – Metsulfuron methyl or any other herbicide may be transported to off-site soil by runoff or percolation. Both runoff and percolation are considered in estimating contamination of ambient water. For assessing off-site soil contamination, however, only runoff is considered. This approach is reasonable because off-site runoff will contaminate the off-site soil surface and could impact nontarget plants. Percolation, on the other hand, represents the amount of the herbicide that is transported below the root zone and thus may impact water quality but should not affect off-site vegetation.

Based on the results of the GLEAMS modeling (Section 3.2.3.4.2), the proportion of the applied metsulfuron methyl 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 regions with very high rainfall rates.

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

The levels of exposure associated with this scenario will depend on the concentration of metsulfuron methyl in the ambient water used for irrigation and the amount of irrigation water that is applied. As detailed in Section 3.2.3.4, metsulfuron methyl is relatively mobile and contamination of ambient water may be anticipated and can be quantified (i.e., 0.002 [0.00001 to 0.01] mg a.e./L at an application rate of 1 lb a.e./acre [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). This variability is addressed further in the risk characterization (Section 4.4.2.2).

Based on the estimated concentrations of metsulfuron methyl in ambient water and an irrigation rate of 1 inch per day, the estimated functional application rate of metsulfuron methyl to the irrigated area is 1.36×10^{-6} ($6.78 \times 10^{-9} - 6.78 \times 10^{-6}$) 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 1.80×10^{-2} lb a.e./acre (Worksheet G04) and offsite movement from drift can result in functional offsite application rates of about 6×10^{-4} lb a.e. after ground broadcast applications (Worksheet G05a).

4.2.3.5. Wind Erosion – Soil may be eroded or blown offsite by wind. In this risk assessment, this process is referred to simply as *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 metsulfuron methyl, this mechanism has been associated with the environmental transport of other herbicides (Buser 1990). Numerous models have been developed for wind erosion (e.g., Streck and Spaan 1997; Streck 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) recently 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 metsulfuron methyl on soil particles by wind, 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 (1 m^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 [$(0.05 \text{ g/cm}^2) \div (2 \text{ g/cm}^3)$]. The average amount per day would be about 0.00007 cm/day (0.025 cm per year \div 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 ($0.00007 \div 5 = 0.000014$) to 0.0001 cm/day ($0.00007 \times 2 = 0.00014$).

The amount of metsulfuron methyl 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 metsulfuron methyl would

be neither substantial or nor significant. For this risk assessment, it will be assumed that metsulfuron methyl 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 metsulfuron methyl in runoff, the deposition of the metsulfuron methyl 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. Limited data are available on the toxicity of metsulfuron methyl to microorganisms (Section 4.1.2.5). The toxicity data are expressed in units of soil concentration – i.e., mg metsulfuron methyl/kg soil which is equivalent to parts per million (ppm) concentrations in soil. The GLEAMS modeling discussed in Section 3.2.3.4 provides estimates of concentration in soil as well as estimates of off-site movement (runoff, sediment, and percolation). Based on the GLEAMS modeling, concentrations in clay, loam, and sand over a wide range of rainfall rates are summarized in Table 4-1. As indicated in this table, peak soil concentrations in the range of about 6 ppm are likely in relatively arid soils at an application rate of 1 lb a.e./acre. As rainfall rate increases, maximum soil concentrations are substantially reduced in sand and, to a lesser extent, in loam because of losses from soil through percolation. The potential consequences of such exposures are discussed in Section 4.4 (Risk Characterization).

4.2.5. Aquatic Organisms. The potential for effects on aquatic species are based on estimated concentrations of metsulfuron methyl 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 metsulfuron methyl is 0.002 (0.00001 to 0.01) mg a.e./L at an application rate of 1 lb a.e./acre. For longer-term exposures, average estimated rate of contamination of ambient water associated with the normal application of metsulfuron methyl is 0.0002 (0.0001 to 0.0004) 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., 0.03 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 for metsulfuron methyl is based on the same data as the human health risk assessment (i.e., the chronic NOAEL of 25 mg/kg/day from a 2-year feeding study in rats is used to assess both acute and chronic risk). None of the exposure scenarios, acute or longer term, result in exposure estimates that exceed this NOAEL. Birds appear to be substantially less sensitive to metsulfuron methyl than mammals with an acute NOAEL of 1043 mg/kg/day from a 5-day feeding study and a longer-term NOAEL from a reproduction study of 120 mg/kg/day. For terrestrial invertebrates, based on direct spray studies in honey bees, no mortality would be expected following acute exposure to doses up to 270 mg/kg. Soil microorganisms are sensitive to metsulfuron methyl at concentrations of 5 ppm (or 5 µg/g soil), but most effects appear to be transient.

The toxicity of metsulfuron methyl to terrestrial plants is relatively well characterized. Metsulfuron methyl is a potent herbicide that causes adverse effects in a variety of target and nontarget plant species. Results of pre-emergent and post-emergent application studies in a variety of plant species yield LOELs ranging from 0.00022 to 0.0036 lbs/acre. For assessing the potential consequences of exposure to nontarget plants via runoff, an LOEC for seedling emergence of 0.00022 lb/acre is used for sensitive species and the corresponding value for tolerant species is 0.00089 lb/acre. For assessing the impact of drift, an LOEC for vegetative vigor of 0.00022 lb/acre is used for sensitive species and the corresponding value for tolerant species is 0.0036 lb/acre.

The data on toxicity to fish and aquatic invertebrates were obtained in only a few species – rainbow trout, bluegill sunfish and *Daphnia magna*. Metsulfuron methyl has a low order of toxicity to fish. Mortality is not likely to occur in fish exposed to metsulfuron methyl concentrations less than or equal to 1000 mg/L. For acute exposures in fish, the NOEC of 10 mg/L in rainbow trout is used for the most sensitive species and the NOEC of 1000 mg/L in bluegill sunfish is used for the most tolerant species. The toxicity value used to assess the potential for chronic effects may be based on the 90-day exposure of rainbow trout in which the NOEC was 4.5 mg/L. This value is used directly as a longer term NOEC in sensitive species because the rainbow trout appears to be a relatively sensitive species in acute toxicity assays. Using the relative potency for acute exposures of 100 (rainbow trout 100-times more sensitive than bluegill sunfish), an NOEC for tolerant species is estimated at 450 mg/L. Similarly, aquatic invertebrates do not appear to be sensitive to metsulfuron methyl. Since the only studies identified in aquatic invertebrates were in a single species, data obtained in *Daphnia magna* are used for both the sensitive and tolerant species. For acute exposure, a 48-hour NOEC for immobility of 420 mg/L is used. For chronic exposures, the NOEC of 17 mg/L for growth inhibition is used, although higher chronic NOECs, ranging from 100 to 150 mg/L, have been reported for survival, reproduction and immobility.

Aquatic plants appear to be much more sensitive to metsulfuron methyl than aquatic animals. An NOEC for plant damage of 0.00016 mg/L in duckweed is used to quantify effects for both acute and chronic exposure in aquatic macrophytes. This value is comparable to other studies in aquatic macrophytes and there is no basis for differentiating sensitive and tolerant species of aquatic macrophytes. For algae, the same data are used to quantify risk for both acute and chronic exposures. The most sensitive algal species appears to be *Selenastrum capricornutum*,

with a 120-hour NOEC of 0.01 mg/L and the most tolerant species appear to be *Anabaena flosaquae* and *Navicula pelliculosa*, both with a 120-hour NOEC of 0.09 mg/L.

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), the Office of Pesticide Programs of the U.S. EPA used an acute NOAEL of 34 mg/kg/day (for decreased body weight) as a NOAEL for acute exposures (Section 3.3.3) and a chronic NOAEL of 25 mg/kg/day (also based on decrease body weight) as the basis of the chronic RfD (Section 3.3.2). As discussed in Section 3.3, the acute NOAEL is very close to and not substantially different from the chronic NOAEL. In addition, all of the estimated mammalian acute and chronic exposures are below the chronic NOEL of 25 mg/kg/day. Consequently, the NOAEL of 25 mg/kg/day is used directly and without elaboration for both acute and chronic exposure scenarios.

4.3.2.2. Birds – As discussed in Section 4.1.2.2, results of all acute exposure studies in birds show that metsulfuron methyl has very low toxicity, with LD₅₀ values exceeding 2250 mg/kg by gavage and exceeding 5620 ppm in the diet. Several studies report a decrease in body weight gain following short-term dietary exposure to metsulfuron methyl (details provided in Section 4.1.2.2 and Appendix 2). Results of 14-day gavage study in adult quail show that body weight gain was decreased at metsulfuron doses of 292 mg/kg and greater (Beavers 1984b); however, dietary exposure is considered to be more relevant to this risk assessment. In young mallard ducks exposed to dietary metsulfuron methyl for 5 days, the NOAEL for decreased body weight gain was reported as 1780 ppm (Beavers 1984a, Fink et al. 1981b) and in young quail the NOAEL ranged from 1780 to 3160 ppm (Beavers 1984c, Fink et al. 1981a). Since the degree of decreased weight gain was modest (< 15%) and no other signs of toxicity are reported in these birds or in adult birds exposed to 5000 ppm, the NOAEL for acute exposure to birds is taken as 3160 ppm (1043 mg/kg/day). Conversion of dietary concentrations of metsulfuron methyl to a daily dose of metsulfuron methyl was made by multiplying the average fractional weight of food consumption per bird (0.33) by the concentration of metsulfuron methyl in food (3160 ppm or mg/kg). The average fractional weight of food consumption of 0.33 was determined by dividing the average food consumption/bird/day (10.7 g) by average body weight (32 g). Body weights were reported as group averages for each treatment group at the beginning of the exposure period (Day 1) and 3 days after the end of exposure (Day 8). To determine an average body weight of 32 g, the average of Day 1 (23 g) and Day 8 (41 g) weights was taken. Food consumption was reported as the total estimated food consumption during the 5-day exposure period for each exposure group – a value of 537 g over 5 days for the group of 10 birds; thus, the amount of food consumed per bird per day is approximately 10.7g (537 g ÷ 10 birds ÷ 5 days).

For chronic exposure, metsulfuron methyl does not appear to be toxic to adult birds at dietary concentrations up to 1000 ppm for up to 22 weeks (Section 4.1.2.2). This NOAEL was observed in both mallard ducks and in quail (Beavers et al. 1996a,b). Thus, for this risk assessment, the NOAEL of 1000 ppm (120 mg/kg/day) in mallard ducks is used to characterize risks from chronic exposures. To convert the concentration of 1000 ppm to units of mg/kg/day, the average fractional weight of food consumption per bird (0.12) was multiplied by the concentration of metsulfuron methyl in food (1000 ppm or mg/kg). The average fractional food consumption of 0.12 was determined by dividing the average food consumption/bird/day of 150 g, (individual

animal data provided in Table 2, p. 30 of Beavers et al. 1996b) by an average body weight during the 22-week study of 1125 g (individual animal data provided in Table 1, p. 27 of Beavers et al. 1996b). For the similar study in bobwhite quail, the fractional weight of food consumption per bird was 0.13, yielding a dose conversion of 1000 ppm to 120 mg/kg/day – a value that is essentially the same as that observed in mallard ducks. Since acute and chronic NOAELs for birds greatly exceed all exposure scenarios, it is not necessary to elaborate this dose-response assessment.

4.3.2.3. Terrestrial Invertebrates –Several standard bioassays were conducted on the toxicity of metsulfuron methyl to bees, as detailed in Section 4.1.2.3 and Appendix 3. Results of these studies are unremarkable, yielding LD₅₀ values of metsulfuron methyl greater than the highest doses tested in each study – a range of 25 to 100 µg/bee. Using a body weight of 0.093 g for the honey bee (USDA/APHIS 1993), these values correspond to doses ranging from about 270 to 1075 mg/kg [0.025 mg/0.000093 kg to 0.1 mg/0.000093 kg]. For the purposes of this risk assessment, the NOAEL 270 mg/kg will be used for risk characterization. Since this NOAEL greatly exceed all exposure scenarios, it is not necessary to elaborate this dose-response assessment.

While standard toxicity studies in bees do not suggest that bees are any more or less sensitive to metsulfuron methyl than experimental mammals, there is one study (Samsøe-Petersen 1995) using the Rove beetle which notes a 15% reduction in egg hatching after direct spray of 0.067% product (20% a.i.) at a level of 6 µL/cm². The 0.067% solution corresponding to a metsulfuron methyl concentration of 0.00134 mg/µL:

$$0.067\% = 0.0067 \cdot 0.2 \text{ g/mL or } 0.2 \text{ mg/}\mu\text{L} = 1.34 \text{ }\mu\text{g/}\mu\text{L}$$

and the application of 6 µL/cm² corresponds to an application rate of 0.00804 mg/cm²:

$$6 \text{ }\mu\text{L/cm}^2 \cdot 1.34 \text{ }\mu\text{g/}\mu\text{L} = 8.04 \text{ }\mu\text{g/cm}^2.$$

By comparison, the typical application rate of 0.03 lbs a.i./acre corresponds to an application rate of 0.2263 µg/cm² and the highest labeled application rate of 0.15 lbs a.i./acre corresponds to an application rate of 1.68 µg/cm².

4.3.2.4. Terrestrial Plants (Macrophytes) – Metsulfuron methyl is a herbicide and causes adverse effects in a variety of nontarget plant species (Section 3.1.2.4 and Appendix 4). The most relevant studies for assessing the effects of direct spray or drift are the series of bioassays conducted by Drake (1988) and Heldreth and McKelvey (1996). As noted in Section 4.1.2.4, these bioassay results are consistent with a number of field studies summarized by Obrigawitch et al. (1998). The more recent bioassay by Heldreth and McKelvey (1996) clearly defines NOEC's for growth inhibition whereas the earlier study by Drake (1988) did not define NOEC's for most species (Appendix 4 with discussion in Section 4.1.2.4).

For assessing the potential consequences of exposure to nontarget plants via runoff, results of pre-emergence studies are used from the study by Heldreth and McKelvey (1996). In this assay, the most sensitive species based on the NOEC were cucumber and onion with an NOEC of

0.000037 lb/acre. The most tolerant species based on the NOEC was wheat with an NOEC of 0.0056 lb/acre). These values are used in Worksheet G04 to assess the risks to nontarget plant species from soil contamination associated with the runoff of metsulfuron methyl from the application site.

For assessing the impact of drift, bioassays on vegetative vigor from the study by Heldreth and McKelvey (1996) will be used. As also noted in Section 3.1.2.4 and detailed Appendix 4, the cucumber was also the most sensitive species in the post-emergence assay with an NOEC of 0.000037 lb/acre, identical to that in the pre-emergence assay. The most tolerant species in the post-emergence assay was wheat, with an NOEC of 0.0039 lb/acre. These NOEC values are used in Worksheets G05a and G05b for characterizing risks associated with off-site drift.

4.3.2.5. Terrestrial Microorganisms – As discussed in section 4.1.2.5, the sensitivity of terrestrial microorganisms appears to operate and be governed by the same mechanism involved in plant toxicity. Results of a single study in 77 species of *Pseudomonas* show that growth is reduced in some strains at soil concentration of 5 ppm metsulfuron methyl and growth of nearly all strains reduced at a soil concentration of 300 ppm (Boldt and Jacobsen 1998). However, most effects on soil microorganisms appear to be transient and recovery occurs within 9 to 14 days (Ismail et al. 1996, 1998). Thus, even at concentrations in soil that would likely cause adverse effects in a large number of macrophytes (i.e., 5 ppm) effects on soil microorganisms appear to be transient.

4.3.3. Aquatic Organisms.

The toxicity values used in this risk assessment are summarized in Worksheet G03 based on the information presented in Section 4.1.3.

4.3.3.1. Fish – As discussed in Section 4.1.3.1, fish do not appear to be highly sensitive to metsulfuron toxicity, with acute LC₅₀ values ranging from > 150 mg/L to > 1000 mg/L (Hall 1984a,b; Muska and Hall 1982; Phillips and Hall 1982a). Sublethal effects of metsulfuron methyl, including erratic swimming behavior, laying on the bottom, lethargy and color changes, were observed in rainbow trout at concentrations of \geq 100 mg/L, with a NOEC of 10 mg/L (Hall 1984b). Similar results in rainbow trout were reported by Muska and Hall (1982), with an NOEC for toxicity of 100 mg/L. No signs toxicity was observed in bluegill sunfish at concentration up to 1000 mg/L (Hall 1984a, Phillips and Hall 1982a). Thus, for this risk assessment, the NOEC of 10 mg/L for sublethal effects in rainbow trout is used for the most sensitive species and the NOEC of 1000 mg/L in bluegill sunfish is used for the most tolerant species. Thus, rainbow trout appear to be approximately 100 times more sensitive to metsulfuron methyl toxicity than bluegill sunfish.

The potential for chronic effects is based on the available egg-and-fry/early life stage by Kreamer (1996). The results of this study yield an NOEC of 4.5 mg/L based on standard length of surviving fingerlings at 90 days. Based on the results of acute exposure studies as described above, rainbow trout appear to be more sensitive than bluegill sunfish to metsulfuron methyl toxicity. Thus, for this risk assessment, the NOEC of 4.5 mg/L will be used for the most sensitive species for chronic exposure. Although no data are available to determine the most tolerant species for chronic exposures, parallels can be drawn to the acute exposure studies. As

discussed above, the relative potency factor comparing rainbow trout to bluegill sunfish is 100 (i.e., rainbow trout are 100-times more sensitive to metsulfuron toxicity than bluegill sunfish in acute exposures). Using the relative potency factor for acute exposures of 100 and the chronic NOEC in rainbow trout of 4.5 mg/L, an NOEC for bluegill sunfish is estimated to be 450 mg/L. This surrogate NOEC for chronic exposure in bluegill sunfish will be used to estimate the chronic NOEC for the most tolerant species.

4.3.3.2. Aquatic Invertebrates – The only studies assessing the toxicity of metsulfuron methyl in aquatic invertebrates that were identified from the available literature are in *Daphnia magna*. Therefore, it is not possible to identify a most sensitive and most tolerant species. As detailed in Section 4.1.3.3 and Appendix 6, *Daphnia* appear to be relatively tolerant to metsulfuron methyl toxicity, with LC₅₀ values >150 mg/L. For this risk assessment, the 48-hour NOEC of 420 mg/L based on immobility (Wetzel 1984) will be used for acute exposures. For chronic exposures, the lowest NOEC (21-days) reported 17 mg/L based on growth (Hutton 1989), although higher chronic NOECs, ranging from 100 to 150 mg/L, have been reported for survival, reproduction and immobility (Drottar and Krueger 1998, Hutton 1989). Thus, taking the most conservative approach, for the purposes of this risk assessment, the NOAEL 17 mg/kg will be used for risk characterization for chronic exposures of aquatic invertebrates.

4.3.3.3. Aquatic Plants – The relevant data on the toxicity of metsulfuron methyl to aquatic plants is summarized in Appendix 7. The most sensitive algal species appears to be *Selenastrum capricornutum*, with an 120-hour NOEC based on growth inhibition of 10 µg/L (0.01 mg/L) (Forbis 1987). A somewhat higher NOEC (0.038 mg/L) for this species has been reported by Nystrom and Blanck (1998), but the difference is not substantial. Based on review of the available literature, the most tolerant species of algae are *Anabaena flosaquae* and *Navicula pelliculosa*, both with a 120-hour NOEC for growth inhibition of 95 µg/L (0.095 mg/L) (Hicks 1997a). All durations of exposure for the studies in algae ranged from 72 to 95 hours; no long-term exposure studies were identified in the available literature. Therefore, for risk characterization for both acute and chronic exposure, the NOEC of 0.01 mg/L will be used for the most sensitive species and the NOEC of 0.09 mg/L will be used for the most tolerant species.

Limited information is available on the toxicity of metsulfuron methyl to aquatic macrophytes. Only two studies, one in duckweed and one in Northern watermilfoil, showing toxicity of metsulfuron methyl to aquatic plants were identified in the available literature. As discussed in Section 4.1.3.4, similar EC₅₀ values were reported for both species. A 14-day NOEC of 0.16 µg/L (0.00016 mg/L) was reported for duckweed (Douglas and Handley 1988). This value will be used for characterization of acute and chronic exposure for both sensitive and tolerant species.

4.3.3.4. Aquatic Microorganisms – Based on the report by Peterson et al. (1994), the effect level for growth inhibition in three species of cyanobacteria is 0.003 mg/L. By analogy to the effects on terrestrial bacteria and aquatic algae, it seems plausible that aquatic bacteria and fungi will be sensitive to the effects of metsulfuron methyl at concentrations that are substantially higher than those affecting aquatic algae or macrophytes.

4.4. RISK CHARACTERIZATION

4.4.1. Overview. Metsulfuron methyl is an effective and potent herbicide. Adverse effects on some nontarget terrestrial plant species and, to a lesser degree, some aquatic plant species are plausible under some conditions. For terrestrial plants, the dominant factor in the risk characterization is the potency of metsulfuron methyl relative to the application rate. The typical application rate considered in this risk assessment, 0.03 lb/acre, is over 800 times higher than the NOEC in the vegetative vigor (direct spray) assay of the most sensitive nontarget species – i.e., 0.000037 lb/acre – and approximately 8 times higher than the NOEC for the most tolerant species in the same assay – i.e., 0.0039 lb/acre. The highest application rate that may be considered in Forest Service programs – i.e., 0.15 lb/acre – is over 4000 times the NOEC in sensitive species and a factor of about 40 above the NOEC in tolerant species. Given these relationships, damage to sensitive nontarget species could be expected in ground broadcast applications at distances up to about 500 feet from the application site in areas in which off-site drift is not reduced by foliar interception. This risk characterization applies only to ground broadcast applications. When used in directed foliar applications (i.e., backpack), offsite drift could be reduced substantially but the extent of this reduction cannot be quantified.

The NOEC values for soil exposures (assayed in the seedling emergence test) are 0.000037 lb/acre for sensitive species and 0.0056 lb/acre for tolerant species. The offsite movement of metsulfuron methyl via runoff could be substantial under conditions that favor runoff – i.e., clay soils – and hazard quotients in the range of about 40 to nearly 500 are estimated for sensitive species over a wide range of rainfall rates – i.e., 15 inches to 250 inches per year. In very arid regions in which runoff might not be substantial, wind erosion could result in damage to nontarget plant species. The plausibility of observing such damage would, however, be highly dependent on local conditions. This risk characterization for the potential effects of runoff would be applicable to either broadcast ground or directed foliar applications.

The potential for damage to aquatic plants, particularly macrophytes, appears substantially less than for terrestrial plants. All hazard quotients for aquatic macrophytes were based on an NOEC of 0.000016 mg/L in duckweed for both acute and chronic exposures. No sensitive or tolerant species were identified. Except for the hazard quotient of 2 associated with acute exposures based on the peak concentrations of metsulfuron methyl, all hazard quotients are below the level of concern, with a range of 0.002 to 2 for acute exposures and 0.02 to 0.08 for chronic exposures. Thus, if metsulfuron methyl is applied in areas where transport to water containing aquatic macrophytes is likely, it would be plausible that detectable but transient damage could be observed.

Aquatic algae do not appear to be as sensitive as aquatic macrophytes to metsulfuron methyl. The highest hazard quotient observed for acute exposure is 0.03 associated with the upper range for the most sensitive species, based on an NOEC for growth inhibition. For chronic exposures, the highest hazard quotient is 0.001 associated with the upper range for the most sensitive species. Both values were based on an acute NOEC. Therefore, it is not anticipated that adverse effects in aquatic algae would result from exposure to metsulfuron methyl at application rates used by the Forest Service.

There is no clear basis for suggesting that effects on terrestrial or aquatic animals are likely or would be substantial. Adverse effects in mammals, birds, terrestrial insects, and microorganisms are not likely using typical or worst-case exposure assumptions at the typical application rate of 0.03 lb a.e./acre or the maximum application rate of 0.15 lb a.e./acre. As with the human health risk assessment, this characterization of risk must be qualified. Metsulfuron methyl has been tested in only a limited number of species and under conditions that may not well-represent populations of free-ranging nontarget species. Notwithstanding this limitation, the available data are sufficient to assert that no adverse effects are anticipated in terrestrial animals.

Similarly, the risk characterization for aquatic animals is relatively simple and unambiguous. Metsulfuron methyl appears to have a very low potential to cause any adverse effects in aquatic animals. All of the hazard quotients for aquatic animals are extremely low, with a range in fish from 0.0000000003 (acute exposures in tolerant fish) to 0.00003 (longer-term exposures to sensitive fish). It should be noted that confidence in this risk characterization is reduced by the lack of chronic toxicity studies in potentially tolerant fish – i.e., bluegill sunfish trout. At the maximum application rate of 0.15 lbs/acre, all of the hazard quotients would be increased by a factor of about 5. However, this difference has no impact on the risk characterization for fish. Hazard quotients in aquatic invertebrates range from 0.0000000007 (acute exposure in *Daphnia*) to 0.0000007 (acute exposure in *Daphnia*). Thus, there is no basis for asserting that adverse effects on aquatic animals are likely.

4.4.2. Terrestrial Organisms.

4.4.2.1. Terrestrial Vertebrates – The quantitative risk characterization for mammals and birds is summarized in Worksheet G02. The toxicity values used for each group of animals is summarized at the bottom of Worksheet G02 and refer to values derived in the dose-response assessment (Sections 4.3.2.1 and 4.3.2.2). In this worksheet, risk is characterized as the estimated dose, taken from Worksheet G01, divided by toxicity value. This ratio is referred to as the hazard quotient (HQ). All exposures summarized in Worksheet G01 are based on the typical application rate of 0.03 lb a.e./acre. At this application rate, an HQ of one or less indicates that the estimated exposure is less than the toxicity value. When this is the case, there is no basis for asserting that adverse effects are plausible.

As discussed in Section 2 (Program Description), the maximum application rate that might be used in Forest Service programs is 0.15 lb a.e./acre. Because exposure is directly related to application rate, the level of concern for the hazard quotients given in Worksheet G02 for an application rate of 0.15 lb a.e./acre is 0.2 [$0.03 \text{ lb a.e./acre} \div 0.15 \text{ lb a.e./acre} = 0.2$].

As indicated in Worksheet G02, the highest hazard quotient for any acute exposure is 0.08 [8e-02], the upper range of the hazard quotient for the consumption of contaminated insects by a small mammal. Thus, there is no basis for asserting that adverse effects are likely from the application of metsulfuron methyl at any application rate, even the maximum application rate of 0.15 lb a.e./acre, that might be used in Forest Service programs.

For chronic exposures, all hazard quotients are well below one. The highest hazard quotient observed is 0.02 [2e-02] associated with the upper range for chronic consumption of vegetation by a large mammal feeding exclusively on treated vegetation (i.e., labeled “on-site” in Worksheet

G02). This scenario, as well as the similar exposure scenario for mammals consuming vegetation on-site, is essentially used in these risk assessments as a very conservative/extreme screening scenario. The scenarios assume that the vegetation is treated and that the animal stays in the treated area consuming nothing but the contaminated vegetation. Given that most forms of vegetation treated at an effective (i.e., herbicidal) application rate would likely die or at least be substantially damaged, this exposure scenario is implausible. It is, however, routinely used in Forest Service risk assessments as a very conservative upper estimate of potential exposures and risks. Even considering this conservative scenario, the hazard quotient of 0.02 is 10-fold less than the level of concern of 0.2 associated with the maximum application rate of 0.15 lb a.e./acre. Thus, it is unlikely that adverse effects are likely to results, even at the highest application rate.

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 chronic exposure assumptions at the typical application rate of 0.03 lb a.e./acre or the maximum application rate of 0.15 lb a.e./acre. As with the human health risk assessment, this characterization of risk must be qualified. Metsulfuron methyl has been tested in only a limited number of species and under conditions that may not well-represent populations of free-ranging nontarget terrestrial mammals or birds. Notwithstanding this limitation, the available data are sufficient to assert that no adverse effects are anticipated in terrestrial mammals or birds.

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 – As shown in Worksheet G02, for the honey bee, the hazard quotient of 0.02 [2e-02] is well below the level of concern of one associated with the typical application rate of 0.03 lb a.e./acre and the level of concern of 0.2 associated with the maximum application rate of 0.15 lb a.e./acre. Thus, there is no basis for anticipating the occurrence of adverse effects in bees exposed to metsulfuron methyl at application rates that might be used in Forest Service programs.

As summarized in Section 4.3.2.3, Samsoe-Petersen (1995) report a reduction in egg hatching in the Rove beetle after direct spray of 0.067% product (20% a.i.) at a level of 6 µL/cm², which corresponds to an application rate of 8.04 µg/cm². By comparison, the typical application rate of 0.03 lbs a.i./acre corresponds to an application rate of 0.3363 µg/cm² and the highest labeled application rate of 0.15 lbs a.i./acre corresponds to an application rate of 1.68 µg/cm². Thus, the typical application rate of 0.03 lbs a.i./acre is a factor of about 24 below the effect level [$8.04 \mu\text{g}/\text{cm}^2 \div 0.3363 \mu\text{g}/\text{cm}^2 = 23.9$] and the maximum labeled application rate is a factor of about five below this effect level [$8.04 \mu\text{g}/\text{cm}^2 \div 1.68 \mu\text{g}/\text{cm}^2 = 4.6$]. Although these ratios cannot be treated as hazard quotients, they suggest that adverse effects are not likely to occur.

4.4.2.3. Soil Microorganisms – As noted in Table 4-1, the maximum concentration of metsulfuron methyl in soil at an application rate of 1 lb/acre is approximately 6 mg/kg soil. At the maximum application rate of 0.15 lb/acre, the corresponding concentration in soil would be 0.9 mg/kg soil [$6 \text{ mg}/\text{kg soil} \times 0.15 \text{ lb}/\text{acre} / 1 \text{ lb}/\text{acre}$]. This projected maximum concentration in soil is below concentrations that appear to be toxic – i.e., the LOEC of 5 ppm (5 mg/kg) based

on reduced growth in *Pseudomonas* reported by Boldt and Jacobsen (1998) (Section 4.3.2.5). Using the 5 mg/kg LOEC, the hazard quotient for soil microorganisms for maximum application rate of 0.15 lb a.e./ acre can be calculated at 0.18 [$0.9 \text{ mg/kg} \div 5 \text{ mg/kg} = 0.18$]. As shown by Ismail et al. (1996, 1998), most effects on soil microorganisms appear to be transient and recovery occurs within 9 to 14 days.

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

Metsulfuron methyl is an effective and potent herbicide and adverse effects on some nontarget plant species due to drift are likely under certain application conditions and circumstances. As indicated in Worksheets G05a and G05b, off-site drift of metsulfuron methyl associated with ground broadcast applications may exceed the NOEC for sensitive plant species at distances of about 500 feet from the application site. The closer that the nontarget species is to the application site, the greater is the likelihood of damage. Whether or not damage due to drift would actually be observed after the application of metsulfuron methyl would depend on several site-specific conditions, including wind speed and foliar interception by the target vegetation. In other words, in some 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 metsulfuron methyl and might show relatively little damage unless they were directly sprayed.

As summarized in Worksheet G04, runoff could pose a substantial risk to sensitive nontarget plant species under conditions in which runoff is favored – i.e., clay soil over a very wide range of rainfall rates. The NOEC for tolerant plants species is exceeded modestly under conditions which favor runoff (clay soil) and in regions with high rainfall rates.

The situational variability in the exposure assessments for runoff, wind erosion, and irrigation water does have a substantial impact on the characterization of risk for sensitive 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. less than that in arid regions.

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 (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 metsulfuron methyl is most plausible in

relatively arid environments and in areas where local soil surface and topographic conditions favor wind erosion.

The simple verbal interpretation for this quantitative risk characterization is that sensitive plant species could be adversely affected by the off-site drift or runoff of metsulfuron methyl under a variety of different scenarios depending on local site-specific conditions. If metsulfuron methyl is applied in the proximity of sensitive crops or other desirable plant species, site-specific conditions and anticipated weather patterns will need to be considered if unintended damage is to be avoided.

4.4.3. Aquatic Organisms.

4.4.3.1. Aquatic Animals – The risk characterization for aquatic animals is relatively simple and unambiguous. Metsulfuron methyl 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 metsulfuron methyl in ambient water over prolonged periods of time are estimated to be no greater than 0.000012 mg/L and peak concentration of metsulfuron methyl associated with runoff or percolation are estimated to be no more than 0.0003 mg/L. As summarized in Worksheet G03, all of the hazard quotients for aquatic animals are extremely low, ranging from 0.0000000003 [3e-10] (acute exposures in tolerant fish) to 0.00003 [3e-05] (longer-term exposures to sensitive fish). Thus, there is no basis for asserting that effects on nontarget aquatic species are likely. As detailed in Section 4.3.3.1, confidence in this risk characterization is reduced by the lack of chronic toxicity studies in potentially tolerant fish – i.e., bluegill sunfish trout. Based on the use of the relative potency method to account for the potential magnitude of the higher tolerance in bluegill sunfish, the upper range of the hazard quotient is 0.0000003, a factor of approximately 3.3 million below the level of concern at the typical application rate.

As with other risk characterization worksheets, Worksheet G03 is based on the typical application rate of 0.03 lbs/acre. At the maximum application rate of 0.15 lbs/acre, all of the hazard quotients would be increased by a factor of about 5 [$0.15 \text{ lbs/acre} \div 0.03 \text{ lbs/acre} = 5.0$]. This difference would have no impact on the risk characterization for aquatic animals – i.e., the highest hazard quotient 0.00003 in Worksheet G03 would be increased to 0.00015, below the level of concern by a factor of over 6000.

4.4.3.2. Aquatic Plants – The risk assessment for aquatic plants differs substantially from that of aquatic animals, particularly for macrophytes. For acute exposures based on the peak concentrations of metsulfuron methyl, aquatic macrophytes appear to be at risk at the upper range of plausible exposures, with a hazard quotient of 2. Hazard quotients for the central estimate is 0.4 and for the lower range is 0.002, both below the level of concern of one. For chronic exposures, all hazard quotients are below the level of concern, ranging from 0.002 for the lower range to 0.08 for the upper range. It should be noted that the risk characterization is based on NOEC values. As with terrestrial plants, aquatic macrophytes appear to be at some risk if metsulfuron methyl is applied near bodies of water containing aquatic macrophytes. In such applications, it would be desirable to take measures that would substantially reduce the anticipated levels of exposure.

Algae appear to be much less sensitive to metsulfuron methyl than macrophytes and neither sensitive or tolerant species of algae would be at risk in either chronic or acute exposures scenarios. Based on the upper range of exposure, the highest hazard quotient for sensitive algae for acute exposure is 0.03 and for chronic exposure is 0.00003, both well below the level of concern. Thus, algal species do not appear to be at risk based on estimated longer term concentrations of metsulfuron methyl in water.

4.4.3.2. Aquatic Microorganisms– As discussed in Section 4.1.3.5, significant inhibition in growth was noted in three species of aquatic cyanobacteria at a concentration of 0.003 mg/L (Peterson et al. 1994). As detailed in Section 4.2.3 and summarized in Worksheet G03, concentrations of metsulfuron methyl in ambient water over prolonged periods of time are estimated to be no greater than 0.000012 mg/L and peak concentration of metsulfuron methyl associated with runoff or percolation are estimated to be no more than 0.0003 mg/L. Since effects in aquatic microorganisms are observed at concentrations ranging from 10- to 250-fold greater than the estimated peak concentration of metsulfuron methyl in water, it is not anticipated that aquatic microorganisms will be at significant risk. However, confidence in this assessment is reduced since it is based on data obtained from only one study.

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Table 2-1. Identification and Physical/Chemical Properties of Metsulfuron Methyl.

Property	Value	Reference
Synonyms	Methyl-2-[[[(4-methoxy-6-methyl-1,3,4-triazin-2-yl)amino]-carbonyl]amino]sulfonyl]benzoate] Formulations: Escort (Du Pont) Other synonyms: DPX-T6376, DPX-L5300	Du Pont 2001-2002
CAS Number	74223-64-6	USDA/ARS 1995
U.S. EPA Registration Number	352-439	Du Pont 2001-2002
MW	381.4	USDA/ARS 1995
Henry's Law Constant (atm m ³ /mole)	2.32 × 10 ⁻¹⁰ at 25°C, pH 5 4.50 × 10 ⁻¹¹ at 25°C, pH 7 5.97 × 10 ⁻¹³ at 25°C, pH 9	USDA/ARS 1995 USDA/ARS 1995 USDA/ARS 1995
pK _a	3.3 3.64 3.7	USDA/ARS 1995; Abdullah et al. 2001; Sarmah et al. 1998 Chamberlain et al. 1996 Berger and Wolfe 1996a
Vapor pressure	300 × 10 ⁻¹⁵ Pa at 25°C	Sarmah et al. 1998
Water solubility	109 mg/L at 25°C in distilled water (pH 4.1) 9500 mg/L at 25°C, pH 6.7 1750 mg/L at 25°C, pH 5.4 270 mg/L at 25°C, pH 4.6 548 mg/L at 25°C, pH 5 1100 at pH 5, 20°C 2790 mg/L at 25°C, pH 7 213,000 mg/L at 25°C, pH 9	Du Pont 1985a,b,c Du Pont 1984 Du Pont 1984 Du Pont 1984 USDA/ARS 1995; Barefoot and Cooke 1990 Sarmah et al. 1998 USDA/ARS 1995; Barefoot and Cooke 1990 USDA/ARS 1995; Barefoot and Cooke 1990
log K _{o/w} (acid)	-1.7 at 25°C, pH 7 -1.74 1.58, acidic pH 1.78, pH 2	USDA/ARS 1995 Du Pont 1985a,b,c Chamberlain et al. 1996 Wei et al. 1999
K _{o/c} (acid, ml/g)	42 (4 to 206)	USDA/ARS 1995

Table2-2: Use of Metsulfuron Methyl by USDA Forest Service in 2001 by Type of Use (USDA/FS 2002)

Use Classification	Total Pounds	Total Acres	Pounds per acre average	Proportion of Use	
				by Pounds	by Acres
Noxious Weed Control	208.89	8,058.11	0.030	0.8865	0.8780
Conifer Release	15.75	522.00	0.030	0.0668	0.0569
Rights-of-Way	11.00	598.00	0.018	0.0467	0.0652
Grand Total	235.64	9,178.11	0.026	1	1

Table 2-3: Use of metsulfuron methyl by USDA Forest Service in 2001 by Region (USDA/FS 2002)

Region	Pounds	Acres	lbs/acre	Proportion of Total Pounds	Proportion of Total Acres
Northern (R1)	12.73	361.30	0.035	0.054	0.04
Rocky Mountain (R2)	35.70	4301.79	0.008	0.151	0.47
Southwestern (R3)	72.00	1150.00	0.063	0.306	0.13
Intermountain (R4)	88.46	2245.02	0.039	0.375	0.24
Southern (R8)	15.75	522.00	0.030	0.067	0.057
Eastern (R9)	11.00	598.00	0.018	0.047	0.065
Total	235.64	9178.11	0.03	1	1

Table 3-1: Summary of toxicity tests of triazine amine, a plant and animal metabolite of metsulfuron methyl (all data taken from O'Neal 1987)

Toxicity Test (species)	Exposures	Results
oral LD ₅₀ (rats)	1400 - 3000 mg/kg	LD ₅₀ = 1680 mg/kg; weight loss and stained peritoneal area at nonlethal doses
inhalation LD ₅₀ (rats)	2.6 - 5.0 mg/L	LD ₅₀ = 2.7 mg/L; weight loss, wet or stained peritoneal area, and red ocular or nasal discharges
dermal LD ₅₀ (rabbits)	2250 - 5000 mg/kg	LD ₅₀ > 5000 mg/kg; slight dermal erythema and edema
dermal sensitization (guinea pigs)	3% and 30% solutions	non-sensitizer
eye irritation (rabbits)	10 mg	mild irritation and corneal opacity up to 3 days; reversible within 7 days
Ames mutagenicity (<i>Salmonella typhimurium</i>)	500 - 10000 µg/plate	negative, with and without S-9 activation
subacute oral exposure (rats)	300 mg/kg 5 days per week for 2 weeks	moderate weight loss and nonspecific clinical observations of toxicity/stress; reversible cardiotoxic effects (slight congestion, degeneration, myocarditis); liver cell hypertrophy

Table 3-2: Chemical and site parameters used in GLEAMS Modeling for metsulfuron methyl.

Chemical Specific Parameters				
Parameter	Clay	Loam	Sand	Comment/Reference
Halftimes (days)				
Aquatic Sediment	140	140	140	Note 1
Foliar		30		Knisel and Davis 2000
Soil	120	120	120	Note 2
Water	1213	1213	1213	Note 3
K _{o/c} , mL/g	35	35	35	Note 4
K _d , mL/g	0.25	0.20	0.15	Note 5
Water Solubility, mg/L		2790 mg/L		Note 6
Foliar wash-off fraction		0.8		Knisel and Davis 2000
Note 1	Friedman 19?? [MRID 00141833] reports a range of 35 to 140 days in silt loam and sandy loam sediment and a halftime of 36 days is reported by Swanson (1988) for sandy loam sediment. The upper range from Friedman 19?? is used as a conservative value.			
Note 2	The reported halftimes for metsulfuron methyl are highly variable and probably depend strongly on the microbial populations in the soil. The value of 120 days is taken from Knisel and Davis 2000 and is near the upper range of reported halftimes (see Appendix 10). Much more rapid degradation may be expected in some soils.			
Note 3	Metsulfuron methyl is stable at neutral pH (Appendix 10). The value of 1213 days is based on the observation that <2% hydrolyzes over a 35 day period at pH 7 (McFetridge and Cadwgan 1985). [$1 - 0.2 = e^{-k \cdot 35}$].			
Note 4	Recommended value from Knisel and Davis 2000. As indicated in Appendix 10, reported K _{o/c} values vary substantially suggesting that the organic content of the soil may not be the sole determinant of soil binding.			
Note 5	Values for clay and sand taken from Oliveira et al. (2001) and value for loam taken as the mid-point of this range. Except for the study by Abdullah et al. (2001), these are similar to other values reported in the literature (see Appendix 10).			
Note 6	Value for at 25°C at pH 7 from Barefoot and Cooke (1990).			
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 3-3: Summary of modeled concentrations of metsulfuron methyl in streams (all units are $\mu\text{g/L}$ 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	0.00115	0.13810	0.00000	0.00000	0.00042	0.01611
20	0.00196	0.29420	0.00002	0.00162	0.00315	0.05819
25	0.00265	0.46168	0.00038	0.00992	0.00602	0.08221
50	0.00480	1.19651	0.00410	0.05440	0.01259	0.28359
100	0.00621	2.01544	0.00693	0.11708	0.01331	0.51232
150	0.00630	2.05550	0.00707	0.14097	0.01160	0.60227
200	0.00605	1.97717	0.00668	0.14751	0.01009	0.63261
250	0.00570	1.86554	0.00616	0.14618	0.00887	0.64881

Table 3-4: Summary of modeled concentrations of metsulfuron methyl in ponds (all units are $\mu\text{g/L}$ 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	0.20971	0.26104	0.00000	0.00000	0.03703	0.11101
20	0.21307	0.29676	0.00037	0.00363	0.21449	0.36265
25	0.21561	0.40388	0.01091	0.03358	0.34020	0.46725
50	0.20758	0.80931	0.09781	0.14124	0.42543	0.60872
100	0.17956	1.42501	0.12918	0.16185	0.31505	0.72823
150	0.15529	1.58624	0.11308	0.16056	0.24311	0.74203
200	0.13685	1.62616	0.09688	0.15221	0.19820	0.73509
250	0.12234	1.61017	0.08396	0.14161	0.16748	0.71799

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

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	1.26270	5.86822	1.42575	5.38478	0.91462	4.30936
10	0.62983	4.86331	0.52698	3.97821	0.31920	3.60085
15	0.37600	4.19977	0.24440	3.53551	0.11227	3.52805
20	0.26056	3.99362	0.14771	3.52762	0.06257	3.52516
25	0.19845	3.99217	0.10040	3.52589	0.04228	3.52516
50	0.07893	3.99075	0.03248	3.52516	0.01961	3.52516
100	0.01416	3.99075	0.01622	3.52516	0.01452	3.52516
150	0.01358	3.99075	0.01419	3.52516	0.01316	3.52516
200	0.01327	3.99075	0.01356	3.52516	0.01251	3.52516
250	0.01308	3.99075	0.01324	3.52516	0.01215	3.52516

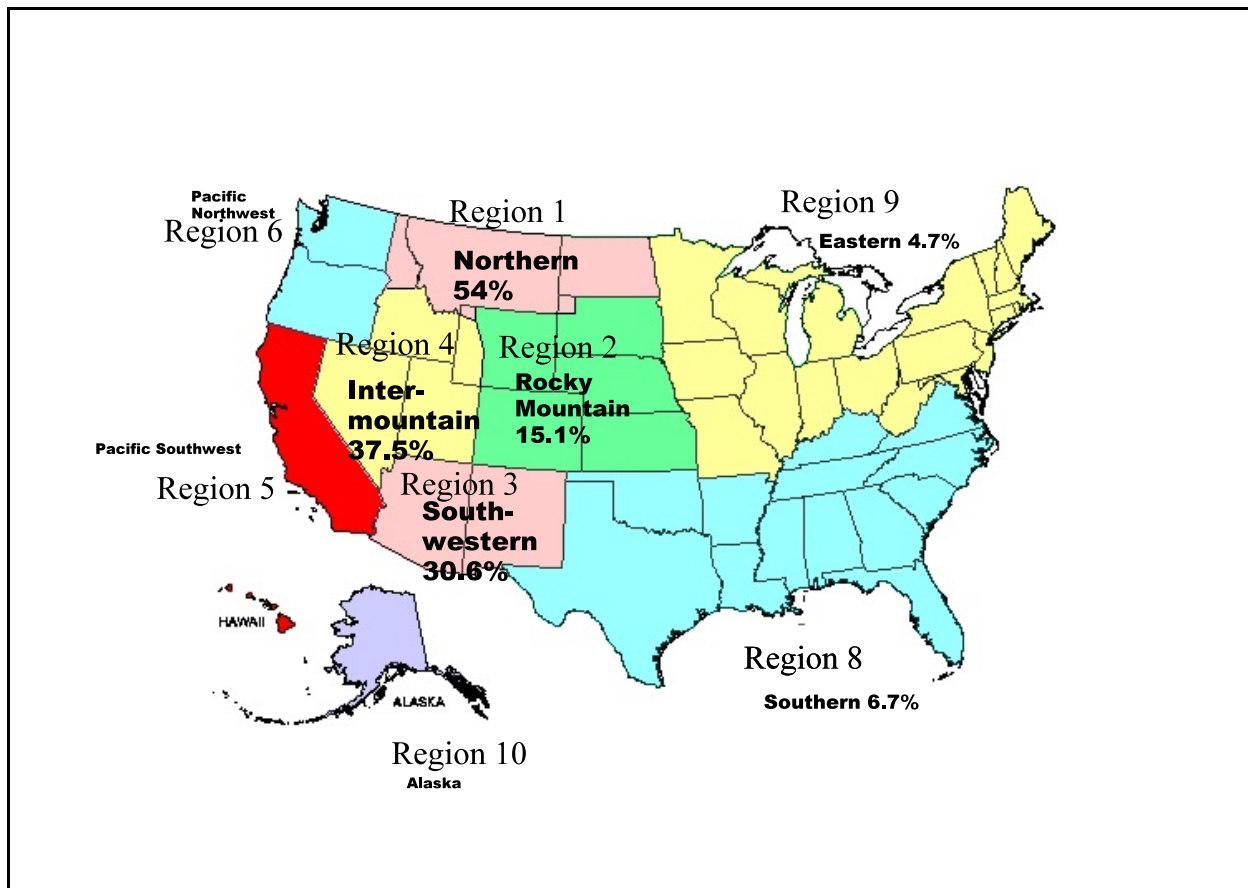


Figure 2-1. Use of metsulfuron methyl by the USDA Forest Service in various regions of the United States based on percentages of total use by FS.

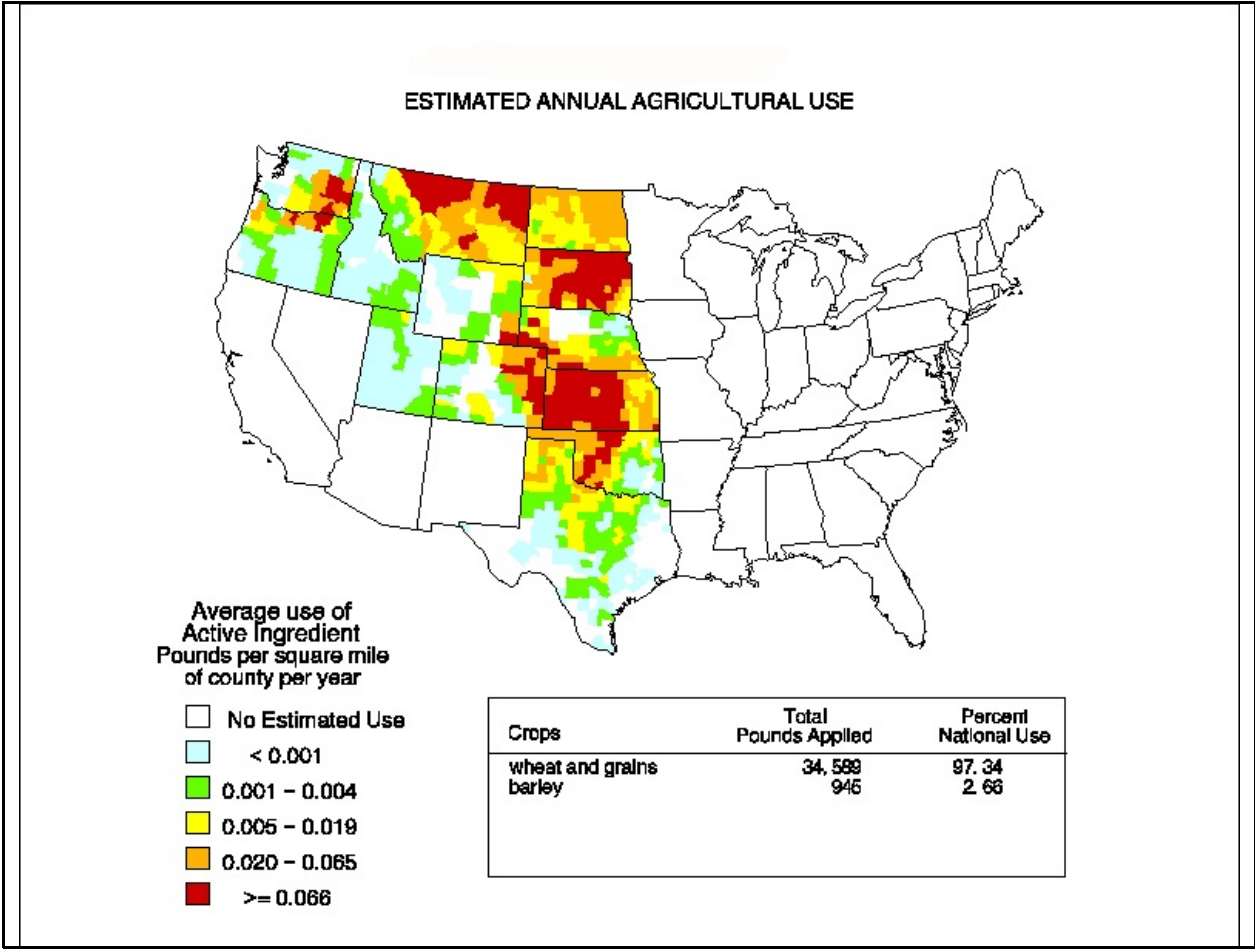


Figure 2-2. Agricultural use of metsulfuron methyl in the United States for 1992 (USGS 1998).

APPENDICES

- Appendix 1:** Acute toxicity of metsulfuron methyl to experimental mammals
- Appendix 2:** Toxicity of metsulfuron methyl to birds
- Appendix 3:** Toxicity of metsulfuron methyl to terrestrial invertebrates
- Appendix 4:** Toxicity of metsulfuron methyl to terrestrial plants
- Appendix 5:** Toxicity of metsulfuron methyl to fish
- Appendix 6:** Toxicity of metsulfuron methyl to aquatic invertebrates
- Appendix 7:** Toxicity of metsulfuron methyl to aquatic plants
- Appendix 8:** Laboratory and simulation studies on the environmental fate of metsulfuron methyl

Appendix 1: Toxicity of metsulfuron methyl to experimental mammals

Animal	Dose/Exposure	Response	Reference/ Comment
ORAL			
<i>Acute - single dose</i>			
Rats, CD, males, ~8 weeks old, 1 rat per dose group	100, 500, 1000, 2000, 4000 mg/kg single gavage administration of test material (91% a.i.) in corn oil; 14-day post exposure observation period.	At 1000 mg/kg, the rat (initial bw = 270 g) exhibited yellow stained perineum and had a severe weight loss (13% of initial body weight) 1 day after dosing. Mortality (% or absolute mortality was not reported - only that mortality occurred) occurred in the two high dose groups 1 day after dosing. Initial bw of rats = 276 g (2000 mg/kg dose) and 243 g (4000 mg/kg dose). No other effects of treatment were observed during the 15-day study.	Sarver 1990 MRID 41393202 No control group

Appendix 1: Toxicity of metsulfuron methyl to experimental mammals

Animal	Dose/Exposure	Response	Reference/ Comment
Rats, CD, 10 males and 10 females per dose group, fasted ~24 hours	1000, 2000, or 3000 mg/kg bw single gavage administration of test material (94.9% a.i.) in corn oil, 14- or 15-day post-exposure observation period.	LD ₅₀ >3000 mg/kg Signs of clinical toxicity included lethargy; hunched posture; high carriage; ocular, nasal, or oral discharge; and wet or yellow-stained perineum. Gross pathology indicated stress from acute systemic toxicity but did not indicate specific target organ specificity.	Sarver 1991 MRID 42545901 Synthesis difficulties limited the amount of available test material and precluded the determination of an LD ₅₀ .
Rats, CD, 5 males and 5 females, fasted - 24 hours	5000 mg/kg bw single gavage administration of test material (metsulfuron methyl, technical grade), in corn oil, 14-day post-exposure observation period	Mortality data: 1000 mg/kg: males 2/10 (avg bw = 227 g), females 0/10 (avg bw = 172 g); 2000 mg/kg: males 2/10 (avg bw = 229 g), females 1/10 (avg bw = 172 g); 3000 mg/kg: males 1/10 (avg bw = 232 g), females 4/10 (avg bw = 175 g) This study has an appendix of tables for individual bw, individual clinical observations, and acute toxicity LD ₅₀ >5000 mg/kg Signs of clinical toxicity included stained and wet peritoneal area and weight loss (female rats only) Gross pathology findings were a few dark red scattered foci in the lungs (1 male) and enlarged liver (1 female) No mortalities occurred during the study.	No control group in this study Dashiell and Hall 1982a MRID 00125826

ORAL

Acute - single dose (continued)

Rats, CD, 5 males and 5 females, 8-9 weeks old	5000 mg/kg body weight single gavage administration of test materia (dry flowable formula containing 60% a.i.) in corn oil	LD ₅₀ >5000 mg/kg Signs of clinical toxicity included wet and/or stained peritoneum in males and females and lung noise, diarrhea, red ocular discharge, and slight-moderate weight loss in females. Gross pathological observations included a dark red nodule on the spleen in one female rate and moderate, bilateral dilation of the renal pelvis in another female rat. These findings were not considered as dose-related. No abnormalities were observed in male rats.	Redgate 1984 MRID 00141822
Rats, Sprague-Dawley, 49 days old, 15 males and 15 females per dose group	0, 50, 500, or 5000 mg/kg single gavage administration of test material (96.8% a.i.); groups of 5 males and 5 females sacrificed 6, 24, or 48 hrs later for bone marrow sampling. Negative controls received corn oil by gavage Positive controls were treated with cyclophosamide.	No mortalities occurred during the study. Clinical signs of toxicity included red discharge from eyes, nose, or mouth in two females at 50 mg/kg, one female at 500 mg/kg, and five males and eight females at 5000 mg/kg; red, orange, or yellow-stained perineal areas in one male at 50 mg/kg and four males and six females at 5000 mg/kg; other sporadically occurring clinical signs of toxicity included wheezing (one mid- and one high-dose male), lethargy (one high-dose male), hunched back (one high-dose female), sensitivity to touch (two high-dose females), one closed eye (one high-dose female). Diarrhea observed in several treated and control rats was attributed to corn oil vehicle. At 24-hours, decreased weight gain was evident in males in the mid-dose group and was statistically significant (p<0.001) in males and females in the high-dose group; at 48 hours, weight gain was significantly decreased (p<0.01) in males and females in the mid-dose group and males and females in the high dose group (p<0.001). Mortality was not reported.	Ullman 1985a MRID 00148642 This is an in vivo mutagenicity study.

ORAL

Acute - single dose (continued)

Mice, CD, 43- days old, 18 males and 18 females	0, or 5000 mg/kg single gavage administration of test material (96.8% a.i.); groups of 6 treated and 5 control males and 6 treated and 5 control females were sacrificed at 24, 48, or 72 hrs later for bone marrow sampling.	At 4 hrs, there were no clinical signs of toxicity among control or treated mice; at 6 hrs after treatment, tremors, hyperactivity, and hypersensitivity were observed in one treated male; on day after dosing, clinical signs of toxicity included tremors (4/18 males), hyperactivity (2/18 males), moribundity (1/18 males, 1/18 females), diarrhea (1/18 males), decreased activity (1/18 females), hypersensitivity (1/18 males), and death (1/18 females). At 48 hours after treatment, the previously moribund mice were dead and 1/11 remaining treated males was hyperactive. No clinical signs of toxicity were observed in the remaining mice at 72 hours.	Ullman 1985b MRID 00148644
	Negative controls received corn oil by gavage		This is an in vivo mutagenicity study.
	Positive controls were treated with cyclophosamide.	There was no significant loss in body weight or decreased weight gain among treated mice, compared with negative controls.	

ORAL

Subacute - 13 weeks (91 days) or less

Rats, CD, 16 rats per dose group per sex	Dietary levels of 0, 100, 1000, or 7500 ppm INT-6376-16 (97% pure) for 90 days. [Average mean daily intake for males (from Table IX, p. 40): 0, 7, 68, or 521 mg/kg/day; average mean daily intake for females (from Table X, p. 41): 0, 8, 84, or 659 mg/kg/day.] Partial scarifice (10/group) at 90 days; other animals allowed to mate.	Females in the 7500 ppm group had an overall body weight gain that was 12% less than that of the control group; male rats in the 100, 1000, and 7500 ppm groups and female rats in the 100 and 1000 ppm groups had comparable or superior mean body weights and weight gains, compared with controls. No effects on food consumption, food efficiency, or intake of the test material at any dose level. No mortalities occurred during the study. Overall fertility was low in the control and test groups, pre-cluding the evaluation of the test substance on fertility. No adverse effects on other indices of reproduction and lactation performance or weanling body weights were observed. Effects not considered treatment related by the authors, include significantly increased total leukocyte counts and 24-hr urine volume in males at 100 ppm; significant increase in GOT activity in females at 100 ppm, but not at higher doses; significantly lower serum protein values in females at 7500 ppm; significantly decreased urine pH in females at 1000 and 7500 ppm not supported by abnormal histopathology; a dose-related statistically significant increase in the incidence of cytoplasmic clearing of hepatocytes related to significantly decreased relative liver weights in males and females.	Wiechman et al. 1982 MRID 00125834 90-day feeding and one-generation reproduction study.
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ORAL

Subacute - 13 weeks (91 days) or less (continued)

Rats, CD, 16 males and 16 females per dose group

0, 100, 1750, or 5000 ppm (99% a.i.) in the diet for 90 days. Partial sacrifice after 90 days; survivors allowed to mate

NOEL = 100 ppm

Mean body weights and mean body weight gains of males and females were significantly lower (~20-50%) than controls throughout the 90 day.

At 1750 and 5000 ppm, overall daily food consumption values for male and females were 15-25% lower compared with controls (weeks 0-13); mean food efficiency values were also lower than control values for males and females; an increased incidence of colored nasal discharge was observed in males and considered treatment related; significant decreases in serum glucose, globulin, and total protein concentration were noted in males at the 2- and 3-month evaluations; significantly lower serum glucose and higher serum cholesterol were observed in females at 1- and 3-month evaluations; the same effect was observed in the high dose females at 2 months, but was not statistically significant; absolute heart, liver, and kidney weights of males and females were significantly lower than controls as were the absolute brain weights of the males in the high dose group; significant increases in relative brain, heart, spleen, and kidney weights were observed in males and females; mean relative liver weights were significantly increased in females in the 1750 and 5000 ppm groups and in males in the 5000 ppm group; relative testes weights were significantly increased in males; no gross or histological changes were observed; one female in the high dose group died probably due to compound-related cachexia. No effects on reproduction or lactation performance were observed in the 100 and 1750 ppm groups; in the 5000 ppm groups, 0-4 and 1-4 day viability indices were 15-20% lower than controls; mean pup body weights were decreased significantly at 24-hrs, 4- and 21-day postpartum in the 1750 and 5000 ppm groups; and dam body weights were significantly lower at 1750 and 5000 ppm.

Brock 1985
MRID
00148638

90-Day
feeding and 1-
generation
reproduction
study

ORAL

Subacute - 13 weeks (91 days) or less

Rats, CD, ~40 to 60 g, ~21 days old, 20 males and 20 females per dose group	0, 25, 500, or 5000 ppm test material (96% a.i.) in the diet for 90 days	No effect on reproduction or lactation performance. Decreased mean body weight of F ₀ and F _{1B} male and female rats in the high dose group was the only compound-related effect.	Pastoor 1985 MRID 00151028
Rats, Sprague-Dawley, ~7 weeks old, weighing 192.1 to 262.5 g (males) and 131.0 to 190.5 g (females), 90 rats per sex/group	0, 5, 25, 500, 2500, or 5000 ppm test material (93% a.i.) for 13 weeks.	Statistically significant decrease in growth rates in males and females exposed to ≥500 ppm; body weight gain significantly decreased in males exposed to ≥2500 ppm; food consumption was also decreased significantly in high-dose males and females. In addition, the decrease in terminal body weight in high-dose males was statistically significant as was the decrease in absolute liver weights of males exposed to 5000 ppm and females exposed to ≥2500 ppm. In females exposed to ≥2500 ppm, the liver to body weight ratio was decreased significantly. Significant findings that could not be correlated directly with treatment include elevated platelet counts at week 5 in females exposed to ≥2500 ppm and a similar elevation at week 14 in females exposed to 25, 2500, or 5000 ppm). No hepatic histomorphological changes were associated with treatment.	Burdock et al. 1982 MRID 00125391 First 13 weeks of a chronic oral toxicity and reproduction study.

ORAL

Subacute - 13 weeks (91 days) or less

Dogs, beagles, 24/sex/group	0, 50, 500, or 2500 ppm test material (96.8% a.i.) for 14 weeks.	NOEL = 500 ppm No treatment related effects on mortality, physical condition, food consumption, feed efficiency, clinical chemistry, or urinalyses. In high-dose males, slight decreases in mean body weight progressed throughout the study, reaching almost -6% at termination; mean body weights of mid- and low-dose males and females in all dose groups were comparable to or slightly greater than controls. Hematological changes in high-dose males included a slight decrease in mean corpuscular hemoglobin concentration at month 2 and a slight increase in mean platelet and mean total leukocyte counts at month 3; there were no hematological effects observed in females at any dose level. Mean thyroid/parathyroid weights and thyroid/parathyroid to body weight ratios increased in the high-dose males and females; however, only the increase in thyroid/parathyroid weight in females was statistically significant. Sporadically occurring gross and microscopically postmortem findings were not considered treatment related.	Daly 1985 00148639
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ORAL

Teratogenicity/Reproduction

Rats, CD, females, weighing 230 to 288 on day 0 of gestation, 25 rats/group	0, 20, 125 or 500 mg/kg/day by gavage (in aqueous 0.5% Methocel®) on days 6-15 of gestation. Test material 94.2% pure	<p>No abortions occurred and no litters were delivered during the study. No mortality was attributed to treatment.</p> <p>Maternal toxicity was expressed as a statistically significant increase in salivation at 500 mg/kg/day, stomach ulcerations in one rat at 500 mg/kg/day, which may be an effect of treatment, statistically significant ($P \leq 0.01$) decreases in body weight gain and food consumption at 125 or 500 mg/kg/day, a significant decrease in average body weight in the high dose group, which persisted despite a significant increase in average food consumption ($p \leq 0.01$) after the treatment period [corrected maternal body weights were significantly decreased ($p \leq 0.01$) at 125 and 500 mg/kg/day], a dose-dependent, significant increase ($p \leq 0.01$) in average liver/body weight ratios at 125 and 500 mg/kg/day, a statistically significant decrease ($p \leq 0.01$) in average uterine weights at 500 mg/kg/day, which is considered to be related to the significantly decreased body weight, low incidence of resorption ($p > 0.05$) and the significant decrease ($p \leq 0.01$) in fetal body weights.</p> <p>The maternally toxic doses of 125 and 500 mg/kg/day resulted in significantly decreased ($p \leq 0.01$) fetal body weights, dose-dependent increases in the litter incidence of incomplete ossification of the thoracic and caudal vertebrae, sternbrae, xiphoid and pubes, which was statistically significant ($p \leq 0.05$ to $p \leq 0.01$) at 500 mg/kg/day [bifid thoracic vertebral centra and unossified caudal vertebrae were significantly increased ($p \leq 0.05$) at 125 mg/kg/day], and at 500 mg/kg/day increased incidences of edema, enlarged fontanelle, unossified suproccipital, altered ossification of the lumbar and sacral vertebrae and unossified metacarpals and metatarsals which were not statistically significant ($p > 0.05$) were considered thought to be treatment related.</p> <p>There were no significant dose-related incidences of other fetal alterations observed by external, soft tissue, or skeletal examination.</p>	Christian and Doll 1985 MRID 00148640
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ORAL

Teratogenicity/Reproduction (continued)

Rats, CD, females, weighing 234 to 324 g on day 4 of gestation, 24 rats/group	0, 40, 250, or 1000 mg/kg/day (concentration of a.i.) by gavage (corn oil suspension) on days 5 to 14 of gestation.	No teratogenicity or embryo-fetal toxicity. Maternal toxicity observed at ≥ 250 mg/kg/day, manifested as increased incidence of salivation (significantly higher among 1000 mg/kg/day dose group), significantly decreased body weight at 1000 mg/kg/day days 5-8 ($p=0.004$) and days 5-14 ($p<0.1$). Post-administration of test substance, maternal body weight rebounded and weight gain was significantly increased in the 250 and 1000 mg/kg/day dose groups..	Feussner et al. 1982a MRID 00125835 Embryo-fetal toxicity and teratogenicity study in rats.
Rats, Wistar, 10 males and 20 females per dose group, females weighed 160-200 g, males weighed 180-220 g	0, 10, 50 or 250 mg/kg bw (in corn oil) by gavage daily for two generations (approximately 70 days in males during spermatogenic cycle and 14 days in females to cover up to two estrous cycles)	There were no treatment related signs of toxicity or behavioral changes observed. At 10 or 50 mg/kg bw there were no signs of adverse effects on reproductive performance. One male rat in the high dose group died during the premating dose period. A treatment-related, dose-dependent statistically significant decrease in pup growth was observed in all four litters (F_{1a} , F_{1b} , F_{2a} , F_{2b}) at the high dose and in three litters (F_{1b} , F_{2a} and F_{2b}) at 50 mg/kg bw. There were no malformed pups in any of the treated groups.	Shriram Institute for Industrial Research 1995 MRID 44163302 2-Generation reproduction study

ORAL

Teratogenicity/Reproduction

Rabbits, New Zealand, white, ~5 months old, weighing 2.87 to 5.03 kg	0, 25, 100, 300, or 700 mg/kg/day (concentration of a.i.) (aqueous 0.5% Methocal suspension) on days 6-18 of gestation	<p>No teratogenicity or embryo-fetal toxicity.</p> <p>Overt maternal toxicity manifested as a statistically significant increase in mortality ($p < 0.001$) at 700 mg/kg/day (12/20 animals); mortality in the 100 mg/kg/day group was 1/19; mortality in the 300 mg/kg/day group was 2/20. Signs of toxicity prior to death included anorexia and red or orange-colored urine (≥ 100 mg/kg/day), decreased motor activity and impaired righting reflex (≥ 300 mg/kg/day), and an isolated incident in the 300 mg/kg/day dose group of red or orange exudate found in cage pan. The incidence of abortion was 2/19, 2/20, and 1/20 in the 100, 300, and 700 mg/kg/day dose groups, respectively. Except for 1/19 in the 100 mg/kg/day group, anorexia was observed prior to abortion and all of the rabbits died subsequent to the abortions.</p> <p>Maternal toxicity also manifested as statistically significant decrease in body weight gain on days 6 through 9 in the 100 and 300 mg/kg/day dose groups.</p> <p>NOEL for maternal toxicity = 25 mg/kg/day.</p>	<p>Feussner et al. 1982b MRID 00125836</p> <p>Teratogenicity study in New Zealand white rabbits.</p>
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Chronic - >90 days

Rats, Sprague-Dawley, 6 groups of 90 males and 90 females, initial weights: 192.1 to 262.5 g (males), 131.0 to 190.5 g (females).

0, 5, 25, 500, 2500 or 5000 ppm (purity of test material ranged from 93 to 95.8% a.i.) in the diet for 52 weeks. Interim sacrifices conducted at 13 and 52 weeks.

Using a conversion factor of 1 ppm dietary equal to 0.05 mg/kg body weight/day, the U.S. EPA (1990), these doses convert to 0, 0.25, 1.25, 25, 125, and 250 mg/kg/day.

Males exposed to 2500 or 5000 ppm had a statistically significant and treatment-related decrease in group mean body weights at 13 weeks, and the same effect was observed at 52 weeks in males and females exposed to 5000 ppm; depressed body weight gain, compared with controls, was observed in males and females exposed to 500, 2500, or 5000 ppm at 13 weeks and again at 52 weeks in males and females exposed to 5000 ppm; initial decreased food consumption for males exposed to 500, 2500, or 5000 ppm and females exposed to 2500 or 5000 ppm, which continued to be depressed throughout the study for males and females in the 5000 ppm dose group was not considered a toxic effect; rough coat may have been related to treatment and secondary to the poor nutritional status of the rats; alopecia (especially in females) was the most frequently noted clinical observation and appeared to be treatment related; sporadically occurring effects on hematology and clinical chemistry, which were statistically significant from controls were not consistent with a dose-related trend or effect; there was a possible relationship of dose with a darker, cloudy appearing urine with slightly decreased pH, notably in males; at 13 weeks, terminal body and absolute liver weights of 5000 ppm males were statistically less than controls as were the absolute and relative liver weights of females in the 2500 and 5000 ppm groups; at 52 weeks there were several remarkable findings regarding significantly increased organ weights, but the toxicological significance is unclear.

Feeding study with concurrent 2-generation reproduction study in rats: 52-Week interim report (represents the results of the 1st year of the toxicity and oncogenicity phase of the study; results of the reproduction study are reported separately.

NOEL for weight gain: 500 ppm (equivalent to 25 mg/kg/day)

Burns 1984
MRID 00145007

On the basis of the data, and assuming that the effect on body weight gain can be attributed to palatability rather than toxicity, the investigators conclude that the NOEL for this study after 52 weeks of treatment is 500 ppm.

Chronic - >90 days (continued)

Rats, Sprague-Dawley, ~7-weeks old, body weights: 192.1 to 262.5 (males) and 131.0 to 190.5 (females)	0, 5, 25, 500, 2500, or 5000 ppm (purity of test material ranged from 93 to 95.8% a.i.) in the diet on a continuous basis for 104 weeks. Group 5 (2500 ppm) was sacrificed during weeks 61 and 62. Interim sacrifices were made after 13 and 52 weeks.	NOEL (104 wks) = 500 ppm, assuming that loss of body weight in males and females at 500 ppm is due to palatability and is not a toxic effect. body weight: statistically significant, treatment related decrease in mean body weight in males (2500 and 5000 ppm) at 13 weeks and in males and females (5000 ppm) at 52 weeks; statistically significant decrease in body weight gain, compared with controls, in males and females (500, 2500, and 5000 ppm) at 13 weeks and in males and females (5000 ppm) at 52 weeks. food consumption (as g/week): initial decrease in food consumption in males (500, 2500, and 5000 ppm) and in females (2500 and 5000 ppm); decrease through week 26 in females (5000 ppm) thought to be result of small animal size and/or food refusal. hematology and clinical findings: sporadic, statistically significant differences from control values for hematology and clinical chemistry not consistent with dose-related trend or effect; trend (especially in males) toward “darker, cloudy appearing urine with slightly increased occult blood and hydrogen ion concentration (decreased pH) may have been dose related. necropsy: no remarkable findings liver weights: at 13 weeks, statistically significant decrease in terminal body weight and absolute liver weights of males (5000 ppm); at 52 weeks, statistically significant decrease in absolute and relative liver weights in females (2500 and 5000 ppm). organ weights at 52 weeks: statistically significant increases in mean absolute brain weights in males (25, 500, 2500, and 5000 ppm) and in females (2500 and 5000 ppm), mean absolute heart weights in males and females (2500 and 5000 ppm), mean kidney weights in males (2500 ppm), relative brain and heart weights of males and females (2500 and 5000 ppm), and relative kidney weights of males (2500 and 500 ppm). At terminal sacrifice, statistically significant increase in relative brain and relative kidney weights of males.	Burdock and Hamada 1985 MRID 00151029 Chronic feeding study with concurrent 2-generation reproduction study in rats: Chronic phase. Investigators state that “increases in relative organ weights, compared with controls, can be explained by decreased body weight of the treated group.”
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Chronic - >90 days (continued)

<p>Mice, CD-1, ~1 month old, weighing 16.6 to 33.9 g (males) and 15.1 to 28.5 g (females), 90 males and 90 females per dose group</p>	<p>0, 5, 25, 500, 2500 or 5000 ppm (concentration of test material, 92.9% a.i.) for 18 months. Partial sacrifice at 90 days; 2500 ppm group sacrificed at 12 months.</p>	<p>NOEL = 5000 ppm, assuming that decreased body weights in treated mice were related to dietary intake of test compound.</p> <p>body weight: although decreases in mean body weight were observed in all treatment groups and body weights of all treated males and 500 and 5000 ppm females were statistically lower than controls, there was no dose-response relationship between body weight or body weight gain and treatment.</p> <p>food consumption: slightly lower than controls, but no evidence of dose-response relationship.</p> <p>clinical observations and mortality: no indication of treatment related toxicity.</p> <p>organ weights: statistically significant differences were not considered treatment related and no there was no evidence of a dose-response relationship.</p>	<p>Stadler 1984 MRID 00151135</p> <p>90-Day and 18 month feeding study</p>
<p>Dogs, purebred beagles, 3 groups of 10 males and 10 females, 18-20 weeks old</p>	<p>0, 50, 500, or 5000 ppm (concentration of a.i.) in the diet for 1-year. Four beagles per group sacrificed at 13 weeks.</p>	<p>No mortalities occurred during the study.</p> <p>NOEL (males) = 500 ppm</p> <p>NOEL (females) = 5000 ppm</p> <p>Only evidence of a systemic effect was a slight decrease in food consumption in males exposed to 5000 ppm. There was a consistent decrease in serum lactate dehydrogenase in all groups of both sexes at two or more intervals. Nonetheless, since all mean values (control and treated groups) were within historical control range, investigators are uncertain of biological significance of this finding. The authors report several instances of statistically significant changes among the study parameters but acknowledge no evidence that the effects were treatment related.</p>	<p>Burdock 1984 MRID 00141821</p> <p>Combined 3-month and 1-year feeding study</p>

INHALATION

Rats CD, 10 males (weighing 229 to 260 g) and 10 females (weighing 160 to 182 g) per dose group	0 or 2.3-8.3 (mean 5.3) mg/L for single 4-hour exposure; observation period = 14 days. Test material purity: 92.9% a.i. Controls exposed to air only.	All rats (treated and control) exhibited slight red nasal discharge and ocular discharge during exposure; faces of treated rats covered with test material; increased incidence of slight weight loss lasting 1 day after exposure in treated rats; "a few" treated rats (male and females) exhibited slight brown nasal discharge on day 1 after exposure.	Burgess et al. 1983 MRID 00125830 5 mg/L is the limit test specified by EPA Health Effects Test Guidelines
		LC ₅₀ >5.0 mg/L	
Rats, CD, 10 males and 10 females, 8 weeks old, per dose group	0, 1.3, or 6.7 mg/L for single 4-hour exposure; observation period = 14 days. Test material purity: 96.8% a.i. Control (2 groups) exposed to air only.	No mortality; significant adverse clinical signs included mass on the abdomen of one female in 1.3 mg/L group, and hair loss from legs in one female and two males, all during week 2 of recovery; common clinical signs in rats exposed to 6.7 mg/L included wet or stained perineum, nasal or oral discharges, hair loss from face and faces stained by test material; one female at 6.7 mg/L had lung noise; most clinical signs were observed 1 to 3 days after exposure. No pathological abnormalities observed in treated rats at either concentration level.	Hutt 1985 MRID 00148634 5 mg/L is the limit test specified by EPA Health Effects Test Guidelines
		LC ₅₀ >5 mg/L	

OCULAR

Rabbits, New Zealand white, young adult females	50 mg (95.8% a.i.) aliquot administered to lower conjunctival sac of left eyes, which remained unwashed; right eyes served as controls; eyes examined 1, 24, 48, and 72 hours after treatment.	Observations included slight corneal opacity in one rabbit; mild conjunctival redness in six rabbits, and slight chemosis in one rabbit. There was no occurrence of corneal injury. Test material classified as a mild eye irritant under the conditions of this study.	Brock 1987a MRID 40858801 This is a primary eye irritation study; it includes individual eye irritation scores.
Rabbits, New Zealand white, 3 males, 3 females (age not specified)	0.1 mL of test substance (0.03 g of a.i., assayed as 98.1% pure) applied to lower conjunctival sac of right eyes; left eyes served as controls; animals observed at 1, 24, 48, 72 hours after application; test substance washed out immediately after the 24 hour observation	Animals observed for corneal opacity, iritis, conjunctival redness and chemosis. The only positive effect observed was slight conjunctival redness 1 hour after application of test substance in 5/6 rabbits. There was no evidence of corneal injury. Test material classified as practically non-irritating under the conditions of this study.	Kuhn 2002 MRID 45631802 This is a primary eye irritation study; it includes individual eye irritation scores.
Rabbits, New Zealand white, 9 males (age not specified)	0.1 mL of test substance (28.8 mg of formulation containing 70% a.i.) applied to lower conjunctival sac of right eyes; left eyes served as controls; in 3 rabbits test substance was washed out after 2 minutes; in 6 animals test substance remained throughout the observation period; animals observed at 1,2 and 3 days after application of test material	In rabbits with unwashed eyes, observations included slight corneal clouding (1/6 rabbits), mild conjunctivitis (6/6 rabbits), and mild discharge (3/6 rabbits). Eyes were normal within 3 days. In rabbits with washed eyes, had mild conjunctivitis and were normal in 2 days Test material classified as a mild eye irritant under the conditions of this study.	Dashiell and Hinckle 1982b MRID 00125831 This is a primary eye irritation study; it includes individual eye irritation scores.

DERMAL

Rabbits, New Zealand white, 5 males (weighing 2314 to 2765 g) and 5 females (weighing 2253 to 2598 g) per dose group	2000 mg/kg (stated purity of test material: assumed to be 100% pure) applied to skin abraded with minor incisions and left in contact with skin for 24 hours by means of a rubber damming nonabsorbent binder.	No mortality; LD ₅₀ >2000 mg/kg; all rabbits gained weight and appeared normal throughout the study except for three, which had restraining collars in their mouths on days 1 and 3; dermal effects included Grade 2 (well defined) erythema, Grades 1 and 2 (very slight to slight) edema, and thickening in four males and four females on day 1 and compound adhering to the skin in all rabbits on days 1 and 3. Erythema and edema could not be scored in one male and one female on day 1 due to the compound adhering to the skin.	Gargus 1985a MRID 00162609
Rabbits, New Zealand white, 5 males (weighing 2342 to 2772 g) and 5 females (weighing 2575 to 2759 g) per dose group	2000 mg/kg applied to abraded skin and occluded for 24 hours. A value of 100% a.i. was used for calculation purposes.	No mortality; LD ₅₀ >2000 mg/kg; no dermal effects, anorexia was observed in one rabbit on days 3 and 4 and in another rabbit on day 5; all animals except one gained weight throughout the study.	Gargus 1985b MRID 40622702
Rabbits, New Zealand white, 6 young adult males	0.5 g Escort® Herbicide (a 60% formulation) applied to a localized shaved test site on back of each rabbit and covered with semi-occlusive dressing for ~4 hours	No clinical signs of toxicity; desquamation, eschar, sloughing, and epidermal scaling observed during the study; by 1 hour after patch removal, erythema (score of 1 or 2) in all rabbits; one rabbit had edema (score of 1); at 24 and 48 hours, erythema (scores of 1, 2, or 3) observed in all rabbits; 5/6 rabbits had edema (scores of 1, 2, or 3); at 72 hours, erythema (scores of 1, 2, 3, or 4) observed in all rabbits; 5/6 rabbits had edema (scores of 1 or 2); by day 10 erythema and edema resolved in all rabbits; all dermal effects resolved by day 13 after treatment. Escort® Herbicide classified as an “IRRITANT” under conditions of this study. Scores: <u>Erythema</u> 1=very slight; 2=well defined; 3= mod to severe; 4=severe (in depth injuries) <u>Edema</u> 1=very slight; 2=slight; 3=moderate; 4=severe (extending beyond exposed area)	Finlay 1996 MRID 43945401

DERMAL

Rabbits, 6 males (age not specified)	0.5 g test material (70% formulation) applied to skin abraded with minor incisions and left in contact with skin for 24 hours by a rubber nonabsorbent binder. Observations made at 24, 48, and 72 hours and 6 and 9 days after treatment.	Mild skin irritation of intact and abraded skin was observed in all rabbits 24 hours after treatment. Irritation scores decreased with each observation period and was not present in any rabbit by day 9 after treatment. It was concluded that the test product was 'not a primary irritant' under the conditions of this study.	Dashiell and Hall 1982b MRID 00125832 This is a primary skin irritation study
Rabbits, New Zealand white, 6 young males	0.5 g test material (95.8% a.i.) a localized shaved test site on back of each rabbit and left in contact with skin for 4 hours by a rubber nonabsorbent binder. Observations made at 4, 24, 48, and 72 hours after treatment.	No dermal irritation was observed in any test animal throughout the study. Under the conditions of this study, the test material was not a skin irritant	Brock 1987a MRID 40858802 This is a primary skin irritation study

DERMAL

Albino guinea pigs, (3 males for the range finding study and 10 males for primary irritation and sensitization testing)

For range finding testing, 5%, 20%, 35%, and 50% suspension of test material (a 70% formulation) was applied to the shoulder area; observation time not specified.

For primary irritation testing, 0.05 mL of 3.5% and 35% suspension of test material (a 70% formulation) was applied to shaved, intact skin on the shoulder area; observations were made at 24 and 48 hours after treatment. For sensitization studies, weekly sacral intradermal injections of 0.1 mL of a 1% solution of test material (a 70% formulation) were administered for 4 consecutive weeks; after a 14 day rest period, dermal applications of 0.05 mL of 3.5% and 35% suspensions were made to shaved, intact skin on the shoulder area;

Results of the range finding study show that no skin irritation was observed following application of the 5% and 20% solutions of test material. Mild skin irritation was observed following application of the 35% and 50% solution of test material.

Results of the primary irritation study show no skin irritation for the 3.5% solution 24 or 48 hours after application. For the 35% solution, moderate erythema was observed in 9/10 animals 24 hour after application and in 3/10 animals 48 hours after application.

Results of the sensitization testing show no sensitization was observed at challenge.

Dashiell and Hall
1982c
MRID 00125833

This is a primary
skin irritation
study

DERMAL

Duncan Hartley albino guinea pigs; 2 males and 2 females for the range finding study; 10 males and 10 females in the sensitization study

For range finding testing, 0.4 mL 5%, 10%, 25%, and 100% solutions of test material (95.8% a.i.) was applied to the shoulder area and occluded for 6 hours; observations were made 24 hours after application. For sensitization testing, 0.4 mL of 100% solution of test material (95.8% a.i.) was applied to shaved, intact skin on the back and area was occluded for 6 hours, then test material was removed. Application of test material was repeated weekly for 3 weeks; after a 2-week rest period, animals were challenged with a single application of 0.4 mL of 100% test material for 6 hours and observations were made approximately 24 and 48 hours after treatment.

In the range finding study, no dermal irritation was observed for any test site

In the sensitization study, slight patchy erythema was observed in 2 animals 24 hours after the first induction treatment. No other dermal irritation was observed in any of animals during the induction phase. During the challenge phase, one animal exhibited slight patchy erythema 48 hours after treatment. No other dermal irritation was observed in any of the animals throughout the challenge phase.

The test material did not produce delayed hypersensitivity or allergic reactions under these study conditions.

Brock 1987b
MRID 40858803

This is a skin irritation study

DERMAL

Rabbits, New Zealand white, 5 males and 5 females	2000 mg/kg test material (92.9% a.i.) applied to abraded skin, occluded and left in contact with skin for 24 hours. Animals observed for 14 days following treatment. Gross pathological examination performed on 2 males.	No mortality; LD ₅₀ >2000 mg/kg; no dermal effects were reported; no gross pathological were observed; intermittent weight loss was the only clinical sign observed.	Dashiell and Hinckle 1982a MRID 00125828
Rabbits, New Zealand white, 5 males (weighing 2180 to 2515 g) and 5 females (weighing 2210 to 2490 g)	2000 mg/kg of test material (60% formulation) applied to skin abraded with minor incisions and left in contact with skin for 24 hours by means of a rubber damming nonabsorbent binder. Animals observed for 14 days.	No mortality; LD ₅₀ >2000 mg/kg; weight gain was observed for all animals at termination of the study; one female exhibited transient anorexia; no other signs of systemic toxicity were observed; dermal effects included erythema ranging from mild to severe and slight edema.	Gargus 1984a MRID 00141823
Rabbits, New Zealand white, 5 males (weighing 2138 to 2390 g) and 5 females (weighing 2086 to 2153 g)	2000 mg/kg of test material (98.6% a.i.) applied to skin abraded with minor incisions and left in contact with skin for 24 hours by means of a rubber damming nonabsorbent binder. Animals observed for 14 days.	No mortality; LD ₅₀ >2000 mg/kg; weight gain was reported for 9/10 animals and weight loss reported for 1 animal; no other signs of systemic toxicity were observed;	Gargus 1984b MRID 00148632

DERMAL

Rabbits, New Zealand white, 5 males and 5 females per dose group

Doses of 0 (control) 125, 500, or 2000 mg/kg test material (92.9% a.i.) applied to intact skin on the backs of rabbits, occluded and left in contact with skin for 6 hours; daily application made for 21 consecutive days; animals observed daily during the dosing period and for 14 days following cessation of treatment.

Two deaths occurred that were not attributable to the test material; LD₅₀ >2000 mg/kg; clinical signs observed included sporadic weight loss and diarrhea, which were not attributed to test material; gross and clinical pathology yielded no finding that were attributable to test material; no hemotological effects were observed; histological examination showed mild testicular degeneration or atrophy at all dose levels, but this was not considered to be related to the test material; no treatment-related microscopic changes were observed in females.

Wylie 1983
MRID 00141827

Appendix 2: Toxicity of metsulfuron methyl to birds.

Animal	Dose	Response	Reference
ACUTE STUDIES - 1 to 14 days			
Mallard ducks (<i>Anas platyrhynchos</i>) 8 days old, 10 ducks/dose group	562, 100, 1780, 3160, or 5620 ppm of test material (96.8% a.i.) in diet for 5 days.	No mortalities among treated birds, a dose-related decrease in body weight gain was observed at 3160 and 5620 ppm groups during the exposure period. NOEL = 1780 ppm LD ₅₀ > 5620 ppm	Beavers 1984a MRID 00148647
Bobwhite quail (<i>Colinus virginianus</i>), ~6 ½ months old, 5 males and 5 females/dose group	0, 292, 486, 810, 1305, or 2250 mg/kg of test material (96.8% a.i.) by gavage for 14 days [vehicle = corn oil]	LD ₅₀ >2250 mg/kg (HDT) No treatment-related mortality at any dose group, dose-related effect on body weight observed at ≥292 mg/kg (days 0-3) and slight effect on food consumption in females at ≥486 and possible in males at 2250 mg/kg (days 0-3) NOEL <292 mg/kg	Beavers 1984b MRID 00148645
Bobwhite quail (<i>Colinus virginianus</i>), 10 days old, 10 quail/dose group	0, 562, 1000, 1780, 3160, or 5620 ppm of test material (96.8% a.i.) in the diet for 5 days.	No mortality among treated birds, appearance remained normal throughout the study, a decrease in body weight gain was observed in the 3160 and 5620 ppm dose groups. NOEL = 1780 ppm LD ₅₀ > 5620 ppm	Beavers 1984c MRID 00148646
Bobwhite quail (<i>Colinus virginianus</i>), 14 days old, 10 birds/dose group	0, 562, 1000, 1780, 3160, or 5620 ppm of test material (assumed to be 100% a.i. by authors) in diet for 5 days, followed by 3-day observation period; [positive controls given 15.9, 25.1, 39.8, 63.1, or 100 ppm technical dieldrin (87% pure)]	LC ₅₀ >5620 ppm. NOEL = 3160 No mortality at any dose level; all treated ducks normal in appearance and behavior at all dose levels, except for slight decrease in body weight gain (15%) in the 5620 ppm dose group. Positive controls: LC ₅₀ = 35 ppm	Fink et al. 1981a MRID 00128820

Appendix 2: Toxicity of metsulfuron methyl to birds.

Animal	Dose	Response	Reference
ACUTE STUDIES - 1 to 14 days (continued)			
Mallard ducks (<i>Anas platyrhynchos</i>), 14 days old, 10 birds/dose group	0, 562, 1000, 1780, 3160, or 5620 ppm of test material (assumed to be 100% a.i. by authors) in diet for 5 days, followed by 3-day observation period; [positive controls given 72, 100, 130, 193, or 269, technical dieldrin (87% pure)]	LC ₅₀ >5620 ppm. NOEL = 1780 ppm No mortality at any dose level; all treated ducks normal in appearance and behavior at all dose levels, except for possible lethargy observed in 5620 ppm dose group; only sign toxicity was a slight decrease in food consumption and body weight gain in the 3160 and 5620 ppm dose groups. Postive controls: LC ₅₀ = 162 ppm	Fink et al. 1981b MRID 00128819
SUBCHRONIC REPRODUCTION STUDIES - 24 weeks			
Northern bobwhite (<i>Colinus virginianus</i>), 19 weeks old, 16 males and 16 females/dose group	0, 40, 200, or 1000 ppm in the diet for 23 weeks.	No mortalities in treated birds at any dose level, no overt signs of toxicity in treated birds, no treatment-related effects on body weight or food consumption, no adverse effects on reproductive parameters tested. NOEL = 1000 ppm (HDT)	Beavers et al. 1996a MRID 44115701
Mallard ducks (<i>Anas platyrhynchos</i>), 27 weeks old, 16 males and 16 females/dose group	0, 40, 200, or 1000 ppm ai in the diet for 24 weeks	No mortality among treated birds, no treatment related effects on body weight or food consumption, no effects on reproduction at any dose level. NOEL = 1000 ppm (HDT)	Beavers et al. 1996b MRID 44115702

Appendix 3: Toxicity of metsulfuron methyl to terrestrial invertebrates

Animal	Exposure	Response	Reference
Insects			
Three insect-plant interactions were tested: <i>Pieris brassicae</i> (large white butterfly) / <i>Brassica napus</i> (oilseed rape) , <i>Gastrophysa polygoni</i> (beetle)/ <i>Fallopia convolvulus</i> (black bindweed), <i>Sitobium avenae</i> (grain aphid)/ <i>Triticum aestivium</i> (wheat)	Plants sprayed with Ally (a 60% formulation of metsulfuron methyl) applied at rates ranging from 0.0125 to 0.8 time the recommended field rate in Denmark of 4 g a.i./ha. [rates are equivalent to 0.05 g to 3.2 g a.i./ha or 0.00004 to 0.003 lbs a.i./acre]	Newly hatched larvae were placed on leaves after spraying at various application rates. No effects on survival or growth rate of insects were found. However, host plants had significantly reduced root and shoot growth rate.	Kjaer and Heimbach 2001
Honey bees (<i>Apis mellifera</i> L.), two replications of 10 bees each per treatment level, body weight data not provided	6.25, 12.5, or 25 µg/bee; in 1 mL acetone; a micropipette was used to apply the dose dorsally to the thorax of immobilized bees. Positive controls (20 bees) received dermal applications of 0.125, 0.25, 0.5, 1, 2, or 4 µg/bee of carbaryl.	48 hr LD ₅₀ = >25 µg/bee; test material was considered to be relatively nontoxic to the honey bee. Mortality was 20% in the positive control group 48 hr LD ₅₀ (carbaryl) = 0.786 µg/bee These are the results of Test A in this study. No negative control group of untreated bees was used in Test A.	Meade 1984a MRID 00141829
Honey bees (<i>Apis mellifera</i> L.), two replications of 10 bees each per treatment level, body weight data not provided	0, 3.125, 6.25, 12.5, or 25 µg/bee in 1 mL acetone; a micropipette was used to apply the dose dorsally to the thorax of immobilized bees. Positive controls (20 bees) received dermal applications of 0.125, 0.25, 0.5, 1, 2, or 4 µg/bee of carbaryl.	Mortality in bees treated with test material was 10% at 25 µg/bee, 20% at 12.5 µg/bee, and 15% at 6.25 µg/bee; no mortality occurred at 3.125 µg/bee. 48 hr LD ₅₀ = >25 µg/bee; test material was considered to be relatively nontoxic to the honey bee. 48 hr LD ₅₀ (carbaryl) = 1.05 µg/bee There was no mortality among negative controls.	Meade 1984a MRID 00141829

<p>Honey bees (<i>Apis mellifera</i> L.), four replications of 10 bees each per treatment level, body weight data not provided</p>	<p>12.5, 25, 50, or 100 µg/bee in 2 mL acetone; a micropipette was used to apply the dose dorsally to the thorax of immobilized bees.</p> <p>Positive controls received 0.125, 0.25, 0.5, 1, 2, or 4 µg/bee of carbaryl.</p>	<p>There was no mortality among bees treated with the test material even at 100 µg/bee (HDT). 48 hr LD₅₀ = >100 µg/bee; test material was considered to be relatively nontoxic to the honey bee.</p> <p>48 hr LD₅₀ (carbaryl) = 0.963 µg/bee; 48 hr LD₉₀ (carbaryl) = 2.287 µg/bee; slope = 3.4127.</p> <p>There was no mortality among untreated bees; mortality in control groups treated with acetone only were 3% at 24 and 48 hours.</p> <p>These are the results of Test B in this study. A negative control group of untreated bees was used in Test B.</p>	<p>Meade 1984b MRID 00148650</p>
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Soil Microbes

<p>77 strains of fluorescent <i>Pseudomonas</i> isolated from an agricultural soil in Denmark</p>	<p>Soil concentrations of metsulfuron methyl 5, 50, and 300 ppm in soil (purity of metsulfuron methyl not specified).</p>	<p>Metsulfuron methyl reduced growth in 76 of 77 strains tested, with 15 strains affected at the 5 ppm concentration, and 48 strains affected at the 50 ppm concentration. EC₅₀ values not determined.</p>	<p>Boldt and Jacobsen 1998</p>
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Appendix 4: Toxicity of metsulfuron methyl to terrestrial plants

Plant	Exposure	Response	Reference
Dicots: soybean, cocklebur, cotton, morningglory, wild buckwheat, sugar beet Monocots: corn, barnyardgrass, rice nutsedge	Single application of metsulfuron methyl (technical 99%+); solvent: AGWT (8 mL Tween 20, 150 mL glycerine, 160 mL water, and 3000 mL acetone). Single application rates (both pre- and post-emergence): 0.25, 1, 4, 16, 50 or 125 g ai/ha; equivalent to 0.00025, 0.001, 0.004, 0.016, 0.05, and 0.125 kg/ha; equivalent to 0.00022, 0.00089, 0.0036, 0.014, 0.045, and 0.22 lb/acre.	50 g ai/ha () toxic to all test plants in green-house studies. For pre-emergent applications (Table 1) – 0.25 g/ha (0.00022 lbs/acre) - the lowest dose tested: Growth inhibition (%) was observed: cocklebur (20%), morningglory (70%), sugar beet (40%), and rice (20%). No inhibition in other species. 1 g a.i./ha (0.00089 lbs/acre) - growth inhibition (%) was observed: soybean (70%), cotton (95%), wild buckwheat (80%), corn (30%), barnyardgrass (20%), nutsedge (20%). 4 g/ha (0.0036 lbs/acre) - 30% to 90% inhibition. 16 g/ha (0.014 lbs/acre) - 50% to 100% inhibition. For post-emergent applications (Table 2)– 0.25 g/ha (0.00022 lbs/acre) - the lowest dose tested: growth inhibition (%) was observed in soybean (80%), cocklebur (50%), morningglory (20%), nutsedge (20%). No growth inhibition in Cotton or corn. 1 g/ha (0.00089 lbs/acre) - growth inhibition was observed 7 species ranging from 20% in morningglory to 100% in sugar beat. No inhibition in corn or barnyardgrass. 4 g/ha (0.0036 lbs/acre) - 20% (barnyardgrass) to 100% (soybean cocklebur, buckwheat, and sugar beet) inhibition in all species tested. [Rice was only species not tested at this rate.] 16 g/ha (0.014 lbs/acre) - 50% to 100% inhibition.	Drake 1988 MRID 40639301
Dicots: soybean, cocklebur Monocots: yellow nutsedge, rice, barnyard-grass, nutsedge Ferns: bracken fern, horsetail, fishtail Conifers: loblolly pine, ponderosa pine	Application at various rates of Ally or Escort herbicides (dry flowable powder) before, during, or after emergence of target plants (weeds).	Ally applied at 14-70 g/ha (0.012 to 0.062 lb/acre) toxic to most dicots tested; monocots tolerated treatment in varying degrees; conifers demonstrated tolerance to Escort applications. These are the results of the Tier 3 studies performed under field conditions. There are several tables of raw data. The application rates vary according to crop.	Drake 1988 MRID 40639301

Appendix 4: Toxicity of metsulfuron methyl to terrestrial plants

Plant	Exposure	Response	Reference
See Drake 1988 (Tier 1&2 Studies)	See Drake 1988 (Tier 1&2 Studies)	See Drake 1988 (Tier 1&2 Studies). This fiche contains additional methods and materials information for the Tier 1 & Tier 2 studies conducted by Drake 1988. There are no further results or conclusions.	Drake 1989 MRID 41118001
Corn, cucumber, onion, pea, rape, sugar beet, sorghum, soybean, tomato, wheat	Pre- and Post-emergence assays. Single application of up to 2.40 oz ai/acre Ally® Herbicide (60% dry flowable). Lowest application rates varied with species. The lowest rates used was with sugar beet – i.e., 0.0000183 oz ai/acre) in pre-emergence assay and 0.0000366 oz/acre in post-emergence assay.	<p>Conversion notes: 2.4 oz/acre = 0.15 lb/acre. 1 oz/acre = 0.0625 lb/acre.</p> <p>Pre-emergence assay: The most sensitive species based on the NOEC, were cucumber and onion with an NOEC of 0.000586 oz/acre (0.000037 lb/acre). The most tolerant species based on the NOEC is wheat with an NOEC of 0.0889 oz/acre (0.0056 lb/acre). [Data from p. 11 of study.]</p> <p>Post-emergence assay: The most sensitive species based on the NOEC is cucumber with an NOEC of 0.000586 oz/acre (0.000037 lb/acre), the same as in the pre-emergence assay. The most tolerant species based on the NOEC is wheat with an NOEC of 0.0624 oz/acre (0.0039 lb/acre). [Data from p. 12 of study.]</p>	Heldreth and McKelvey 1996 MRID 44050301
monkey-flower, bur-marigold, wild mustard, beans (variety Kentucky blue), barnyardgrass	1% (0.045 g a.i./ha, equivalent to 0.00004 lbs/acre) and 10% (0.45 g a.i./ha, equivalent to 0.0004 lbs/acre) of recommended label rate of Ally® Herbicide (60% dry flowable) with surfactant (Agral 90). Plants sprayed at 4 different growth stages: seedling, the two true-leave stage or four to five blades for grass, flower bud initiation, and commencement of flowering	At 0.45 g a.i./ha rate, all species exhibited marked effects on vegetative growth and reproductive performance. At 0.045 g a.i./ha rate, significant but less pronounced effects observed. Plants were assessed by biomass, height, number of lateral branches, and number of nodes on main stem. Seedling stage most susceptible for all species. EC ₅₀ values not given.	Boutin et al. 2000

Appendix 5: Toxicity of metsulfuron methyl to fish.

Species	Exposure	Response	Reference /Comments
Rainbow trout (<i>Salmo gairdneri</i>), 2.8 cm mean length, 0.17 g mean wgt, 10 trout per concentration	0, DMF (dimethyl formamide) positive) control, 5, 25, 50, 100, or 150 mg/L for 96 hours, static, no aeration. Higher concentrations not tested due to low water solubility and limited solubility in carrier solvents of test material. DPX-T6376 (purity = 92.9%)	No mortality at concentration up to 150 mg/L during 96-hour exposure period. At 24 hours, 3 fish exposed to 150 mg/L exhibited erratic swimming, rapid breathing and were lying on the bottom of the test container; 2/3 fish recovered completely by 48 hours; the third fish was affected throughout the entire study. LD ₅₀ > 150 mg/L NOAEL (for toxicity) = 100 mg/L	Muska and Hall 1982 MRID 00125816
Bluegill sunfish (<i>Lepomis macrochirus</i>), 3.6 cm mean length, 0.87 g mean wgt, 10 fish per concentration	0, DMF control, 5, 25, 50, 100, or 150 mg/L for 96 hours, static, no aeration. Higher concentrations not tested due to low water solubility and limited solubility in carrier solvents of test material. DPX-T6376 (purity = 92.9%)	No mortality or acute toxicity at concentrations up to 150 mg/L during 96-hour exposure period. LD ₅₀ > 150 mg/L NOAEL (for mortality and toxicity) = 150 mg/L	Phillips and Hall 1982a MRID 00125817
Bluegill sunfish (<i>Lepomis macrochirus</i>), 3.9 (range 3.4 to 4.7) cm mean length, 1.17 g (range 0.78 to 2.00) mean wgt, 10 fish per concentration	0, NaOH control, 1, 10, 100, or 1000 mg/L for 96 hours, static, no aeration. pH adjustment (1N NaOH) to accomplish solubility of compound purity of test material not specified	No mortality or acute toxicity at concentrations up to 1000 mg/L during 96-hour exposure period. LD ₅₀ > 1000 mg/L NOAEL (for mortality and toxicity) = 1000 mg/L	Hall 1984a MRID 00148648
Bluegill sunfish (<i>Lepomis macrochirus</i>), 4-5 cm in length, 2-4 g each, 4 groups of 75 fish	0.01 or 1.0 ppm [phenyl- ¹⁴ C] DPX-T6376 for 4 weeks in dynamic flow through study Exposure phase followed by 14-day depuration phase. purity of test material not specified	No adverse effects noted in any of the groups of fish, no mortality, and fish behavior appeared normal. The average bioaccumulation factor was <1 for all tissues and dose levels. Two diluter malfunctions occurred during the study, which increased test concentrations briefly in exposure aquaria.	Han and Anderson 1984 MRID 00149407

Appendix 5: Toxicity of metsulfuron methyl to fish.

Species	Exposure	Response	Reference /Comments
Rainbow trout (<i>Salmo gairdneri</i>), 4.1 (range 3.7 to 4.5) cm mean length, 0.82 (range 0.53 to 1.20) g, 10 fish per concentration	0, NaOH control, 1, 10, 100, or 1000 mg/L for 96 hours, static, no aeration. pH adjustment (1N NaOH) to implement solubility of compound purity of test material not specified	Three fish in the 100 mg/L group died (1 at 72 hours; 2 at 96 hour); however, the investigators do not consider this effect significant because there was no mortality at the 1000 mg/L concentration. Clinical signs observed in some fish exposed to ≥ 100 mg/L include darkening in color, swimming at the surface, lethargy, erratic swimming, rapid respiration and laying at the bottom. LD ₅₀ > 1000 mg/L NOAEL (toxicity) = 10 mg/L	Hall 1984b MRID 00149672
Rainbow trout (<i>Oncorhynchus mykiss</i>) 22-hour-old embryos	Nominal test concentrations of 2.4, 4.7, 9.5, 19, 38, 75, or 150 mg/L D{X-T6376 (99.13% ai) for 90 days.	No significant effect on hatch rate, last day of hatching, first day of swim up, survival, abnormalities, or weight of surviving fingerlings. Differences in first day of hatching and surviving fingerling length were small but significant at >8.0 mg/L. NOEC = 4.5 mg/L based on mean measured concentrations, first day of hatching and standard length of surviving fingerlings at 90 days. MATC = 6.0 mg/L LOEC = 8.0 mg/L No meaning estimates of LC ₅₀ or EC ₅₀ were calculated because the highest percent affected in any test concentration was <17%.	Kreamer 1996 MRID 44122801 This is a 400 page hard text report with many tables, etc. Can be used to elaborate the dose/response assessment
Common carp (<i>Cyprinus carpio</i> LINN) 4.90 (+0.86) cm in length and 4.16 (+0.65) g in wgt and Nile tilapia (<i>Oreochromis niloticus</i> PETERS) 4.99 (+0.37) cm in length and 3.23 (+0.54) g in wgt, 20 fish per concentration	5-6 (NOS) concentrations of ALLY 10/10WP were used in standardized static bioassay. Concentrations of the test solutions were not verified by analysis and the results are based on nominal concentrations expressed in ppm.	96-hr LC ₅₀ for carp = 3320.5 ppm 96-hr LC ₅₀ for tilapia = 2334.6 ppm This study was conducted in Indonesia to meet a registration requirement for an herbicide formulation of 10% metsulfuron methyl and 10% chlorimuron ethyl. This formulation is not registered in the United States and registration action is not pending. The study was submitted because it reports observations in species not previously evaluated.	Research Institute for Freshwater Fisheries 1995 MRID 44015401

Appendix 6: Toxicity of metsulfuron methyl to aquatic invertebrates.

Plant or Animal	Exposure	Response	Reference
Daphnids (<i>Daphnia magna</i>), <24 hours old, 10 daphnids per concentration	0, DMF control, 5, 25, 50, 100, or 150 mg/L for 48 hours, static, no aeration. DPX-T6376 (purity = 92.9%)	No mortality and no acute toxicity. 48-hour EC ₅₀ > 150mg/L NOEC (for mortality) = 150 mg/L	Phillips and Hall 1982a MRID 00125818
Daphnids (<i>Daphnia magna</i>) <24 hours old, 10 daphnis per concentration	0, NaOH control, 100, 130, 180, 240, 320, 420, 560, 750, or 1000 mg/L metsulfuron methyl (purity 96.8%) for 48 hours, static, no aeration. NaOH solution added to stock solution ot raise the pH to 9.0 to implement solubility	In replicate exposure chambers, exposure to 750 mg/L caused 60% and 80% immobility after 48 hours, while exposure to 1000 mg/L caused 90% and 100% immobility. 48-hr EC ₅₀ =720 mg/L (95% CI=6506 and 780 mg/L) NOEC = 420 mg/L	Wetzel 1984 MRID 00148649
Daphnids (<i>Daphnia magna</i>), <24 hours old, 4 daphnids per concentration, 10 replicates	Nominal concentrations of 5, 10, 19, 38, 75, and 150 mg/L DPX-T6376 (98.8% pure) for 21 days Measured test concentrations were 5.1, 11, 17, 39, 77, and 150 mg/L	EC ₅₀ for immobilization >150 mg/L measured concentration (HCT) The 14- and 21-day survival rates were not significantly different from controls, except for the 77 mg/L group (in replicates 9 & 10, 3/4 daphnids died). But because the 150 mg/L group showed 100% survival, the NOEC for survival is considered to be >150 mg/L measured concentration. The true LOEC and MATC are considered >150 mg/L NOEC for reproduction >150 mg/L The decreased number of daphnids in the 77 mg/L group resulted in statistically significant reduced offspring, but the effect was not seen when reproduction was calculated as offspring/surviving adult. The LOEC for reproduction (offspring/surviving adult) is just above 150 mg/L and the MATC for reproduction is also >150 mg/L The NOEC, LOEC, and MATC for growth were 17 mg measured concentration/L . Although decreased in growth were observed at concentrations of 5.1 to 17, these differences were not statistically significant compared to controls. It is not known whether this effect is biologically significant.	Hutton 1989 MRID 43490601 In terms of growth, the differences in daphnid length were within one standard deviation of the control group values, did not demonstrate a dose response below 39 mg/L and were decreased by <6% from controls

Appendix 6: Toxicity of metsulfuron methyl to aquatic invertebrates.

Plant or Animal	Exposure	Response	Reference
Cladoceran (<i>Daphnia magna</i>), <24 hours old	Negative dilution control, nominal concentrations of 3.1, 6.3, 13, 25, 50, and 100 mg DPX-T6376/L (measured concentrations of 3.0, 6.2, 13, 25, 50, and 100 mg DPX-T6376/L) for 21 days under semi-static test conditions	NOEL = 100 mg/L for survival, reproduction, and growth (based on measured concentrations). No statistically significant differences in survival between controls and treated groups ($p > 0.05$); reproduction not decreased significantly in any treatment group ($p > 0.05$); and no significant differences in growth, compared with controls, in any treatment group.	Drottar and Krueger 1998 MRID 44704901
<i>Daphnia magna</i>	metsulfuron methyl (>95% purity) up to concentrations approaching saturation; two metabolites also tested (structures given, but not named)	Exposure of new-born <i>Daphnia</i> to test compounds did not result in any significant toxicity at concentrations approaching saturation at pH 7. Authors speculate that resistance because compounds were mainly in the ionized form and, therefore, could not be absorbed by the organisms.	Wei et al. 1999

Appendix 7: Toxicity of metsulfuron methyl to aquatic plants

Plant or Animal	Exposure	Response	Reference
Aquatic Plants			
Duckweed (<i>Lemna minor</i>), 3 groups of 5 plants (2-3 fronds/plant)	0.04, 0.08, 0.16, 0.32, or 0.64 µg/L DPX-T6376 Technical white powder (99.2% pure) with media renewal 3 times/week, 14-day exposure. one control and one solvent control	14-day EC ₅₀ = 0.36 µg/L (95% CI = 0.29-0.43 µg/L) NOEL = 0.16 µg/L No adverse effects in control cultures or in treated cultures at 0.04, 0.08, 0.16, or 0.32 µg/L; chlorosis of fronds observed at 0.64 µg/L (day 12); more pronounced chlorosis and blackening of fronds at 0.64 µg/L (day 14). After 7-day recovery period, all test and control cultures except 0.64 µg/L showed appreciable increase in frond numbers. Chlorosis and blackening of fronds in the 0.64 µg/L still evident at the end of the “recovery” period.	Douglas and Handley 1988 MRID 41773902
macrophyte <i>Myriophyllum sibiricum</i> (a free-floating, submerged, perennial aquatic herb) (Northern Watermilfoil)	14-day exposure to a range of concentrations of Escort®	Shoot growth IC ₂₅ = 0.00015 mg a.i./L (0.15 µg/L) IC ₅₀ = 0.00039 mg a.i./L (0.39 µg/L) Root number IC ₂₅ = 0.00019 mg a.i./L (0.19 µg/L) IC ₅₀ = 0.00029 mg a.i./L (0.29 µg/L) Root dry mass IC ₂₅ = 0.00006 mg a.i./L (0.06 µg/L) IC ₅₀ = 0.00022 mg a.i./L (0.22 µg/L) Concentrations are well below the expected environmental concentration of 1.33 mg a.i./L	Roshon et al. 1999
Algae			
<i>Selenastrum capricornutum</i> (Freshwater, unicellular, non-motile, green alga)	0, 1, 5, 10, or 45 µg/L DPX-T6376 (metsulfuron methyl, 99% pure)	The 45 µg a.i./L nominal test concentration (maximum label application rate) caused a significant inhibition effect on growth, compared with controls, at 120 hours. 120-hr NOEL = 10 µg a.i./L (level of cell inhibition = 37%).	Forbis 1987 MRID 40639302

Appendix 7: Toxicity of metsulfuron methyl to aquatic plants

Plant or Animal	Exposure	Response	Reference
Freshwater filamentous blue-green algae (<i>Anabaena flos-aquae</i>)	5-day exposure without media renewal at a single concentration of 110.3 µg ai/L DPX-T6376 (Ally® Herbicide)	<p>DPX-T6376 did not inhibit growth and reproduction parameters of cell density and growth rate for <i>Anabaena flos-aquae</i></p> <p>Inhibition of >50% not observed at or above the maximum use rate for the <i>Anabaena flos-aquae</i> algal species.</p> <p>120-hr NOEC (cell density) = 95.4 µg ai/L 120-hr NOEC (area under curve) = <95.4 µg ai/L (significantly different from pooled controls) 120-hr NOEC (growth rate) = 95.4 µg ai/L 120-hr EC₂₅ estimated to be >95.4 µg ai/L 120-hr EC₅₀ estimated to be >95.4 µg ai/L</p>	Hicks 1997a MRID 44244001 Test concentration represents the expected concentration in a 6"-deep body of water after direct over spray at the maximum labeled use rate of 0.15 lbs ai/acre.
Freshwater, unicellular, non-motile diatom (<i>Navicula pelliculosa</i>)	5-day exposure without media renewal at a single concentration of 110.3 µg ai/L DPX-T6376 (Ally® Herbicide)	<p>DPX-T6376 did not inhibit growth or reproduction of <i>Navicula pelliculosa</i>.</p> <p>This is a 120-hour static acute algal screen study. It includes a table of measured cell counts at 24, 48, 72, 96, and 120 hours.</p> <p>Inhibition of >50% not observed at or above the maximum use rate for <i>Navicula pelliculosa</i>.</p> <p>120-hr NOEC (cell density) = 95.6 µg ai/L 120-hr NOEC (area under curve) = <95.6 µg ai/L 120-hr NOEC (growth rate) = 95.6 µg ai/L 120-hr EC₅₀ (cell density) estimated >95.6 µg ai/L 120-hr EC₅₀ (area under the curve) estimated >95.6 µg ai/L 120-hr EC₅₀ (growth rate) estimated >95.4 µg ai/L</p>	Hicks 1997b MRID 44420901
Freshwater, unicellular, non-motile, green alga (<i>Selenastrum capricornutum</i>)	For growth inhibition studies, concentrations of metsulfuron methyl (purity not specified) of 0, 0.2, 0.78, 3.1, 13, 25 µmol/L for 3 days (72 hours).	<p>72-hrEC₅₀ (growth inhibition): 4.1 µmol/L (1.56 mg/L)</p> <p>Since the purity of metsulfuron methyl was not specified by the authors, 100% purity is assumed.</p> <p>Addition of branched-chain amino acids decreased the effects of metsulfuron methyl on growth inhibition</p> <p>Protein synthesis observed at concentrations that inhibited growth.</p> <p>Incorporation of adenosine into cold-TCA-insoluble macromolecules was inhibited in a dose-dependent fashion at concentrations ranging from 0.46 to 25 µmol/L.</p>	Nystrom and Blanck 1998

Appendix 7: Toxicity of metsulfuron methyl to aquatic plants

Plant or Animal	Exposure	Response	Reference
Freshwater, unicellular, non-motile, green alga (<i>Selenastrum capricornutum</i>)	62.5, 125, 250, 500, or 1000 µg metsulfuron methyl 60 DF/L of nutrient medium (ppb) for 72 hours without test medium renewal Trade name = Escort® 60 DF purity = 61.5%	There was a dose-response relationship between increased dose and corresponding decreases in cell density, area under the growth curve, and growth rate. Cell density: EC ₅₀ = 372 µg/L (95% CI = 312-466 µg/L) NOEC = 125 µg/L Area under the growth curve: EC ₅₀ = 359 µg/L (95% CI = 306-430 µg/L) NOEC = 125 µg/L Growth rate: EC ₅₀ = 1307 µg/L (95% CI = 1161-1524 µg/L) NOEC = 125 µg/L In the recovery test, Metsulfuron methyl 60 DF was determined to be algistatic at concentrations ≤ 1000 µg/L	Sloman and Leva 1998 MRID 44650101
<i>Chlorella pyrenoidosa</i> (green algae)	metsulfuron methyl (>95% purity), concentrations not specified and 2 metsulfuron metabolites (structures given but not named)	Endpoint: growth inhibition 96-hour log EC ₅₀ (mg/L): -0.21 (EC ₅₀ = 0.62 mg/L). 96-hour log EC ₅₀ for metabolites: 2.89 and 1.97.	Wei et al. 1999

Appendix 8: Laboratory and simulation studies on environmental metsulfuron methyl.

Data Summary	Reference
Aquatic Sediments	
Degradation of ¹⁴ C-metsulfuron methyl studied under anaerobic conditions in 3 pond water/sediment systems. Water/sediment systems had the following characteristics –	Friedman 19?? MRID 00141833
Landberg, PA: soil type silt loam (25% sand, 74% silt, 1% clay); water pH = 5.8; sediment pH = 5.6; organic matter (%) = 3.7; CEC (meq/100g) = 11.0; t1/2 about 5 weeks (35 days).	
Salina, Kansas: soil type sandy loam (54.5% sand, 28.5% silt, 17% clay); water pH = 7.3; sediment pH = 6.6; organic matter (%) = 2.2; CEC (meq/100g) = 10.0; t1/2 about 15 weeks (105 days days).	
Pendleton, Oregon: soil type silt loam (36% sand, 58% silt, 6% clay); water pH = 7.9; sediment pH = 6.36; organic matter (%) = 1.2; CEC (meq/100g) = 15.3; t1/2 about 20 weeks (140 days).	
Degradation in sterilized systems was slower, indicating breakdown by microbial action. Major metabolites were saccharin and 2-(aminosulfonyl)benzoic acid. Partitioning of metsulfuron methyl into pond sediment increased with incubation time.	
Bioconcentration	
Bluegill sunfish exposed to 0.01 and 1.0 ppm ¹⁴ C-DPX-T6376 for four weeks to investigate accumulation in edible tissue, viscera and liver.	Han 1982 MRID 00138701
In edible tissue: At 0.1 ppm, bioconcentration factor (BCF) after 24 hours was 0.07 and highest BCF was 0.61 after 7 days of exposure. At 1.0 ppm, BCF after 24 hours was 0.06 and highest BCF was 0.45 after 28 days of exposure.	
In liver: At 0.1 ppm, BCF after 24 hours was 0.18 and highest BCF was 2.89 after 14 days of exposure. At 1.0 ppm, BCF after 24 hours was 0.11 and highest BCF was 2.05 after 14 days of exposure.	
In viscera: At 0.1 ppm, BCF after 24 hours was 0.21 and highest BCF was 2.11 after 14 days of exposure. At 1.0 ppm, BCF after 24 hours was 0.07 and highest BCF was 1.93 after 14 days of exposure.	
Hydrolysis	
Hydrolysis of ¹² C-phenyl DPX-T636 studies at 15 and 25°C, pH 5, 7, 9, and at concentration of 0.5 and 5 ppm.	Friedman 19?? MRID 00125823
At pH 5: material hydrolyzed with a half-life of 3 weeks at 15°C and >3 weeks at 25°C. Principle hydrolysis product was saccharin	
At pH 7: stable for 7 days at both concentrations	
At pH 9: stable for 7 days at both concentrations	
¹⁴ C-metsulfuron methyl in solutions of pH 5, 7, and 9 did not photolyze in aqueous buffer under light or dark conditions. Hydrolysis occurred at the following rates: at pH 5, t1/2 = 17 days; at pH 7, < 2% hydrolyzed in 35 days; at pH 9, 10% hydrolyzed in 35 days	McFetridge and Cadwgan 1985 MRID 00153321

Appendix 8: Laboratory and simulation studies on environmental metsulfuron methyl.

Data Summary	Reference
Investigated hydrolysis in aqueous buffer solutions at pH 5.2 ($t_{1/2} = 5.2$ days) and pH 11.2 ($t_{1/2} = 11.2$ days).	Sarmah et al. 2000
Photolysis	
Degradation of ^{14}C -DPX-T6376 studied in distilled water, standard water reference, and brandywine River water, with and without sediment, all exposed to light at 25°C. Half-lives in each water type – distilled water: 1 days; standard water reference: 4 days; and brandywine River water with sediment: 7-8 days; without sediment: 7-8 days	Friedman 19?? MRID 00141831
^{14}C -metsulfuron methyl in solutions of pH 5, 7, and 9 did not photolyze in aqueous buffer under light or dark conditions. Hydrolysis occurred at the following rates: at pH 5, $t_{1/2} = 17$ days; at pH 7, < 2% hydrolyzed in 35 days; at pH 9, 10% hydrolyzed in 35 days	McFetridge and Cadwgan 1985 MRID 00153321
Metsulfuron methyl in aqueous solution (pH 6.2) is degraded by uv light, with a half-life of 15 hours. Under dark conditions, <5% was degraded after 40 hours. Three metabolites were identified.	Samanta et al. 1999
Soil Degradation/Transport	
Investigated the adsorption-desorption and leaching behavior of metmet in selected Malaysian agricultural soils. Soils mixed together in different proportions. Two soil types investigated (Sagamet and Penor soils).	Abdullah et al. 2001
pKa of metsulfuron methyl: 3.3 Koc values: 194.79 to 345.34 Kd values: 5.56 to 38.18	
Soil adsorption decreases as pH of the soil was increased by the addition of lime.	
Simulation of rainfall of 211.6 mm over a 10-day period following application of metsulfuron methyl at a rate of 75g/ha resulted in leaching up to 15 cm of the soil column.	
Investigated vertical and horizontal variability in degradation rates from the vadose zone to a Danish aquifer (potential for aerobic mineralization in a vertical profile from the plough layer down to the sandy aquifer 7.7 m below surface), effects of aerobic vs anaerobic conditions, and importance of concentration kinetics. Results: Metsulfuron methyl not degraded in any investigation.	Albrechtsen et al. 2001
Laboratory study. Investigated bacterial mineralization of several sulfonylureas in sandy soil from 9 different depths in a sandy soil horizon from an agricultural field near a creek bed.	Andersen et al. 2001
Results: metsulfuron methyl had highest mineralization amount (40%) was 126 days after application (concentration of 20 $\mu\text{g}/\text{kg}$ in soil) which varied according to soil depth; mineralization was faster at soil from upper depths and was correlated to higher microbial counts; residual amounts correlated to the accumulated amount mineralized.	

Appendix 8: Laboratory and simulation studies on environmental metsulfuron methyl.

Data Summary	Reference
<p>¹⁴C-metsulfuron methyl applied to columns for 4 soil types. Kds determined as follows: Sassafras loamy sand (Kd = 0.05); Fargo silty clay (Kd = 0.12); Gardena silt loam (Kd = 0.13); and Keyport silt loam (Kd = 0.45).</p>	Barefoot 1985 MRID 00148653
<p>Review Article reporting the following parameters: Koc (mL/g) = 35 (pH 7) (soil type not specified). half-life = 30 days (soil type not specified), water solubility = 2.79 g/L (pH 7)</p>	Bergstrom and Stenstrom 1998
<p>Investigated mobility and persistence of metsulfuron methyl in cropping soils of Australia. Biologically active residues were estimated in field pea bioassays to 80 cm depth.</p>	Black et al. 1999
<p>Results: Residues mobile and persistent at low levels, leaching occurred below the lowest sampling depth during the winter-spring growing season</p>	
<p>Photodegradation of ¹⁴C-metsulfuron methyl studied in Keyport silt loam after application of 0.5 oz/acre. T1/2 < 7 days under light condition; similar half-life under dark conditions. Conclusion: photolysis not important degradation mechanism for metsulfuron methyl.</p>	Buchta 1985 MRID 00153322
<p>Standard column leaching test in 4 soils – Fallsington sandy loam, Flanigan silt loam, Keyport silt loam, and Myakka sandy soils applied at a rate of 1.1 kg/ha. ¹⁴C-DPX-T6376 percolated through all soil columns with 20 inches of water within 20 hours. Percolation time increased in aged soils.</p>	Chrzanowski 1981 MRID 00141833
<p>Aerobic decomposition of ¹⁴C-metsulfuron methyl studied under greenhouse conditions on 3 soil types (Fallsington sandy loam, Flanighan silt and Keyport silt loam) at an application rate of 100 g/ha. On all soils, the average half-life was 10 days. Primary decomposition product was saccharin</p>	Chrzanowski 1982 MRID 00125825
<p>Laboratory study: ¹⁴C-DPX-T6376 applied to Keport silt loam. Half-life was 2 to 3 weeks (14 to 21 days). Major metabolites were saccharin and 2-(aminosulfonyl)benzoic acid. After 24 weeks, 36% of applied ¹⁴C was degraded to CO₂ in sterile soil but no CO₂ formed in sterile soil. Under sterile conditions, major degradation product was 2-(aminosulfonyl)benzoic acid.</p>	Friedman 19?? MRID 00125824
<p>Photolysis of ¹⁴C-metsulfuron methyl studied on the surface of Keyport silt loam under artificial daylight for 30 days. Extrapolated half-life of 40 days Major breakdown products were sachharin and 2-(aminosulfonyl)benzoic acid. <1% of ¹⁴C releases as CO₂, indicated minimal microbial activity</p>	Friedman 19?? MRID 00141832
<p>Laboratory study to determine rate and pattern of metabolism of ¹²C-DPX-T6376 in sterile and non-sterile soil under aerobic, dark conditions at 0.1 ppm (equivalent to 210 ga.i./ha). In non-sterile soil at 20°C, t1/2 = 11 days. Principle degradate was CO₂, indicating microbial breakdown. Only insignificant amounts of CO₂ formed in sterile soil.</p>	Gorman et al. 1997 MRID 44491

Appendix 8: Laboratory and simulation studies on environmental metsulfuron methyl.

Data Summary	Reference
<p>Laboratory Investigation of persistence of metsulfuron methyl in soil under various conditions: autoclaved and non-autoclaved soil; different soil temperatures; different soil moisture contents. For biological assays for persistence in soil, cucumber was used.</p> <p>Results: Significant degradation in non-autoclaved soil, indicating importance of microbial breakdown. Half-life in soil decreased as soil moisture content increased. Half-life in soil decreased as temperature decreased</p>	Ismail and Arlizan 2002
<p>Soil analyzed but type not specified. In non-autoclaved soil, range for half-life in soil at 20°C, 20% soil moisture = 5.59 to 6.42days; range for half-life in soil at 30°C, 20% soil moisture = 3.19 to 5.11days</p>	
<p>Review article. Range for half-life in soil (types not specified) 222 days to > 2 years.</p>	Kookana et al. 1998
<p>Field study examining the potential of the riparian fern to mineralize metsulfuron methyl. Mineralization of metsulfuron methyl followed a logarithmic trend. After 473 days, 29% of ¹⁴C-metsulfuron methyl was mineralized under aerobic conditions. Under anaerobic conditions, no mineralization occurred.</p>	Larsen et al. 2001
<p>Laboratory study investigating degradation rates and major metabolites of metsulfuron methyl in sterile and nonsterile aerobic soils in the dark at 20C for 1 year. Soil concentration of metsulfuron methyl was 0.1 mg/kg soil.</p>	Li et al. 1999
<p>Half-life in non-sterile silt loam soil, = 30 days Half-life in sterile silt loam soil = 343 days</p>	
<p>7 metabolites identified; degradation pathways included O-demethylation, cleavage of the sulfonyleurea bridge and triazine ring opening</p>	
<p>Study to determine the rate and pattern of metabolism of ¹⁴C-metsulfuron methyl rate of dissipation and mobility under field conditions. Ally applied at rate of 4.0 oz/acre (2.4 oz a.i./acre) and plots were irrigate to supplement rainfall. Range for half-life was 21 to 33 days.</p>	McMillan 1999a MRID 44826201
<p>Laboratory study investigating sorption characteristics on 6 Brazilian soils using the batch equilibration method. All values estimated from graphs. For Kd, units = L/kg; for Koc, units = L/kg; t1/2 - days Results in -</p>	Oliviera et al. 2001
<p>clay soil (2 soil samples): Kd = 0.25; Koc = 55 and 25; range t1/2 range of 4 to 9 loamy sand: Kd = 0.2; Koc = 25; range t1/2 of 5 to 13 sand: Kd = 0.15; Koc = 15; range 1/2 of 5 to 10 sandy loam: Kd = 0.3; Koc = 10; range t1/2 of 4 to 7 sandy clay loam: Kd = 0.35; Koc = 15; range t1/2 of 4 to 9</p>	
<p>On two nonsterile soils treated with ¹⁴C-DPX-L5300, under dark conditions at 25°C – Keyport silt loam: t1/2 = 1 day; Gardan silt loam: t1/2 = 6 days. Half-life decreased slightly with increasing temperature. In both soils, only 3-6% of applied ¹⁴C was released as CO₂ after 112 day of incubation. Primary metabolic pathway I hydrolytic with formation of tirazine amine as predominant metabolite.</p>	Rapisarda 1985 00148652

Appendix 8: Laboratory and simulation studies on environmental metsulfuron methyl.

Data Summary	Reference
Dissipation of metsulfuron methyl in soil tubes under field conditions at 8 test sites. Application rate = 100 g a.i./ha. For spring applications, half-lives ranged from 1 months (30 days) to 7 months (210 days). For fall applications, half-lives ranged from 2 months (60 days) to 10.5 months (315 days).	Rapisarda and Scott 1986 MRID 42016507
Non-sterile Keyport silt loam soil treated with ¹⁴ C-metsulfuron methyl at a rate of 0.12 ppm and incubated under dark conditions at 25°C and 70-75% moisture retention capacity. After 15 months, 25% of compound remained intact, with an estimated half-life of 8 months (approximately 240 days). After 15 months, 38% of ¹⁴ C was as CO ₂ . Primary metabolite was dihydroxy methyl triazine.	Rhodes 1986 MRID 40340317
Review article – Range of Kd (mL/g): 0.40 to 0.156 Range of soil t _{1/2} (weeks): 3.2 to >31 weeks (22.4 to > 774 days)	Sarmah et al. 1998
Kd is pH-dependent and has a negative correlation with pH. Half-life increases with increasing pH and decreases with decreasing pH. Principle modes of degradation are acid hydrolysis and microbial degradation.	
Rates of degradation measured in 2 soil types at 5 and 25°C – In clay loam: at 5°C, t _{1/2} = 13.5 days; at 25°C, t _{1/2} = 121.6 days In sandy loam: at 5°C, t _{1/2} = 29.8 days; at 25°C, t _{1/2} = 106.6 days	Walker and Jurado-Esposito 1998
Monitoring Studies	
212 water samples were collected from 75 surface-water sites and 25 ground-water sites in the Midwestern U.S. No metsulfuron methyl was detected in any sample (limit of detection of 0.01 µg/L).	Battaglin et al. DATE?
Ground water monitoring study: No metsulfuron methyl was detected in Danish shallow ground water (limit of detection = 0.004 µg/L). 300 samples taken from 1.5 to 5 meters below the surface.	Spliid and Koppen 1998
17 ground water wells in Oklahoma sampled analyzed for metsulfuron methyl. No metsulfuron methyl was detected in any sample (limit of detection 0.025 µg/L).	USGS - no date